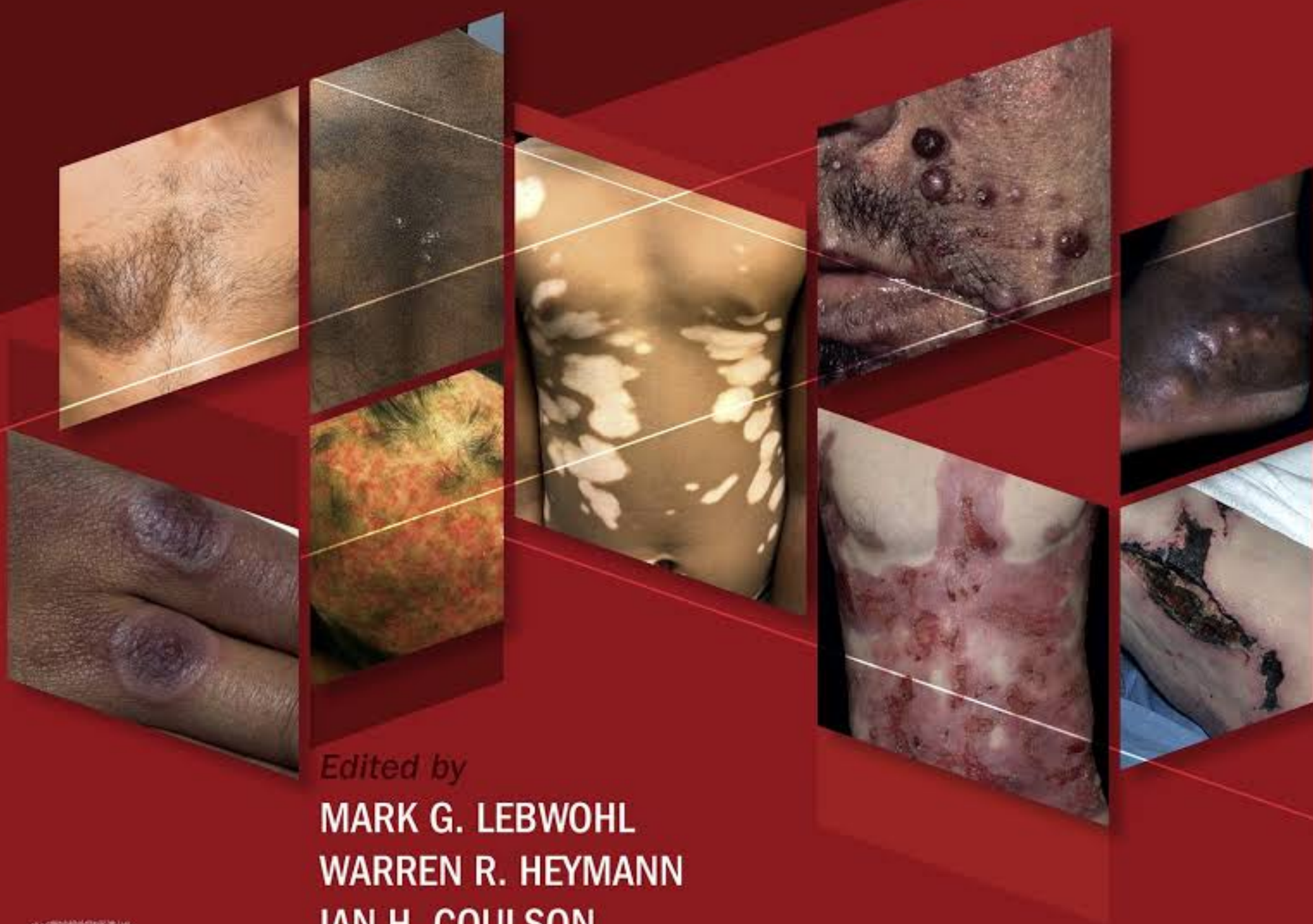


SIXTH EDITION

TREATMENT OF **SKIN DISEASE**

Comprehensive Therapeutic Strategies



Edited by

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SIXTH EDITION

TREATMENT OF SKIN DISEASE

Comprehensive Therapeutic Strategies

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Preface

We began the first edition of *Treatment of Skin Disease* with the following question: ‘Now what do I do?’ Now, over two decades later, our book enters its sixth edition and is published in Chinese, English, Polish, Portuguese, and Spanish. With the first five editions, we hope we have helped many of our colleagues and their patients. With those editions, we were privileged to work with Professor John Berth-Jones, who contributed enormously to the success of our book; however, John has decided to step down. In his place, we have been fortunate to recruit Dedee Murrell, Professor and Chair of the Department of Dermatology at St. George Hospital, UNSW, Sydney, Australia.

The next question to be asked is: ‘Do we need another edition of this book?’ Has enough changed in the treatment of skin diseases to justify another edition? Indeed, the rapid pace of advances in dermatology has improved the way we practice and justifies an updated version of *Treatment of Skin Disease*. Treatments like guselkumab, risankizumab, and tildrakizumab were unheard of a few years ago and are now routine. Biologics were introduced first for psoriasis and now for atopic dermatitis and are being used in a host of other diseases, including pyoderma gangrenosum, sarcoidosis, granuloma annulare, balanitis xerotica obliterans, necrobiosis lipoidica diabetorum, and many others. In upcoming editions, we will be using Janus kinase inhibitors for alopecia areata, vitiligo, sarcoidosis, psoriasis, and atopic dermatitis. Interleukin (IL)-17 blockers, now available for psoriasis, will be used in the future to treat hidradenitis suppurativa. Bimekizumab and other IL-17A and IL-17F blockers will change the way we treat

psoriasis. Lebrikizumab, tralokinumab, and nemolizumab will be used for atopic dermatitis. These treatments undoubtedly will also be applied to conditions like idiopathic pruritus, prurigo nodularis, and severe hand eczema.

When we assigned chapters for the sixth edition, no one had even heard of COVID-19. For this edition, not only have we updated treatments for all the diseases covered, but we also have a new chapter on COVID-19 dermatoses, including the associated pediatric multisystem inflammatory syndrome.

As in prior editions, it is our fervent hope that our book will help our colleagues around the world take better care of their patients. It is that common goal that unites physicians worldwide, and we hope this edition continues to fulfil that goal.

In addition to acknowledging Professor John Berth-Jones for his work on prior editions, we want to acknowledge the authors of chapters in previous editions that have been the basis of the current edition chapters (see ExpertConsult.com). We also want to acknowledge the many individuals who have helped us by providing photographs for the current edition (see page xxix). And, most of all, we would like to acknowledge the patients who have inspired us in our clinical work and in our efforts to spread best practices among our colleagues.

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Finally, we are grateful to our colleagues and residents who provided many of the photos used in this edition.

Dedication

We dedicate this book to our spouses (Madeleine Lebwohl, Rhonda Schnur, Susan Christopher-Coulson, and George Murrell) and our families for their support during many hours of

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Evidence Levels

Each therapy covered has been assigned a letter from A (most evidence) to E (least evidence), signifying the amount of published evidence available to support its use. The following criteria were used in making this classification.

A: Double-Blind Study

At least one prospective randomized, double-blind, controlled trial without major design flaws (in the author's view).

B: Clinical Trial ≥ 20 Subjects

Prospective clinical trials with 20 or more subjects; trials lacking adequate controls or another key facet of design that would normally be considered desirable (in the author's opinion).

C: Clinical Trial < 20 Subjects

Small trials with fewer than 20 subjects with significant design limitations, very large numbers of case reports (at least 20 cases in the literature), or retrospective analyses of data.

D: Series ≥ 5 Subjects

Series of patients reported to respond (at least five cases in the literature).

E: Anecdotal Case Reports

Individual case reports amounting to published experience of fewer than five cases.

Credits

PHOTOS

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TABLES

- Chapter 30:** Table 30.1, Adapted from Veale D, Ellison N, Werner TG, et al. Development of a cosmetic procedure screening questionnaire (COPSs) for body dysmorphic disorder. *J Plast Reconstr Aesthet Surg* 2012; 65(4): 530-532; Table 30.2, From Inamadar AC, Ragunatha S. The rash that becomes an erythroderma. *Clin Dermatol* 2019; 37(2): 88-98, with permission from Elsevier.
- Chapter 78:** Table 78.1, From Inamadar AC, Ragunatha S. The rash that becomes an erythroderma. *Clin Dermatol* 2019; 37(2): 88-98, with permission from Elsevier.

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Acanthosis nigricans

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Acanthosis nigricans is characterized by hyperpigmented, verrucous or velvety plaques that usually appear on flexural surfaces and in intertriginous regions. It is most commonly seen in individuals with insulin resistance states, especially obesity and diabetes, and less frequently in association with other metabolic disorders, genetic syndromes, drugs, and malignancy. Although hyperinsulinemia, hyperandrogenemia, circulating anti-insulin receptor antibodies, tyrosine kinase receptor abnormalities (IGF1R and EGFR), and mutations in fibroblast growth factor receptor have been implicated as causal factors, the precise pathogenesis is not yet known.

MANAGEMENT STRATEGY

The management of patients with acanthosis nigricans addresses the underlying cause, the identification of which requires a salient history, a targeted physical examination, focused diagnostic laboratory tests, and, occasionally, radiologic evaluation.

Relevant historical information includes age at onset, speed of progression from onset, presence or absence of family history, medications, transplant history, and presence or absence of symptoms related to hyperinsulinemia, hyperandrogenemia, hypercortisolism, and internal malignancy.

Drugs reported in association with acanthosis nigricans include niacin, corticosteroids, estrogens, testosterone, insulin, aripiprazole, fusidic acid, protease inhibitors, triazinate, diethylstilbestrol, palifermin, and recombinant growth hormone. Acanthosis nigricans has also been associated with renal and lung transplantation.

Physical examination should document obesity, masculinization, hirsutism, lymphadenopathy, Cushingoid features, and

organomegaly. Initial laboratory screening should include fasting blood glucose and serum insulin tested concurrently to confirm or exclude insulin resistance.

Because obesity is the most common cause of both insulin resistance and acanthosis nigricans, it is the likely cause of acanthosis nigricans in overweight patients with no historical suggestion of culprit drugs or evidence of malignancy.

Rare causes of insulin resistance and acanthosis nigricans include the type A and B syndromes, the former characterized by defective insulin receptors and the latter by circulating anti-insulin receptor antibodies in association with autoimmune disorders such as lupus erythematosus. Other causes of insulin resistance and acanthosis nigricans are polycystic ovarian disease, HAIR-AN syndrome, familial lipodystrophies, and various endocrinopathies.

The most commonly associated malignancy is gastric adenocarcinoma. Less frequent associations are endocrine, genitourinary, lung, and gastrointestinal carcinomas, and, even more rarely, melanoma and cutaneous T-cell lymphomas/Sézary syndrome. Malignant acanthosis nigricans may coexist with other cutaneous markers of internal malignancy, such as tripe palms, the sign of Leser-Trélat, florid cutaneous papillomatosis, and hyperkeratosis of the palms and soles. If malignancy-associated acanthosis nigricans is suspected, age-appropriate cancer screening should be performed. Additional laboratory tests may include a complete blood count, stool test for occult blood, and chest and gastrointestinal radiographs, as well as gastrointestinal endoscopy. Referral to the appropriate specialist would be indicated.

In the absence of objective evidence for a specific cause, the acanthosis nigricans may be labeled as idiopathic, which may or may not be familial. Treatment of the underlying cause, if identified, often leads to the resolution of the acanthosis nigricans. Otherwise, most published treatment modalities are symptomatic and/or cosmetic.

Specific Investigations

- Document obesity based on ideal body weight, height/weight, body mass index (BMI)
- Document blood pressure
- Determine fasting blood glucose and insulin levels in parallel. Consider ordering HbA_{1c}, alanine aminotransferase (ALT), and fasting lipoprotein profile in obese patients
- Consider screening for other endocrine and metabolic diseases
- Consider malignancy: if suspected, refer to the appropriate specialist for the best diagnostic procedure
- Consider drugs as a cause
- Consider transplantation as a cause
- Consider familial/genetic disorders as a cause

Acanthosis nigricans: a practical approach to evaluation and management. Higgins S, Freemark M, Prose N. *Dermatol Online J* 2008; 14: 2.

A review of the diagnosis and management of acanthosis nigricans.

Acanthosis nigricans: a fold (intertriginous) dermatosis. Kutlubay Z, Engin B, Baimov O, et al. *Clin Dermatol* 2015; 33: 466–70.

A review of the classifications, etiopathogenesis, and treatment of acanthosis nigricans.

An approach to acanthosis nigricans. Phiske M. Indian Dermatol Online J 2014; 5: 239.

A review of the pertinent laboratory/radiologic investigations and treatment options of acanthosis nigricans.

Prevalence and significance of acanthosis nigricans in an adult population. Hud J, Cohen J, Wagner J, et al. Arch Dermatol 1992; 128: 941–4.

74% of obese adult patients seen at the Parkland Memorial Hospital Adult Obesity Clinic in Dallas, Texas had acanthosis nigricans. The skin disorder predicted the existence of hyperinsulinemia.

Juvenile acanthosis nigricans. Sinha S, Schwartz RA. J Am Acad Dermatol 2007; 57: 502–8.

A review of the evaluation of children presenting with acanthosis nigricans.

Cutaneous findings and systemic associations in women with polycystic ovary syndrome. Schmidt TH, Khanijow K, Cedars MI, et al. JAMA Dermatol 2016;152: 391–8.

Among the women with polycystic ovarian syndrome, 36.9% had acanthosis nigricans.

Malignant acanthosis nigricans: a review. Rigel D, Jacobs M. J Dermatol Surg Oncol 1980; 6: 923–7.

Gastric carcinoma was reported in 55% of acanthosis nigricans cases associated with internal malignancy.

First-Line Therapy

- Treat the underlying cause

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Acanthosis nigricans with severe obesity, insulin resistance and hypothyroidism: improvement by diet control. Kuroki R, Sadamoto Y, Imamura M, et al. Dermatology (Basel) 1999; 198: 164–6.

A 27-year-old morbidly obese man with acanthosis nigricans was treated with a low-calorie diet. A consequent decrease in weight and insulin-resistant state led to remarkable improvement of his acanthosis nigricans.

Clearance of acanthosis nigricans associated with insulinoma following surgical resection. Ghosh S, Roychowdhury B, Mukhopadhyay S, et al. QJM 2008; 101(11): 899–900.

A case report detailing the disappearance of acanthosis nigricans following surgical resection of an insulinoma.

Acanthosis nigricans in association with congenital adrenal hyperplasia: resolution after treatment. Kurtoğlu S, Atabek ME, Keskin M, et al. Pediatr 2005; 47: 183–7.

A 3-day-old girl with congenital adrenal hyperplasia presented with acanthosis nigricans of both axillae. After corticosteroid and mineralocorticoid therapy for the disease, the acanthosis nigricans resolved.

Second-Line Therapies

- Tretinoin
- Adapalene
- Tazarotene
- Trichloroacetic acid
- Metformin
- Ammonium lactate 12%
- Glycolic acid

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Current treatment options for acanthosis nigricans. Patel NU, Roach C, Alinia H, et al. Clin Cosmet Investig Dermatol 2018; 11: 407–13.

An overview of current treatment options for acanthosis nigricans.

Comparison of the efficacy and safety of 0.1% adapalene gel and 0.025% tretinoin cream in the treatment of childhood acanthosis nigricans. Treerichod A, Chaithirayanon S, Wongjitrat N. Pediatr Dermatol 2019; 36:330–4.

Topical 0.1% adapalene gel and 0.025% tretinoin cream applied daily for 8 weeks significantly improved neck hyperpigmentation without significant differences in efficacy or tolerability.

The efficacy of topical 0.1% adapalene gel for use in the treatment of childhood acanthosis nigricans: a pilot study. Treerichod A, Chaithirayanon S, Wongjitrat N, et al. Indian J Dermatol 2015; 60: 103.

Topical 0.1% adapalene gel applied daily for 4 weeks led to less skin darkening in 16 patients with childhood acanthosis nigricans.

Metformin as adjunctive therapy in acanthosis nigricans treatment: two arms single blinded clinical trial. Alkhayrat A, Alshamrani N, Lama A, et al. Clin Dermatol Res J 2019; 4: 1.

Nine obese patients with acanthosis nigricans were treated with metformin 500mg orally two times daily and topical tretinoin and hydroquinone cream for 24 weeks. Compared to the control group (topical treatment alone), the study group demonstrated greater clinical improvement in the severity of their acanthosis nigricans.

Effective treatment by glycolic acid peeling for cutaneous manifestation of familial generalized acanthosis nigricans caused by FGFR3 mutation. Ichiyama S, Funasaka Y, Otsuka Y, et al. J Eur Acad Dermatol Venerol 2016; 30: 442–5.

Glycolic acid 35% to 70% peel performed on two patients every 2 weeks led to less hyperpigmentation and keratinization. Improvement was maintained with continued peels every 2–5 months.

Third-Line Therapies

- Urea
- Calcipotriol
- Tretinoin, hydroquinone, and fluocinolone acetonide
- Melatonin
- Isotretinoin
- Acitretin
- Octreotide
- Dietary fish oil
- Sitagliptin and pioglitazone
- Laser long-pulsed (5 m-sec) alexandrite laser, fractional carbon dioxide laser

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Acanthosis nigricans associated with primary hypogonadism: successful treatment with topical calcipotriol. Gregoriou S, Anyfandakis V, Kontoleon P, et al. J Dermatol Treat 2008; 19: 373–5.

Topical calcipotriol ointment 50 mcg/g applied twice daily for 8 weeks completely cleared a man's acanthosis nigricans without relapse after 6 months of observation.

Treatment of acanthosis nigricans with oral isotretinoin. Katz R. Arch Dermatol 1980; 116: 110–11.

A woman with acanthosis nigricans had skin clearance with oral isotretinoin (2 mg/kg/day) but long-term therapy was required to maintain clearance.

Generalized idiopathic acanthosis nigricans treated with acitretin. Ozdemir M, Toy H, Mevlitoğlu I, et al. J Dermatolog Treat 2006;17: 54–6.

A male with acanthosis nigricans had clearance of his acanthosis nigricans after 6 weeks of oral acitretin 25 mg taken twice daily. Improvement was maintained on acitretin 0.4 mg/kg/day.

Long-term octreotide treatment reduced hyperinsulinemia, excess body weight, and skin lesions in severe obesity with acanthosis nigricans. Lunetta M, Di Mauro M, Le Moli R, et al. Endocrinol Invest 1996;19: 699–703.

A boy affected by severe obesity was treated with octreotide for 150 days (50 mcg × three daily subcutaneous administrations).

Acanthosis nigricans. Schwartz RA. J Am Acad Dermatol 1994; 31: 1.

A woman with diabetes mellitus and acanthosis nigricans was treated with fish oil supplementation, leading to improvement despite continued hypertriglyceridemia.

Melatonin treatment improves insulin resistance and pigmentation in obese patients with acanthosis nigricans. Sun H, Wang X, Chen J, et al. Int J Endocrinol 2018; 2018: 2304746.

Seventeen obese patients with acanthosis nigricans noted improvement in skin hyperpigmentation after treatment with melatonin 3 mg/day for 12 weeks.

Regression of acanthosis nigricans with the addition of sitagliptin and pioglitazone. Adderley-Rolle EM, Peter S. West Indian Med J 2015; 64: 160–1.

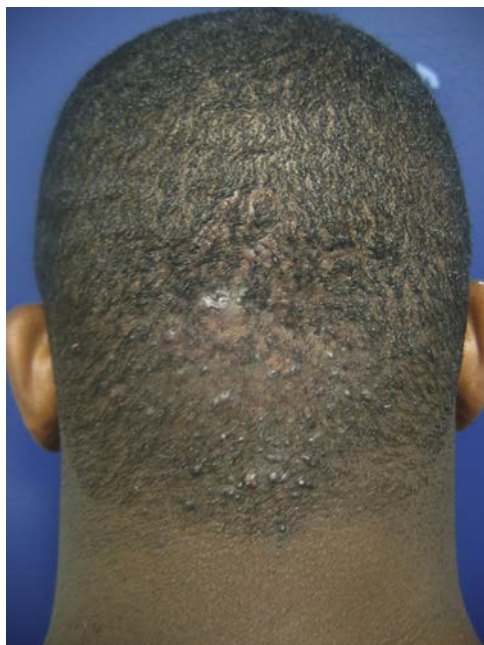
Acanthosis regressed with anti-diabetic medication.

Treatment of acanthosis nigricans of the axillae using a long-pulsed (5-msec) alexandrite laser. Rosenbach A, Ram R. Dermatol Surg 2004; 30: 1158–60.

A woman with axillary acanthosis nigricans was treated with long-pulsed alexandrite laser on one axilla, with the other axilla as an untreated control. The treated axilla showed significant improvement.

Acne keloidalis nuchae

Ahuva D. Cices, Andrew F. Alexis



Acne keloidalis nuchae (AKN) is a chronic disorder predominantly affecting males with Afro-textured hair characterized by inflammatory changes of hair follicles on the posterior neck and scalp that result in fibrotic papules and cicatricial alopecia. Erythematous papules and pustules are the primary inflammatory lesions of AKN. At the time of presentation, most patients will have scarring as a result of the extensive inflammation seen in AKN, manifesting as keloid-like, dome-shaped papules, plaques, or nodules, and scarring alopecia in the affected area. Tufted hairs arising from keloid-like lesions may also be present. AKN is a misnomer without true acne or keloids. The pathogenesis of AKN is poorly understood, but is likely multifactorial, including genetic, immunologic, and environmental factors.

MANAGEMENT STRATEGY

Effective management starts with an accurate diagnosis. AKN is diagnosed clinically by the presence of inflammatory papules, pustules, and scar-like lesions on the occipital scalp and posterior neck of males with Afro-textured hair. Rarely, AKN occurs in females or individuals of non-African descent. The diagnosis is made clinically, without need for biopsy in the vast majority of cases. Characteristic histopathologic features include acute and chronic folliculitis, ruptured pilosebaceous units, and dermal fibrosis. When pustules, scale, or crust is present, bacterial and fungal cultures aid to rule out bacterial folliculitis and/or superinfection, or tinea capitis, respectively. Pustules due to *Staphylococcus aureus* folliculitis can resemble early AKN, but are more superficial, lack induration or keloid-like features, and respond rapidly to appropriate antibiotics.

Treatment of AKN requires suppressing active inflammation and fibrosis as well as avoidance of exacerbating factors using a combination of medical therapies, procedural interventions, and behavioral modification. Disease management is heavily based on clinician experience due to limited evidence or controlled studies and lack of consensus guidelines.

The initial approach comprises *avoidance of close shaving, friction, and rubbing* to prevent disease exacerbations in combination with medical treatments. Mild disease is managed with a combination of topical therapies including *high-potency topical corticosteroids* (group 1 or 2, e.g., clobetasol 0.05% gel or foam), *antimicrobial washes* (e.g., chlorhexidine wash), *topical antibiotics* (e.g., clindamycin phosphate 1% gel or foam), and *topical retinoids* (e.g., tazarotene 0.05% or 0.1% gel). Topical corticosteroids are applied once or twice daily and alternating in 2-week cycles to minimize effects of chronic steroid use. Twice daily application of clobetasol propionate 0.05% foam in alternating 2-week cycles was shown to be effective in a 20-subject, open-label, clinical trial. Improvement is typically achieved in 6–8 weeks and therapy is continued until signs (e.g., papules/pustules) and symptoms (e.g., pruritus, pain) have improved, with reinstitution of therapy for flares. This author (AFA) favors clobetasol propionate 0.05% foam twice daily or a *fixed combination halobetasol 0.01%-tazarotene 0.045% lotion* once daily for 2 weeks followed by application three times weekly.

Antimicrobial washes including *chlorhexidine* and *povidone iodine* are used to prevent secondary infection. If superinfection is suspected, cultures and appropriate antibiotic therapy should be completed prior to initiating steroids. When pustules are present, topical antibiotics are recommended. No formal studies have been completed to evaluate the efficacy of topical antibiotics for AKN. This author (AFA) favors *topical clindamycin 1% gel or foam for treatment of mild pustules*. Efficacy of once-daily topical retinoids, including adapalene, tretinoin, and tazarotene, is unclear, though they are theorized to improve AKN through antiinflammatory effects and prevention of follicular occlusion.

Persistent inflammatory lesions as well as keloid-like scars of AKN can be effectively treated with *intralesional triamcinolone* at varying concentrations ranging from 2.5 to 40 mg/mL with higher concentrations (>20 mg/mL) reserved for large (>3 cm), keloid-like lesions. *Cryosurgery* has also been used successfully, though no studies have evaluated specific parameters for AKN, and hypopigmentation or depigmentation are risks in patients with skin of color.

Failure of the above therapies or moderate-to-severe disease warrants systemic treatments. *Oral antibiotics* are used for several weeks to months to control inflammatory flares. *Tetracyclines* such as *doxycycline* or *minocycline* are the mainstay of oral antibiotic therapy of AKN; however, published evidence is limited. This author (AFA) favors oral doxycycline for its antiinflammatory and antimicrobial effects. When *Staphylococcus aureus* superinfection is present, a course of a first-generation *cephalosporin* or doxycycline at antimicrobial doses (50–100 mg twice daily) is recommended. As an adjunct to topical and intralesional therapy, *subantimicrobial doxycycline* (40 mg/day) for 12–16 weeks is useful in this author's experience. Select cases show effective treatment of refractory inflammatory lesions with *oral retinoids* starting at 0.25–0.6 mg/kg daily followed by lower doses for maintenance.

Light and energy based therapies are effective for long-term disease control. Long-pulse, *long-wave lasers* including *alexandrite 755 nm*, *diode 800–810 nm*, and *neodymium:yttrium-aluminum-garnet (Nd:YAG) 1064 nm* are effective treatment for AKN due to their ability to completely destroy the hair follicle. The 1064-nm Nd:YAG laser has the most favorable profile for hair removal in darker-skinned patient populations: deepest penetration and

least absorption by melanin, thereby maximizing efficacy and minimizing risk of dyspigmentation. Its efficacy has been demonstrated in a prospective controlled trial. *Er:YAG* has been shown to have the same efficacy as *Nd:YAG* for papular disease as well as beneficial effects on larger plaques in a comparative trial. A 12-subject AKN trial showed targeted *ultraviolet B (UVB) phototherapy* administered three times weekly is effective and well tolerated.

Surgical excision, including scalpel, electrosurgical, or laser excision, followed by primary closure or secondary intention healing is effective for refractory and severe disease. Regardless of the surgical technique utilized, successful treatment requires complete removal of hair follicles to prevent recurrence. Horizontal ellipse excision followed by secondary intention healing is recommended for optimal cosmetic outcomes. Postsurgical adjuvant therapies have included intralesional or topical steroids and radiotherapy; however, these are not indicated given the low recurrence rate. Local radiation therapy with 3 Gy and 6 MeV $\times$ 10 sessions on alternating days was successful in treating a case of refractory AKN that recurred after therapy with topicals, oral antibiotics, isotretinoin, and partial excision.

Specific Investigations

- Pustule swab
- Punch biopsy

First-Line Therapies

• Counseling	E
• High-potency topical steroid (class I or II)	B
• Topical antibiotic	E
• Antimicrobial cleansers	E
• Oral antibiotic	E
• Topical retinoid	E

Pseudofolliculitis barbae. Chu T. Practitioner 1989; 233: 307–9.

Topical clindamycin 1% was effective for pseudofolliculitis and acne keloidalis in a limited open-label study.

An open label study of clobetasol propionate 0.05% and betamethasone valerate 0.12% foams in the treatment of mild to moderate acne keloidalis. Callender VD, Young CM, Haverstock CL, et al. Cutis 2005; 75(6): 317–21.

Open-label study in 20 African American patients that showed efficacy and tolerability of topical steroids for treatment of mild-to-moderate scalp AKN. Clobetasol propionate ointment 0.05% foam used twice daily alternating 2 weeks on and 2 weeks off for a total of 8 weeks showed statistically significant improvement of papule/pustule count and pruritus scores. In the second phase, subjects with residual disease ($n = 11$) were treated with betamethasone valerate 0.12% foam twice daily from weeks 8–12 with no statistically significant change in lesion count from weeks 8–12.

Folliculitis keloidalis nuchae and pseudofolliculitis barbae: are prevention and effective treatment within reach? Alexis A, Heath CR, Halder RM. Dermatol Clin 2014; 32(2): 183–91.

Review of treatment options for AKN, which include counseling on preventative measures to avoid disease exacerbations (e.g., avoiding mechanical irritation and manipulation) and medical

treatments including antimicrobial cleansers (e.g., chlorohexidine), topical and oral antibiotics, topical steroids, and topical retinoic acid. Additionally, surgical and laser therapies are also addressed.

Second-Line Therapies

• Alexandrite laser	C
• Targeted UVB	C
• <i>Nd:YAG</i>	C
• <i>Er:YAG</i>	C
• Oral retinoid	E
• Diode laser	E
• Intralesional steroids	E
• Cryosurgery	E
• Imiquimod	E
• Pimecrolimus	E

Improving acne keloidalis nuchae with targeted ultraviolet B treatment: a prospective, randomized, split-scalp comparative study. Okoye GA, Rainer BM, Leung SG, et al. Br J Dermatol 2014; 171(5): 1156–63.

Split-scalp study in 11 patients with AKN treated with targeted UVB (290–320 nm) up to three times weekly for 8 weeks, followed by 8 weeks of full scalp treatment with statistically significant decreased lesion count on treated side at 8 weeks. Authors also noted improvement in clinical appearance and patient satisfaction without tolerability limitations.

Successful treatment of acne keloidalis nuchae with erbium:YAG laser: a comparative study. Gamil HD, Khater EM, Khattab FM, et al. J Cosmet Laser Ther 2018; 20(7–8): 419–23.

In this comparative study, 30 male subjects with AKN were randomly assigned to six sessions *Er:YAG* 2490 nm, 3-mm spot size, pulse duration 300 msec, frequency 5 Hz, and pulse 800–900 mJ in partially overlapping mode or *Nd:YAG* 1064 nm, 13-mm spot size, pulse duration of 35 msec, and a fluence of 30–35 J/cm² in partially overlapping mode. Following treatment, both groups received ice compresses, and topical fusidic acid and betamethasone topically for 3 days posttreatment. Both groups had improvement in papular disease (91.8% vs. 88%). Significant improvement in plaques only in the *Er:YAG*-treated group.

Nd:YAG and *Er:YAG* can be used to treat early papular lesions of AKN. *Er:YAG* is more effective than *Nd:YAG* for the treatment of more advanced disease.

Keratosis follicularis spinulosa decalvans and acne keloidalis nuchae. Goh MS, Magee J, Chong AH. Australas J Dermatol 2005; 46(4): 257–60.

Rapid improvement of inflammatory lesions in biopsy-confirmed concomitant suppurative AKN and keratosis follicularis spinulosa in a 27-year-old Caucasian male with oral isotretinoin 20 mg (0.25 mg/kg) daily for 12 months. Maintenance of response with 20 mg every 2–3 days at 1 year.

Use of imiquimod and pimecrolimus cream in the treatment of acne keloidalis nuchae. Barr J, Friedman A, Balwin H. J Am Acad Dermatol 2005; 52(3 Suppl): 64.

Small open-label study with five subjects randomized to topical imiquimod applied once daily or pimecrolimus twice daily for 8 weeks. All five patients had significant improvement in pruritus and decreased lesion counts.

Imiquimod and pimecrolimus can be used topically for subjects with AKN who fail first-line topical agents and prefer to be managed with topical agents.

A novel treatment of acne keloidalis nuchae by long-pulsed alexandrite laser. Tawfik A, Osman MA, Rashwan I. *Dermatol Surg* 2018; 44(3): 413–20.

Seventeen male subjects with AKN received six sessions of 755-nm alexandrite laser therapy. There was a significant improvement in mean papule and pustule counts, keloidal plaque size, and pliability at the fourth and sixth laser sessions compared with baseline. Improvement in early papule/pustule lesions was significantly greater than improvement in later keloid-like lesions. Adverse effects included reduction of hair density in the treatment areas as well as temporary hair loss in four subjects.

Efficacy of diode laser for treating acne keloidalis nuchae. Shah GK. *Indian J Dermatol Venereol Leprol* 2005; 71(1): 31–4.

Two cases of AKN with 90–95% clearance of AKN after four treatments at 4–6-week intervals with diode laser.

Third-Line Therapies

- Surgical excision with secondary intention healing **B**
- Radiotherapy **E**

The surgical management of extensive cases of acne keloidalis nuchae. Gloster HM Jr. *Arch Dermatol* 2000; 136: 1376–9.

A referred sample of 25 Black men with refractory, extensive AKN were treated as follows: excision with layered closure in stage 1 (20 subjects), stage 2 excision with layered closure (4 subjects), and excision with second intention healing (1 subject). Surgeries

were performed in a sterile fashion, to a depth below hair follicles to fascia or deep fat, with a no. 10 scalpel blade or with an electrosurgical device. All subjects rated cosmetic results favorably and none had full recurrence; 15 patients had mild papules and pustules in the first 4 months and five patients treated with single-stage excision developed hypertrophic scars. Both groups were successfully treated with twice-daily high-potency topical steroids and monthly intralesional triamcinolone.

Surgical excision is the most studied treatment option for severe or refractory AKN. In clinical practice recurrences are seen due to residual hair follicles.

Treatment of acne keloidalis nuchae with carbon dioxide laser. Kantor GR, Ratz JL, Wheeland RG. *J Am Acad Dermatol* 1986; 14(2 Pt 1): 263–7.

Series of six patients treated with CO₂ laser excision at 64,000 watts/cm², one of which had a satellite lesion treated with vaporization and two additional subjects treated with vaporization at 130 to 105 watts/cm². Patients treated with laser excision had no recurrence at time of follow-up (ranging from 3–47 months postoperatively), though two subjects used prophylactic betamethasone valerate ointment 0.1% twice daily. Two of the three subjects treated with vaporization had disease recurrence. Two of these patients successfully treated with laser excision developed mild hypertrophic scars at 3 months postoperatively that responded to intralesional triamcinolone 20–40 mg/mL.

Refractory acne keloidalis nuchae treated with radiotherapy. Millán-Cayetano JF, Repiso-Jiménez JB, Del Boz J, et al. *Australas J Dermatol* 2017; 58(1): e11–e13.

Case report of refractory AKN successfully treated with 3 Gy and 6 MeV × 10 sessions on alternating days.

Radiation therapy is an alternative treatment modality for refractory AKN when other treatments have been ineffective.

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Acne vulgaris

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Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit with multifactorial pathogenesis. Numerous immune mechanisms are involved and are influenced by factors such as diet, genetics, and environment. There are four main pathogenic factors leading to the development of acne: 1) increased sebum production; 2) abnormal keratinization of the follicular infundibulum; 3) *Cutibacterium acnes*-mediated responses; and 4) inflammation.

Acne ranges from mild to severe and fulminant. Types of acne lesions (open or closed comedones, inflammatory papules or pustules, nodules), extent of distribution, involvement of the chest, shoulders and back as well as presence of scarring, postinflammatory hyperpigmentation and erythema should be taken into consideration when choosing an acne treatment regimen.

MANAGEMENT STRATEGY

An effective treatment strategy targets multiple pathogenic factors. Other than the systemic retinoid isotretinoin, there are no other single acne treatments that address all four pathogenic factors. Thus, combination therapy, typically a *retinoid with benzoyl peroxide (BP)* ± *topical or systemic antibiotic*, is used first line to achieve optimal improvement in mild to moderate–severe acne.

Mild Acne

In mild forms of acne, topical therapy is most appropriate. First-line treatment includes a topical retinoid often with BP, or a topical *fixed-dose combination product* (such as *adapalene/BP*). Topical retinoids (*adapalene, tretinoin, tazarotene, trifarotene*) have both comedolytic and antiinflammatory properties. Additionally, topical retinoids have demonstrated efficacy in preventing atrophic acne scarring. All topical retinoids are effective as single agents in treatment of acne, although they are usually combined with BP for its additive

antimicrobial effects. The efficacy of combination therapy is superior to any single agent. Convenient fixed-dose combinations include *adapalene 0.1%/BP 2.5% gel, adapalene 0.3%/BP 2.5% gel and tretinoin 0.025%/clindamycin 1.2% gel*. Topical retinoids differ in strength and tolerability, which can be affected by vehicle, concentration, and skin type. In several randomized, parallel-group studies, adapalene 0.1% gel has consistently demonstrated greater tolerability than tretinoin cream or tazarotene, whereas tazarotene 0.1% gel has had greater reported efficacy than adapalene 0.1% gel and tretinoin 0.025% gel. Trifarotene 0.005% cream, with selective RAR- γ binding, was recently Food and Drug Administration (FDA) approved for use in acne vulgaris involving the face, shoulders, chest, and back. Side effects from all retinoids include local redness, peeling, itching, and stinging at sites of application, particularly within the first 2 weeks. Irritation typically improves with continued use and can usually be controlled with use of a gentle cleanser and daily moisturizer. Sun sensitivity is also reported with topical retinoid use and sun protection measures should be advised. Generic tretinoin formulations are not stable in ultraviolet light or with concomitant BP application; therefore, they should be applied at night and separately from BP. Adapalene 0.1% gel is the only retinoid currently available over the counter without prescription.

Topical antibiotics (erythromycin, clindamycin) have long been used as adjunctive therapies for mild-to-moderate acne, exerting antimicrobial and antiinflammatory effects, thus overlapping mechanisms of action with BP and topical retinoids. *Topical minocycline 4% foam* was recently FDA approved for use in moderate-to-severe acne, demonstrating efficacy in reducing both inflammatory and non-inflammatory lesions. While clinical trials have documented the efficacy of topical antibiotics as single treatment agents, due to widespread antibiotic resistance, topical antibiotics should not be used as monotherapy. If used, they should be combined with BP, either as separate formulations or in fixed-dose combination products (*BP/clindamycin* or *BP/erythromycin*) to prevent the development of antimicrobial resistance. Additionally, randomized, double-blind, placebo-controlled trials comparing fixed-dose combination products (e.g., *BP/clindamycin*) with individual components and placebo have demonstrated greater efficacy in combination than as solo agents. Continuous, long-term use of any antibiotic, topical or systemic, for acne is not recommended.

Alternative treatment options for mild acne include *topical dapsone, azelaic acid, and salicylic acid*. Dapsone is a topical sulfone antimicrobial agent that comes in two concentrations (5% and 7.5%). Its mechanism of action in acne treatment is poorly understood but presumptively antiinflammatory. It is effective in treating inflammatory acne, particularly in women and skin of color. BP should not be applied at the same time as dapsone gel as it may cause a temporary orange discoloration of the skin and fabrics. Azelaic acid 20% cream has efficacy as a comedolytic, antibacterial, and antiinflammatory agent when used twice daily. Additionally, there are limited clinical trials demonstrating the efficacy and tolerability of azelaic 15% foam and gel for the treatment of acne. Lesser strength formulations of azelaic acid are available in many over-the-counter preparations. It is typically less irritating than topical retinoids, though less effective as a comedolytic. Azelaic acid is often used to treat postinflammatory hyperpigmentation. There is limited clinical data to support the use of salicylic acid in acne; however, it is widely available without a prescription, has a reasonable safety profile, and may be a reasonable option for patients with very mild acne.

Moderate Acne

For moderate acne, topical combination therapy (retinoid and BP) as described above is recommended as initial management, with

or without the addition of a systemic antibiotic depending on relative severity. Current acne management guidelines from the US, EU, UK, and Canada recommend that all antibiotics should not be used as monotherapy but used in conjunction with a topical retinoid and BP. Additionally, topical antibiotics should also not be combined with oral antibiotic therapy due to risk of bacterial cross resistance. Tetracyclines (*doxycycline*, *minocycline*, *tetracycline*, *sarecycline*) are considered the first-line antibiotic choice for moderate-to-severe acne due to their lipophilic absorption property allowing greater penetration of the pilosebaceous unit, their antimicrobial effects on *C. acnes*, and their antiinflammatory properties. Systemic doxycycline is typically preferred over systemic minocycline due to a higher risk of rare but serious side effects reported with minocycline, including pseudotumor cerebri, drug rash with eosinophilia and systemic symptoms (DRESS), and drug-induced lupus. Doxycycline and minocycline are typically given at a dose of 100 mg by mouth daily to twice daily. They can be given with food to decrease gastrointestinal upset. Subantimicrobial doxycycline dosing regimens (20 mg twice daily or 40 mg daily) have also shown efficacy in limited studies of moderate and moderate-to-severe acne. Side effects of doxycycline include gastrointestinal upset and photosensitivity, and it is not recommended for pregnant women or children younger than 8 years old due to effects on bones and teeth. Tetracycline, 500 mg twice daily, can alternately be used but must be taken on an empty stomach. Sarecycline, 100 mg daily, has a narrower antimicrobial spectrum than the other tetracyclines, with targeted bactericidal effects on *C. acnes*. Subsequently, it has less potent antimicrobial activity against intestinal microbial flora, including aerobic Gram-negative bacilli and anaerobic bacteria. Importantly, all current acne management guidelines recommend that the use of systemic antibiotics should be limited to 3–4 months whenever possible. Therefore, once improvement in acne is attained, systemic antibiotics should be discontinued, while maintaining the use of a topical retinoid and BP. If acne is not controlled, isotretinoin or hormonal agents (for adolescent girls and women) should be considered. Macrolide antibiotics (*erythromycin*, *azithromycin*) are typically used for pediatric patients and those intolerant of or allergic to tetracyclines. Use of systemic erythromycin is limited due to antimicrobial resistance. In limited randomized, double-blind, non-inferiority studies, azithromycin demonstrated variable equivalent efficacy for acne when compared with doxycycline. Published dosing regimens vary widely and are not standardized. *Azithromycin 500 mg/day, 3 days a week*, is the most commonly reported dosing regimen. Due to greater risk of severe adverse events, particularly DRESS, *trimethoprim-sulfamethoxazole (TMP-SMX)* should be used only in patients intolerant of or unresponsive to tetracyclines. Amoxicillin and cephalexin have little data to support their use in the treatment of acne, with no controlled trials to document safety or efficacy, and are not typically recommended except in pregnant women and patients with drug allergy prohibiting alternate antibiotic therapy.

Hormonal agents are an effective treatment option for females with moderate-to-severe papulopustular acne. *Combination oral contraceptive pills (COCs)* contain both an estrogen and a progestin and control acne by their antiandrogenic effects. There are four COCs approved by the FDA for treatment of acne (in addition to pregnancy prevention), though most COCs with third- and fourth-generation progestins (*norgestimate*, *desogestrel*, *gestodene*, *drospirenone*) have demonstrated efficacy in females with acne. COCs are taken daily, and improvement in acne can be expected 3–6 months after initiation. Two major side effects of concern with COCs are venous thromboembolic events and myocardial infarction. Absolute contraindications to their use include personal history of thromboembolic disorders, cerebrovascular or

coronary artery disease, migraine with aura, hypertension, breast cancer, undiagnosed abnormal genital bleeding, and liver tumors.

An alternative hormonal agent, *spironolactone*, can also be considered for females with acne. Spironolactone is an aldosterone receptor antagonist with potent antiandrogen effects, and in retrospective case series it has been shown effective in adult women with acne and females with polycystic ovarian syndrome/androgen excess. Typical dosing ranges from 50 mg to 200 mg per day as monotherapy or in combination with other acne treatments with improvement in acne noted in 4–8 weeks of treatment. It is typically well-tolerated, with common dose dependent side effects being diuresis, menstrual irregularities, and breast tenderness. Side effects may be ameliorated with concomitant use of a third- or fourth-generation progestin-containing COC. There is a hypothetical risk of feminization of a male fetus if spironolactone is taken during pregnancy and thus its use should be avoided in pregnant patients. Spironolactone is also a potassium-sparing diuretic. In young, healthy patients without renal or cardiovascular disease, serum potassium monitoring is not required while on spironolactone. Potassium levels should be monitored in those with cardiac or renal disease, orthostatic instability, and for those on medications that affect the renin–angiotensin–aldosterone system. Safety and efficacy in pediatric and adolescent acne patients have not been established.

Severe Acne

First-line treatment for severe acne should include topical combination therapy (retinoid and BP) plus an oral antibiotic (see moderate acne). In several studies, approximately 70% of patients with severe acne can achieve clear to almost clear skin with use of an oral antibiotic, topical retinoid, and BP. For severe, nodulocystic acne, acne with severe scarring, or in those intolerant of tetracycline, *isotretinoin* should be considered first line. Systemic isotretinoin is the most effective antiacne drug available and has the potential to induce a durable remission even after discontinuation. Current acne management guidelines recommend initiating isotretinoin at 0.5 mg/kg/day for the first month to prevent isotretinoin-induced flaring and increasing to 1 mg/kg/day thereafter as tolerated, continuing therapy until a total cumulative dose of 120–150 mg/kg is achieved in order to obtain a durable remission. Individual patients may require longer treatment courses to achieve adequate improvement. Prospective case series report efficacy of low-dose (0.1–0.2 mg/kg daily) regimens over variable time frames (6 months to 120 mg/kg cumulative dose to clearance plus one additional month) in patients with moderate acne. Lower dose regimens are associated with a greater tolerability. Lower starting doses and concomitant *prednisone* therapy may be required for those with severe inflammatory acne at risk of isotretinoin-induced acne fulminans. Studies examining relapse rates after a course of isotretinoin have variable definitions of recurrence and are difficult to compare; however, in general, about 20% of patients will need additional acne treatment at 2 years post isotretinoin treatment. Increased risk of recurrence is reported more likely in younger patients, adult females, smokers, patients with macrocomedones and truncal acne, and those with underlying, untreated hyperandrogenism.

Common adverse effects of oral isotretinoin include characteristic dose-dependent mucocutaneous side effects (cheilitis, xerosis, dry mucosae, conjunctivitis, epistaxis), elevation of serum lipids, arthralgia, and myalgia. Rare liver function abnormalities, pseudotumor cerebri, and hyperostosis or extraskeletal calcification have been reported. Routine monitoring of liver function tests, serum cholesterol, and triglycerides at baseline and again once treatment dose is attained (typically at 2 months)

is recommended. A *lidose isotretinoin* formulation allows greater absorption without the need to take with a high fat meal.

Of most importance, the dose-independent teratogenic potential of isotretinoin, which is associated with a high rate of spontaneous abortion and life-threatening congenital malformations, demands the use of highly effective forms of contraception when it is prescribed for persons of reproductive potential. This includes female to male transgender patients who have not undergone gender affirming surgery. All persons of reproductive potential must commit to two forms of contraception or abstinence for 1 month before initiation of treatment, during the entire period of drug administration, and for 1 month after discontinuation. All patients in the US treated with isotretinoin must adhere to the FDA-mandated iPLEDGE risk management program. Oral isotretinoin is strictly contraindicated in pregnancy and during lactation, and should be used with caution in those with severe hepatic dysfunction. Coadministration of additional vitamin A, beyond the recommended daily allowance, is contraindicated. Although a causal relationship has not been decidedly established, deterioration of preexisting depression, suicidal ideation, anxiety, bipolar disorder, psychosis, and schizophrenia have been reported during treatment and psychiatric symptoms should be monitored closely at each visit. An association between inflammatory bowel disease (IBD) and isotretinoin use was suggested; however, large, case-controlled studies and subsequent meta-analysis have refuted an increased risk of IBD in patients treated with isotretinoin.

Regarding cutaneous procedures during and after isotretinoin treatment, limited case reports suggested that isotretinoin use could be associated with development of excessive granulation tissue and scarring after dermatologic procedures. Current expert recommendations suggest only mechanical dermabrasion and fully ablative laser procedures should be avoided until 6–12 months after isotretinoin use.

Acne conglobata is a severe form of acne characterized by polyporous comedones and deep, coalescing nodulocystic lesions involving the face, trunk, buttocks, and thighs. Scarring is severe. Isotretinoin should be used first-line and may require prolonged administration.

Acne fulminans (AF) is a severe variant of acne characterized by abrupt onset of papules, pustules, and nodules with characteristic granulomatous lesions over the face, chest, back, and shoulders. Systemic symptoms of fever and joint pain are common but not seen in all patients, while laboratory and radiographic studies may show leukocytosis, elevated inflammatory markers, and osteolytic bone lesions. AF may occur spontaneously or be isotretinoin-induced, typically occurring within the first month of starting the medication. At the onset of AF, systemic prednisone at a dose of 0.5–1 mg/kg/day is recommended for at least 2–4 weeks until crusted lesions are healed, at which time isotretinoin can be initiated or re-initiated. Isotretinoin should be initiated at a low dose (0.1 mg/kg/day) with overlap with prednisone for at least 4 weeks. Tapering of prednisone over 4–8 weeks is recommended as tolerated, and similarly an increase in isotretinoin is recommended slowly as tolerated. An alternate reported regimen is isotretinoin 0.5 mg/kg divided twice daily and prednisolone 10 mg three times daily. *Topical clobetasol or intralesional corticosteroid injection, in addition to pulsed-dye laser*, can be used to treat the granulation tissue. In patients unresponsive to or intolerant of isotretinoin, alternative treatments include *tumor necrosis factor (TNF) inhibitors (adalimumab, infliximab)*, *cyclosporin*, *methotrexate*, *azathioprine*, systemic dapsone, tetracyclines, and azithromycin.

Maintenance Therapy (Clear/Almost Clear)

Once improvement in acne is attained, topical retinoids are the mainstay of maintenance therapy. To prevent recurrence, daily

retinoid use should be maintained along with BP if a part of the acne treatment regimen.

Cutaneous sequelae from acne include postinflammatory hyperpigmentation (PIH) and erythema and scarring, and should continue to be managed once acne clearance is achieved (see Chapter 200).

Acne scarring is a common sequela occurring in 43% of patients presenting for treatment. Early and aggressive treatment of acne is needed to prevent scarring.

Procedural treatments of atrophic acne scars include selective use of *micro-needling*, *subcision*, *injection of platelet-rich plasma*, and *chemical reconstruction of skin scars (CROSS) with 100% trichloroacetic acid*. Several lasers have demonstrated efficacy in the treatment of acne scarring, including fractional *carbon dioxide lasers*, *1450-nm diode laser*, and *Nd:YAG*. Management of keloidal acne scars includes *intralesional corticosteroid injection* often in combination with laser treatments.

Other Acne Treatments

While there is limited published evidence to support the use of comedone extraction, it is generally considered in expert consensus to be beneficial in select patients. There is limited evidence to support recommendations for *sulfur*, *nicotinamide*, and *sodium sulfacetamide* in the treatment of acne.

Serial chemical peels, including 40% *glycolic acid* and 20–30% *salicylic acid*, may be beneficial in mild-to-moderate comedonal acne. Some laser and light devices have data to support use in active acne treatment. A split-face study of *pulsed-dye laser (PDL)* showed that it is effective in reducing acne lesions with no differences in purpuric and subpurpuric fluences. Photodynamic therapy has also shown efficacy in the treatment of acne.

Published studies suggest a role for high glycemic load diets and dairy consumption, particularly skim milk, in the pathogenesis of acne. However, currently there is not enough evidence to recommend any specific dietary changes in healthy acne patients. In patients with clinical and laboratory evidence of metabolic dysregulation, including insulin resistance and polycystic ovarian syndrome (PCOS), a *low-glycemic load diet* may result in improvements in acne. However, standard acne treatment should be used concomitantly.

Acne in pregnancy can be challenging to manage, as many standard acne treatments are contraindicated or not recommended in pregnancy. Topical treatment options include azelaic acid, erythromycin, and clindamycin, all of which are pregnancy category B. For moderate-to-severe acne in pregnancy not controlled with topicals, short courses of *oral erythromycin* or *cephalexin* may be utilized. Similarly, for severe or fulminant acne in pregnancy, consideration could be given to a short course of oral prednisolone. Management decisions should be made with the patient's obstetrician. Importantly, tazarotene and isotretinoin are both classified as pregnancy category X and are absolutely contraindicated in pregnancy.

Neonatal acne (birth to 6 weeks of age) can affect up to 20% of newborns and may not be true acne. It typically presents without comedones and may be driven at least partially by yeast colonization. Spontaneous resolution will occur, but treatment with a *topical antifungal* (clotrimazole, ketoconazole) could be considered.

In infantile acne (6 weeks–2 years of age) comedones predominate with variable inflammatory lesions noted. Pitted scarring is common. While measurable hormonal abnormalities are very rare in this age group, these infants should be examined for physical signs of hyperandrogenism, including evaluation of growth charts, testicular and breast development, and examination for hirsutism, pubic hair, clitoromegaly, and abnormal genitalia. If any concerning physical signs are present, a referral to a pediatric endocrinologist is warranted. Off-label management can be initiated according to the

above recommendations based on severity of acne, with infant-compatible formulations (i.e., lower strength retinoids and BP, avoiding washes that may get in the baby's eyes). Systemic *azithromycin* or *erythromycin* are used for moderate-to-severe acne. Tetracycline antibiotics must be avoided due to effects on bones and staining of teeth.

Mid-childhood acne (1–7 years of age) is rare as androgen levels are normally low during this stage. Therefore, all patients with mid-childhood acne should undergo endocrinological evaluation to rule out causes of hyperandrogenism. Treatment is indicated based on severity of acne as above, though remains off-label. Tetracycline antibiotics must be avoided due to effects on bones and teeth.

Preadolescent acne (7–12 years of age) is increasingly common and often the first sign of pubertal maturation. Endocrinologic workup is typically unnecessary except in cases of severe, abrupt onset. Early acne may be a sign of more severe adolescent acne. Treatment is indicated based on severity of acne, as above. Safety and efficacy have been established in this age group with tretinoin 0.05% gel (10 years and older) and fixed combination adapalene 0.1%/BP 2.5% gel (9 years and older), though others may be used off-label. Tetracycline antibiotics can be used after age 8 years, depending on permanent tooth development.

Specific Investigations

- Typical presentations of acne do not require any routine investigation
- For sudden-onset severe acne or signs of androgen excess, endocrinologic evaluation is warranted to rule out adrenal or gonadal tumors
- For females with signs of hyperandrogenism (hirsutism, androgenetic alopecia) and menstrual irregularities, PCOS should be considered. Endocrinologic evaluation may include serum DHEA-S, free and total testosterone, LH, and FSH, or referral to a specialist
- Consider microbiology to exclude Gram-positive, Gram-negative, and pityrosporum folliculitis
- Consider skin-scraping to exclude demodicosis
- For pediatric patients under age 7 years, physical examination for signs of pubertal development should be performed. If present, the child should be referred for endocrinologic evaluation

Standardized laboratory monitoring with use of isotretinoin in acne. Hansen TJ, Lucking S, Miller JJ, et al. *J Am Acad Dermatol* 2016; 75(2): 323–8.

Retrospective review of laboratory monitoring in 515 patients with acne treated with isotretinoin. Their conclusions were to check a baseline lipid panel and liver function tests repeated after 2 months of isotretinoin therapy. If findings are normal, they recommend no further testing for healthy patients.

Does exposure to isotretinoin increase the risk for the development of inflammatory bowel disease? A meta-analysis. Lee SY, Jamal MM, Nguyen ET, et al. *Eur J Gastroenterol Hepatol* 2016; 28(2): 210–6.

A meta-analysis of six published studies examining the possible association of IBD with isotretinoin use. The results of the pooled data supported the previous conclusions that there is no increased risk of developing IBD in patients exposed to isotretinoin compared with patients not exposed to isotretinoin.

Clinical practice: polycystic ovary syndrome. McCartney CR, Marshall JC. *N Engl J Med* 2016; 375(1): 54–64.

A concise review of PCOS, including clinical features, diagnostic workup, and treatment.

First-Line Therapies

Mild acne

- Topical retinoid (adapalene, tretinoin, tazarotene, trifarotene) **A**
- Benzoyl peroxide **A**
- Fixed-dose combination adapalene/benzoyl peroxide **A**
- Fixed-dose combination tretinoin/clindamycin **A**
- Benzoyl peroxide, topical retinoid, and topical antibiotic **B**
- Topical dapsone **A**
- Azelaic acid **A**
- Salicylic acid **B**

Moderate acne

- Topical retinoid and BP **A**
- BP and topical antibiotic **A**
- Fixed-dose combination adapalene/benzoyl peroxide **A**
- Fixed-dose combination tretinoin/clindamycin **A**
- Topical retinoid, BP, and topical antibiotic **A**
- Topical retinoid, BP, and oral antibiotic **A**
- Topical retinoid, BP, topical antibiotic, and oral antibiotic **A**
- Fixed-dose combination adapalene/benzoyl peroxide and doxycycline **A**
- Fixed-dose combination tretinoin/clindamycin, BP and minocycline **B**

Severe acne

- Fixed-dose combination adapalene/benzoyl peroxide and doxycycline **A**
- Fixed-dose combination tretinoin/clindamycin, BP and minocycline **B**
- Topical retinoid and BP, and oral antibiotic **A**
- Oral isotretinoin **B**

Acne fulminans

- Oral isotretinoin with oral corticosteroids **C**

Guidelines of care for the management of acne vulgaris. Zaenglein AL, Pathy AL, Schlosser BJ, et al. *J Am Acad Dermatol* 2016; 74: 945–73.

The American Academy of Dermatology's evidence-based guidelines reviewing grading, topical, and systemic management of acne.

Treatment of acne in pregnancy. Chien AK, Qi J, Rainer B, et al. *J Am Board Fam Med* 2016; 29: 254–62.

A review on the safety profiles of common therapies used in pregnancy.

Evidence-based recommendations for the diagnosis and treatment of pediatric acne. Eichenfield LF, Krakowski AC, Piggott C, et al. *Pediatrics* 2013; 131(Suppl 3): S163–86.

Evidence-based recommendations regarding the classification, diagnosis, evaluation, and management of pediatric acne, based on age and pubertal status.

Comparing 2.5%, 5%, and 10% benzoyl peroxide on inflammatory acne vulgaris. Mills OH, Kligman AM, Pochi P, et al. *Int J Dermatol* 1986; 25: 263–7.

Three double-blind studies comparing daily benzoyl peroxide 2.5%, 5%, and 10% with their vehicles in patients with

mild-to-moderate acne, demonstrating equivalent efficacy of all concentrations with higher risk of irritation with higher concentrations.

Adapalene–benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: results of a multicenter, randomized, double-blind, controlled study. Thiboutot DM, Weiss J, Bucko A, et al. *J Am Acad Dermatol* 2007; 57(5): 791–9.

This randomized, double-blind controlled trial compared daily adapalene–benzoyl peroxide combination to adapalene, benzoyl peroxide, or vehicle alone in the treatment of acne vulgaris. The fixed-dose combination gel of daily adapalene and benzoyl peroxide was significantly more effective than respective monotherapies.

Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double-blind investigations. Lookingbill DP, Chalker DK, Lindholm JS, et al. *J Am Acad Dermatol* 1997; 37(4): 590–5.

In the treatment of acne, the topical combination clindamycin/benzoyl peroxide gel was well tolerated and superior in efficacy to either ingredient alone.

Two randomized, double-blind, split-face studies to compare the irritation potential of two topical acne fixed combinations over a 21-day treatment period. Bhatia N, Bhatt V, Martin G, et al. *J Drugs Dermatol* 2016; 15: 721–6.

Clindamycin–BPO 3.75% gel is better tolerated than adapalene 0.3%–BP 2.5% gel in moderate-to-severe acne.

Efficacy and safety of clindamycin phosphate 1.2%/tretinoin 0.025% formulation for the treatment of acne vulgaris: pooled analysis of data from three randomised, double-blind, parallel-group, phase III studies. Dréno B, Bettoli V, Ochsendorf E, et al. *Eur J Dermatol* 2014; 24(2): 201–9.

Combination clindamycin/tretinoin was found to be safe and to have superior efficacy to its individual components and vehicle in the treatment of acne.

A treatment for severe nodular acne: a randomized investigator-blinded, controlled, noninferiority trial comparing fixed-dose adapalene/benzoyl peroxide plus doxycycline vs. oral isotretinoin. Tan J, Humphrey S, Vender R, et al. *Br J Dermatol* 2014; 171(6): 1508–16.

Multicenter randomized controlled non-inferiority trial involving 266 subjects treating severe nodular acne with either doxycycline plus adapalene/benzoyl peroxide or isotretinoin. Combination treatment showed a favorable composite efficacy and safety profile compared with isotretinoin and is an alternative to isotretinoin patients intolerant to or unable or unwilling to take isotretinoin.

Effective and safe combination therapy for severe acne vulgaris: a randomized, vehicle-controlled, double-blind study of adapalene 0.1%-benzoyl peroxide 2.5% fixed-dose combination gel with doxycycline hyclate 100 mg. Gold LS, Cruz A, Eichenfield L, et al. *Cutis* 2010; 85(2): 94–104.

This randomized, double-blind study compared the combination of adapalene/benzoyl peroxide plus oral doxycycline to oral doxycycline plus vehicle and found superior efficacy for the combination therapy in severe acne vulgaris.

Isotretinoin for acne vulgaris—10 years later: a safe and successful treatment. Layton AM, Knaggs H, Taylor J, et al. *Br J Dermatol* 1993; 129(3): 292–6.

Ten-year prospective study following patients with severe acne vulgaris treated with oral isotretinoin showing sustained benefit in the majority of patients and favorable safety profile.

Dairy intake and acne vulgaris: a systematic review and meta-analysis of 78,529 children, adolescents, and young adults. Juhl CR, Bergholdt HKM, Miller IM, et al. *Nutrients* 2018; 10(8): 1049.

A meta-analysis of available data on the association between dairy consumption and acne. The authors concluded that any dairy (milk, yogurt, and cheese) was associated with an increased OR for acne. However, they cautioned that heterogeneity and bias across studies prohibit any firm recommendations.

Second-Line Therapies

Mild acne

- Topical dapsone A
- Azelaic acid A

Moderate acne

- Combined oral contraceptive pills (females) A
- Oral spironolactone (females) B
- Oral isotretinoin A

Efficacy and safety of once-daily dapsone gel, 7.5% for treatment of adolescents and adults with acne vulgaris: first of two identically designed, large, multicenter, randomized, vehicle-controlled trials. Stein Gold LF, Jaratt MT, Bucko AD, et al. *J Drugs Dermatol* 2016; 15: 553–61.

A 12-week, randomized, double-blind, vehicle-controlled, multicenter clinical trial of patients ≥12 years with moderate inflammatory acne, where dapsone gel 7.5% applied topically once daily was shown to be an effective, safe, and well-tolerated regimen.

Efficacy and safety of topical azelaic acid (20 percent cream): an overview of results from European clinical trials and experimental reports. Graupe K, Cunliffe WJ, Gollnick HP, et al. *Cutis* 1996; 57(Suppl 1): 20–35.

Review of studies using azelaic acid in the treatment of mild-to-moderate acne vulgaris indicating favorable efficacy and safety profile compared to other standard acne treatments.

Efficacy and safety of 3 mg drospirenone/20 mcg ethinyl-estradiol oral contraceptive administered in 24/4 regimen in the treatment of acne vulgaris: a randomized, double-blind, placebo-controlled trial. Koltun W, Lucky AW, Thiboutot D, et al. *Contraception* 2008; 77: 249–56.

This non-androgenic progestin-containing contraceptive with strong antiandrogenic activity (drospirenone 3 mg) but reduced concentration of ethinyl estradiol (20 µg) has been shown to be effective and may replace the classic cyproterone acetate/ethinyl estradiol and chlormadinone acetate/ethinyl estradiol oral contraceptives due to an improved side-effect profile.

Meta-analysis comparing efficacy of antibiotics versus oral contraceptives in acne vulgaris. Koo EB, Petersen TD, Kimball AB. *J Am Acad Dermatol* 2014; 71(3): 450–9.

Systemic antibiotics had greater efficacy at 3 months; however, improvement in acne was equivalent between COC and antibiotics at 6 months. The authors concluded that COCs could be used first line as an alternative to systemic antibiotics for the long-term treatment of acne in women.

Low-dose adjunctive spironolactone in the treatment of acne in women: a retrospective analysis of 85 consecutively treated patients. Shaw JC. *J Am Acad Dermatol* 2000; 43(3): 498–502.

Retrospective review of 85 cases of women treated for acne vulgaris with 50–100 mg spironolactone daily as monotherapy or as an adjunct with other acne treatments, showing efficacy and safety in the majority of treated women.

Treatment of acne with spironolactone: a retrospective review of 395 adult patients at Mayo Clinic, 2007–2017. Roberts EE, Newshean S, Davis MDP, et al. *J Eur Acad Dermatol Venereol* 2020 Feb 20. [Epub ahead of print].

Retrospective review of adult women treated for acne vulgaris with spironolactone as monotherapy or as adjunctive treatment. Over 90% of patients had improvement in their acne across all acne grades and had a favorable safety profile.

Effectiveness of conventional, low-dose, and intermittent oral isotretinoin in the treatment of acne: a randomized, controlled comparative study. Lee JW, Yoo KH, Park KY, et al. *Br J Dermatol* 2011; 164(6): 1369–75.

Randomized trial comparing three different dosing regimens for isotretinoin to determine safety and efficacy in patients with moderate acne vulgaris. Both conventional (0.5–0.7 mg/kg daily for 24 weeks) and low-dose (0.25–0.4 mg/kg daily for 24 weeks) regimens were effective with durable remissions, with a more favorable side-effect profile for low-dose treatment. One week per month dosing (0.5–0.7 mg/kg daily) was ineffective.

Third-Line Therapies	
Mild acne	
• Spironolactone (females)	B
• Low-dose isotretinoin	B
• Photodynamic therapy (PDT)	B
• Serial chemical peels (glycolic acid, salicylic acid, others)	B
• Tea tree oil	B
• Nicotinamide	B
Moderate acne	
• Azelaic acid	A
• PDT	B

Low-cumulative dose isotretinoin treatment in mild-to-moderate acne: efficacy in achieving stable remission. Borghi A, Mantovani L, Minghetti S, et al. *J Eur Acad Dermatol Venereol* 2011; 25(9): 1094–8.

In this prospective clinical trial, 150 patients with mild-to-moderate acne were treated with isotretinoin until complete recovery plus an additional 1 month, independent of the total cumulative dose reached, followed by 1 year of topical adapalene 0.1% cream as maintenance. They were followed for an additional 1 year without treatment. At the end of the study, only 13 patients (9.25%) relapsed.

Comparison of a salicylic acid cleanser and a benzoyl peroxide wash in the treatment of acne vulgaris. Shalita AR. *Clin Ther* 1989; 11(2): 264–7.

Very short crossover study comparing salicylic acid and benzoyl peroxide wash for use in acne vulgaris. There was reduction in number of comedones when using salicylic acid as compared to benzoyl peroxide.

The efficacy of 5% topical tea tree oil gel in mild to moderate acne vulgaris: a randomized, double-blind placebo-controlled study. Enshaieh S, Jooya A, Hossein Siadat A, et al. *Indian J Dermatol Venereol Leprol* 2007; 73: 22–5.

This is a single-center controlled trial of 5% topical tea tree oil, applied twice daily for 20 minutes and then washed off, in 60 patients (30 treatment, 30 control) with mild-to-moderate acne. After 45 days, the treatment group experienced a 43.6% reduction in total lesion counts (21.16 before treatment to 11.33 after treatment) versus 12.0% in the placebo group (19.53 before treatment to 17.23 after treatment). Ten percent of the treatment group experienced pruritus.

Clinical evaluation of glycolic acid chemical peeling in patients with acne vulgaris: a randomized, double-blind, placebo-controlled, split-face comparative study. Kaminaka C, Uede M, Matsunaka H, et al. *Dermatol Surg* 2014; 40: 314–22.

A prospective, randomized, double-blind, placebo-controlled, split-face clinical trial of 26 patients with moderate acne who were treated with 40% glycolic acid (pH 2.0) on half the face and placebo on the other half five times at 2-week intervals showed significant improvement of moderate acne in Asians.

Randomized trial comparing a chemical peel containing a lipophilic hydroxy acid derivative of salicylic acid with a salicylic acid peel in subjects with comedonal acne. Levesque A, Hamzavi I, Seite S, et al. *J Cosmet Dermatol* 2011; 10: 174–82.

A split-face study. Twenty subjects received a total of six peels at 2-week intervals. There was no significant difference in response. Lipohydroxy acid is a lipophilic derivative of salicylic acid with comedolytic properties.

A comparative split-face study using different mild purpuric and subpurpuric fluence level of 595-nm pulsed-dye laser for treatment of moderate to severe acne vulgaris. Voravutinnon N, Rojanamatin J, Sadhwani D, et al. *Dermatol Surg* 2016; 42(3): 403–9.

In a split-face study of 62 patients with moderate-to-severe acne, each side of the face was treated with a 595-nm pulsed-dye laser with a 10 mm spot size at either purpuric (pulse duration of 6 milliseconds, fluence from 6 to 7.5 J/cm²) or subpurpuric (pulse duration of 6 milliseconds, fluence of 4 J/cm²). Both treatment protocols resulted in moderate, statistically significant decreases in acne (about 40% reduction in total lesion counts).

Photodynamic therapy for the treatment of different severity of acne: a systematic review. Keyal U, Bhatta AK, Wang XL. *Photodiagnosis Photodyn Ther* 2016; 14: 191–9.

PDT can control inflammatory and non-inflammatory acne lesions and can improve all acne lesions, ranging from mild to severe. More trials are needed to establish standard guidelines regarding concentrations and the incubation period of photosensitizers and optimal parameters of light sources.

Daylight photodynamic therapy with 1.5% 3-butenyl 5-aminolevulinic acid gel as a convenient, effective and safe therapy in acne treatment: a double-blind randomized controlled

trial. Kwon HH, Moon KR, Park SY, et al. *J Dermatol* 2016; 43: 515–21.

A study on the efficacy and safety of daylight PDT in acne treatment. The novel variant of 5-aminolevulinate (ALA)-ester, 1.5% 3-butenyl ALA-bu gel, was applied using daylight only as the potential visible light source. Forty-six acne patients were randomly assigned to either ALA-bu or vehicle application group in a double-blind fashion. Both groups applied the allocated gel to facial acne lesions every other day for 12 weeks. Daylight PDT was effective, very well tolerated, and convenient for treating inflammatory acne lesions.

Topical nicotinamide compared with clindamycin gel in the treatment of inflammatory acne vulgaris. Shalita AR, Smith JG, Parish LC, Sofman MS, Chalker DK. *Int J Dermatol*. 1995; 34(6): 434-7.

A double-blind, comparative trial of nicotinamide 4% gel and clindamycin 1% gel over 8 weeks. Both treatments had comparable efficacy.

Acrodermatitis enteropathica

Joanna E. Gach



Acrodermatitis enteropathica (AE) OMIM 201100 is a rare, autosomal-recessive, inherited disorder of zinc deficiency. It is caused by mutations in the *SLC39A4* gene located on 8q24.3, which encodes for *ZIP4* intestinal zinc transporter expressed in enterocytes that absorb dietary zinc from the small intestine. The estimated prevalence is 1 in 500,000 children worldwide, without apparent predilection for race or gender. AE manifests itself shortly after birth in a bottle-fed infant and sometime soon after weaning in a breast-fed infant. Zinc within breast milk is more bioavailable to infants than within bovine milk due to binding to a low-molecular-weight ligand secreted by the pancreas. Characteristic clinical signs are lesions in acral and periorificial sites; the first signs are eczematous, pink, scaly plaques that can become vesicular, bullous, pustular, or desquamative. They can resemble the severe diaper dermatitis of infancy or biotin deficiency. Angular cheilitis and paronychia can also be seen early. If left untreated, AE usually causes diarrhea, irritability, and alopecia, and skin lesions become secondarily infected with bacteria and *Candida albicans*. Impaired physical and mental development is seen in advanced disease. Appropriate supplementation of zinc in the infant's diet results in a rapid improvement.

The diagnosis of AE is applied only to *inherited* zinc deficiency; non-inherited zinc deficiency is called *acquired zinc deficiency*. Transient neonatal zinc deficiency OMIM 608118, caused by mutations of the *ZnT2/SLC30A2* in mothers, occurs in breast-fed, full-term infants due to low zinc concentrations in the mother's breast milk. Clinical symptoms identical to AE are alleviated with zinc supplementation to the infant, but not to the mother. Long-term therapy and management of zinc deficiency vary depending on the severity of the disorder.

MANAGEMENT STRATEGY

Chronic dermatitis in periorificial and acral areas should suggest the possibility of zinc deficiency but establishing the diagnosis of AE may be difficult. The first step is laboratory determination of blood plasma or serum zinc levels. A blood sample needs to be drawn into a trace element-free bottle with a stainless steel needle. Avoid contact with rubber stoppers as they contain zinc, avoid hemolysis, use zinc-free anticoagulants, and separate plasma or serum from cells within 45 minutes. Zinc levels will decrease in states of hypoalbuminemia because zinc binds albumin in the circulation. If the diagnosis of zinc deficiency has been confirmed, management becomes relatively simple: *oral zinc supplementation* produces dramatic resolution of the problem. High-dose supplementation will allow for increased paracellular zinc absorption despite the absence of a functional *ZIP4* zinc transporter.

The patient or his or her family must understand the need for lifelong management of the disorder in terms of zinc supplementation and medical supervision. Discuss *foods rich in zinc, such as shellfish, nuts, and green leafy vegetables*. Bioavailability of zinc can be reduced by phytates, which naturally occur in plant fibers, and with regular iron supplementation. With age and a more varied diet, the dose of daily zinc supplementation may be reduced. Zinc therapy should be monitored periodically with a morning fasting specimen, full blood count, serum copper level, and stool examination for occult blood. Zinc supplementation has a theoretical risk of reducing copper absorption, leading to refractory microcytic anemia that will not respond to iron therapy until the serum copper level is normalized.

Specific Investigations

- Morning fasting blood plasma or serum zinc levels
- Urine zinc excretion
- Serum albumin and alkaline phosphatase
- Serum copper levels
- Genetic studies

The normal plasma zinc level is 70–110 mcg/dL and in serum 80–120 mcg/dL. Urinary zinc can be measured but is not definitive for diagnosis.

Homozygosity mapping places the acrodermatitis enteropathica gene on chromosomal regions 8q24.3. Wang K, Pugh EW, Griffen S, et al. *Am J Hum Genet* 2001; 68: 1055–70.

Identification of *SLC39A4*, a gene involved in acrodermatitis enteropathica. Küry S, Dréno B, Bézieau S, et al. *Nature Genet* 2002; 31: 239–40.

Overview of inherited zinc deficiency in infants and children. Kambe T, Fukue K, Ishida R, et al. *J Nutr Sci Vitaminol* 2015; 61 Suppl: S44–6.

Genetic causes and gene-nutrient interactions in mammalian zinc deficiencies: acrodermatitis enteropathica and transient neonatal zinc deficiency as examples. Kasana S, Din J, Maret W. *J Trace Elem Med Biol* 2015; 29: 47–62.

First-Line Therapy

- Oral zinc supplementation

A

In most cases, oral supplementation with two to three times the recommended daily allowance of zinc salts in doses of 30–55 mg of elemental Zn^{2+} will be sufficient to restore normal zinc status within days to a few weeks, depending on the degree of depletion. The dose of elemental zinc must be determined by the patient's blood or plasma zinc levels and by body weight. In AE, zinc replacement should begin at 2–3 mg/kg/day of elemental zinc. Serum or plasma zinc should be checked every 3–6 months, adjusting the zinc dosage accordingly. In patients with acquired or dietary zinc deficiency, treatment should begin at 0.5–1 mg/kg/day. Available forms of zinc supplementation include zinc sulfate, zinc acetate, zinc gluconate, and zinc propionate. *Dosage must be based on the amount of elemental zinc present in the preparation, which varies between compounds. For example, a standard 125-mg effervescent tablet of a commercial zinc preparation contains approximately 45 mg Zn^{2+} , which is an adequate daily dose for deficient individuals. A commonly used preparation is Solvazinc, which is zinc sulfate monohydrate.*

A significant side effect of zinc supplementation is gastric irritation with nausea, vomiting, and gastric hemorrhage. Large accidental overdoses of zinc may cause fatal multisystem organ failure.

Zinc deficiency in acrodermatitis enteropathica: multiple dietary intolerance treated with synthetic diet. Barnes PM, Moynahan EJ. Proc Roy Soc Med 1973; 66: 327–9.

In 1973, Barnes and Moynahan were treating children with chronic, unresponsive AE-type acral dermatoses and having poor results. They then tried different medications, one of which was oral zinc. To their surprise, the patients receiving the zinc supplements cleared rapidly and completely.

The role of the Slc39a family of zinc transporters in zinc homeostasis in skin. Bin BH, Hojyo S, Seo J, et al. Nutrients 2018; 10(2): 219. doi: 10.3390/nu10020219.

An excellent review of AE and other zinc deficiency disorders.

Zinc therapy in dermatology: a review. Gupta M, Mahajan VK, Mehta KS, et al. Dermatol Res Pract 2014; 2014: 709152.

A detailed review of the use of zinc in over 20 dermatologic conditions.

Actinic keratosis

Sherrif F. Ibrahim, Marc D. Brown



Actinic keratoses (AKs) are ill-defined, pink to skin-colored, scaly lesions found on chronically sun-exposed areas in light-skinned individuals. They most frequently appear on the face, ears, balding scalp, extensor forearms, and dorsal hands. AKs are a strong predictor for the development of squamous cell carcinoma (SCC) and, to a lesser extent, basal cell carcinoma. Australians have the highest reported prevalence, which approaches 60%, and in the US, AKs are the second most common reason for visits to the dermatologist.

MANAGEMENT STRATEGY

AKs are common dysplastic intraepidermal lesions that are considered to be precursors to SCC. Reports have varied as to the rates of progression to invasive SCC, from 0.025% to over 25% per year, and AKs are commonly located adjacent to SCC histologically. For these reasons, most practitioners advocate the treatment of AKs, as considerable morbidity and potential mortality can be associated with invasive disease. In 2018, Weinstock and colleagues were the first to perform a randomized trial showing that topical treatment for AKs led to a significantly reduced need for surgery for SCC.

The diagnosis of AK is primarily clinical, and because of their superficial nature, a variety of effective management approaches exist. Biopsy of suspected AKs is typically not warranted; however, in patients with a history of multiple skin cancers, immunosuppressed patients, and lesions in high-risk areas such as the lip or ear, clinicians should have a low threshold for biopsy to rule out invasive SCC. Indications for biopsy include tenderness, rapid growth or thickening of lesions, bleeding, hyperkeratosis, and failure to respond to treatment.

Prevention of AKs through sun avoidance and diligent use of broad-spectrum sunscreens and blocking agents is an important aspect of management. This has been shown to prevent the development of new AKs and reduce the incidence of non-melanoma skin cancers.

With cumulative sun exposure and advancing age, rates of AK development increase, necessitating either *ablative* or field treatment. *Cryotherapy* with liquid nitrogen is by far the most commonly employed therapeutic modality for discrete lesions because it can be performed quickly and effectively in the office setting. However, given the common appearance of AKs on a background of diffuse actinic damage, individual lesions may be poorly defined and involve large, contiguous areas requiring field treatment with topical agents such as 5-fluorouracil (5-FU) or *imiquimod*, or with photodynamic therapy. The advantages of field approaches are that they are non-invasive, carry little risk, and can be used for anatomically difficult or cosmetically sensitive areas. Furthermore, they address both clinically apparent as well as subclinical areas of skin in contiguous fashion. Most of these agents must be used for weeks to months, result in some degree of erythema, inflammation, and discomfort, and require adequate patient compliance.

Photodynamic therapy (PDT) with aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) has continued to become more widespread, given its proven therapeutic results and excellent cosmetic outcome. PDT offers a physician-administered approach to field treatment with shorter periods of inflammation and erythema than several topical agents and, thus, higher patient satisfaction. Variations in the light dose, light source, sensitizing agent and its application time, and frequency of treatments may improve efficacy. Most recently, PDT using natural daylight to excite the chemical sensitizer has gained popularity.

Head-to-head trials of different treatment approaches are difficult to perform, as variations in treatment protocols make direct comparisons challenging. Several well-designed trials have suggested topical 5-fluorouracil as the most effective stand-alone topical agent to treat AKs. Recently, there has been a growing trend towards *combination therapy*, such as topical agents either before or after cryotherapy, or sequential use of multiple field modalities with differing mechanisms of action. Other approaches such as *laser resurfacing*, *chemical peels*, and *dermabrasion* may be considered in certain situations when lesions have failed the above treatments, or if severe photodamage is present. Finally, for recalcitrant or hyperkeratotic lesions, *curettage* or *excision* may be appropriate.

Specific Investigation

- Biopsy

Actinic keratoses and the incidence of occult squamous cell carcinoma: a clinical-histopathologic correlation. Ehrig T, Cockerell C, Piacquadio D, et al. *Dermatol Surg* 2006; 32: 1261–5.

Two hundred and seventy-one clinically diagnosed AKs were biopsied. Clinical diagnosis agreed with histology 91% of the time, with about 1 in 25 lesions revealing invasive SCC.

Clinical recognition of actinic keratoses in a high-risk population: how good are we? Venna SS, Lee D, Stadecker MJ, et al. *Arch Dermatol* 2005; 141: 507–9.

Seventeen of 23 lesions (74%) with classic features of AK in patients with a history of previous skin cancer were confirmed histologically. Five lesions (22%) were shown to be SCC.

Actinic keratoses are typically diagnosed clinically. However, there should be a low threshold to biopsy tender, hyperkeratotic, large, or recalcitrant lesions to exclude malignancy.

First-Line Therapies

• Sunscreens	A
• Cryosurgery	B
• Topical 5-FU	A
• Imiquimod	A
• Photodynamic therapy	A

A randomized controlled trial to assess sunscreen application and beta carotene supplementation in the prevention of solar keratoses. Darlington S, Williams G, Neale R, et al. Arch Dermatol 2003; 139: 451–5.

In this Australian study, 1621 adults were randomized to either daily use of sunscreen or application at their usual discretionary rate. There was a 24% reduction in AKs in the daily use group.

Reduction of solar keratoses by regular sunscreen use. Thompson SC, Jolley D, Marks R. N Engl J Med 1993; 14: 1147–51.

In a 6-month randomized, placebo-controlled trial of 588 patients in Australia, SPF 17 sunscreen applied daily was found to both reduce the development of new AKs and increase the remission of existing AKs in comparison to a vehicle cream.

A prospective study of the use of cryosurgery for the treatment of actinic keratoses. Thai K, Fergin P, Freeman M, et al. Int J Dermatol 2004; 43: 687–92.

In this prospective multicenter study, 90 patients with 421 AKs on the face and scalp were treated with cryotherapy with a single freeze–thaw cycle using different freeze times. The patients were reviewed 3 months later. Overall, the complete response (CR) rate was 67.2%, varying from 39% for freeze times less than 5 s to 83% for times longer than 20 s. The authors also found that hypopigmentation was present in 29% of CR lesions. Patients rated cosmetic outcomes as good to excellent for 94% of CR lesions.

Chemoprevention of basal and squamous cell carcinoma with a single course of fluorouracil, 5%, cream: a randomized clinical trial. Weinstock MA, Thwin SS, Siegel JA, et al. JAMA Dermatol 2018 1; 154: 167–74.

In this randomized trial, 932 patients with a prior history of non-melanoma skin cancer received either 5-FU cream or vehicle twice daily for 2–4 weeks. There was a significantly reduced need for surgery to address SCC in the treatment arm.

Effective treatment of actinic keratosis with 0.5% fluorouracil cream for 1, 2 or 4 weeks. Weiss J, Menter A, Hevia O, et al. Cutis 2002; 70: 22–9.

In this randomized, double-blind, parallel-group vehicle-controlled study, 177 patients with at least five AKs were treated with topical 0.5% 5-FU cream daily for 1, 2, or 4 weeks. In patients who were treated for 4 weeks, complete clearance of lesions was observed in 47.5%, compared with 26% who were treated for 1 week ($p < 0.001$ vs vehicle). Moderate-to-severe irritation of the skin was noted in 90% of these patients.

Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind,

parallel group, vehicle-controlled trials. Lebwohl M, Dinehart S, Whiting D, et al. J Am Acad Dermatol 2004; 50: 714–21.

In this report of two phase III double-blind, vehicle-controlled studies, 436 subjects at 24 centers in the US were randomized to either 5% imiquimod or vehicle applied once daily, two days per week, for 16 weeks. The complete clearance rate for the treated arm was 45%, as opposed to 3.2% for the vehicle group. The median percent reduction in AK lesions was 83% for the treated group and 0% for the vehicle group, indicating that a reduced frequency of imiquimod application is quite effective.

Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: results of two placebo-controlled studies of daily application to the face and balding scalp for two 3-week cycles. Hanke CW, Beer KR, Stockfleth E, et al. J Am Acad Dermatol 2010; 62: 573–81.

Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles. Swanson N, Abramovits A, Berman B, et al. J Am Acad Dermatol 2010; 62: 582–90.

These two back-to-back reports demonstrate the efficacy and tolerability of lower concentration formulations of imiquimod as well as alternate dosing schedules. Interestingly, the results were essentially identical for two 3-week cycles as they were for two 2-week cycles, with the 3.75% strength imiquimod proving superior to the 2.5% in both studies and slightly less efficacious than previous studies that have investigated 5% imiquimod used twice weekly for 16 weeks.

A randomised study of topical 5% imiquimod vs. topical 5-fluorouracil vs. cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up. Krawtchenko N, Roewert-Huber J, Ulrich M, et al. Br J Dermatol 2007; 157 Suppl 2: 34–40.

This study compared the baseline and 1-year follow-up rates of clinical clearance, histological clearance, and cosmetic outcomes of imiquimod, 5-FU, and cryosurgery for the treatment of AKs. Patients were randomized to one of the three treatment groups. Clinical clearance was achieved in 68% of those treated with cryosurgery, 96% with 5-FU, and 85% with imiquimod. Histological clearance rate was 32% for cryosurgery, 67% for 5-FU, and 73% for imiquimod. The 1-year sustained clearance rate was 28% for cryosurgery, 54% for 5-FU, and 73% for imiquimod. The patients treated with imiquimod were also judged to have superior cosmetic outcomes.

Randomized trial of four treatment approaches for actinic keratosis. Jansen MHE, Kessels JPHM, Nelemans PJ, et al. N Engl J Med 2019; 380: 935–46.

This study included 624 patients with AKs over a 3-year span and randomized them to receive treatment with 5-FU, 5% imiquimod, MAL-PDT, or 0.015% ingenol mebutate. At 12 months after the end of treatment, 5-FU was the most effective monotherapy.

A real world, community-based cohort study comparing the effectiveness of topical fluorouracil versus topical imiquimod for the treatment of actinic keratosis. Neugebauer R, Levandoski KA, Zhu Z, et al. J Am Acad Dermatol. 2018; 78: 710–6.

The authors studied 5700 patients with a diagnosis of AK treated with either 5-FU or imiquimod in 2007 and followed

them for short-term (2-year) and long-term (5-year) incidence of subsequent AK. They concluded that 5-FU was superior to imiquimod in the short term, with no difference in the long-term prevention of future AKs.

Intraindividual, right-left comparison of topical methyl aminolaevulinate-photodynamic therapy and cryotherapy in subjects with actinic keratoses: a multicentre, randomized controlled study. Morton C, Campbell S, Gupta G, et al. *Br J Dermatol* 2006; 155: 1029–36.

In this 24-week study, subjects received one treatment session of PDT to one side of their face and two cycles of freeze-thaw cryosurgery to the other. Of the 1501 lesions treated, PDT resulted in a higher rate of cure (87% vs 76% reduction from baseline). Both subjects and investigators preferred PDT and also felt it had a better cosmetic outcome. Both treatment regimens were deemed safe and well tolerated.

Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigator-blinded, phase 3, multicenter trials. Piacquadio DJ, Chen DM, Farber HF, et al. *Arch Dermatol* 2004; 140: 41–6.

In this randomized, placebo-controlled study, 243 patients were randomized to receive vehicle or aminolevulinic acid (ALA) followed by PDT within 14–18 hours. Clinical response rate was based on complete clearing of 75% of lesions measured at weeks 8 and 12. Of the PDT-treated group, 77% had a complete response by week 8 and 89% by week 12. This compared to 18% and 13% for the placebo group. Most patients experienced erythema and edema at the treated sites, which improved within 4 weeks of therapy. Stinging, burning, or pain occurred during the treatments, but resolved within 24 hours.

A randomized pilot comparative study of topical methyl aminolevulinate photodynamic therapy versus imiquimod 5% versus sequential application of both therapies in immunocompetent patients with actinic keratosis: clinical and histologic outcomes. Serra-Guillen C, Nagore E, Hueso L, et al. *J Am Acad Dermatol* 2012; 66: e131–7.

In this study, 105 patients with actinic keratoses were randomized to receive MAL-PDT, 5% imiquimod 3 times/week for 4 weeks, or MAL-PDT followed by imiquimod 1 month later. The clinical and histologic response was high for all three groups with imiquimod providing higher response rates than PDT, but sequential treatment performing better than either monotherapy alone. PDT alone was rated the most satisfactory treatment of the three approaches.

Results of an investigator-initiated single-blind split-face comparison of photodynamic therapy and 5% imiquimod cream for the treatment of actinic keratoses. Hadley J, Tristani-Firouzi P, Hull C, et al. *Dermatol Surg* 2012; 38: 722–7.

In this split-faced trial, 61 patients received 5% imiquimod twice weekly to half the face and two sessions of ALA-PDT to the other side of the face. No significant difference was noted with respect to partial or total clearance rate; however, ALA-PDT was superior when mean lesion reduction rate was evaluated.

Treatment of actinic keratosis: a randomized split-site approach comparison of sequential 5-fluorouracil and 5-aminolevulinic acid photodynamic therapy to 5-aminolevulinic acid photodynamic monotherapy. Pei S, Kaminska ECN, Tsoukas MM. *Dermatol Surg* 2017; 43: 1170–5.

These patients received sequential 5-FU and PDT on one side of the face vs PDT alone on the other. The sequentially treated side had a highly significantly improved result in AK clearance at both 6- and 12-months post treatment.

Second-Line Therapies

• Topical adapalene	A
• Topical diclofenac	A
• Topical ingenol mebutate	A

Assessment of adapalene gel for the treatment of actinic keratoses and lentigenes: a randomized trial. Kang S, Goldfarb MT, Weiss JS, et al. *J Am Acad Dermatol* 2003; 49: 83–90.

In this prospective randomized, vehicle-controlled study, 90 patients received either 0.1% adapalene gel, 0.3% adapalene gel, or vehicle gel, initially daily for 4 weeks, then twice daily for up to 9 months. Overall, 62% ($p < 0.01$) of those who received 0.1% adapalene gel and 66% ($p < 0.01$) of those who received 0.3% adapalene gel showed at least a moderate improvement of their AKs, compared with 34% of patients receiving a vehicle cream. Adapalene gel recipients reported a higher level of mild erythema, peeling, and dryness in comparison to control groups.

Three percent diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses: a meta-analysis of the recent studies. Pirard D, Vereecken P, Mélot C, et al. *Arch Dermatol Res* 2005; 297: 185–9.

This meta-analysis pooled 364 patients from three studies that compared diclofenac to hyaluronan vehicle gel. Overall, patients treated with diclofenac had a significantly higher rate of complete clearance of lesions. They concluded that complete response rates were 39% with a mean treatment duration of 75 ± 21 days. Mild-to-moderate skin irritation was the major side effect of the treatment group.

Diclofenac sodium 3% gel in the treatment of actinic keratoses postcryosurgery. Berlin JM, Rigel DS. *J Drugs Dermatol* 2008; 7: 669–73.

This prospective, double-arm, multicenter, open-label, phase 4 study aimed to determine the efficacy of sequential therapy of AKs with cryosurgery followed by diclofenac for 90 days. Forty-six percent of subjects who underwent combination treatment achieved 100% lesion clearance, compared to 21% in the cryosurgery-alone arm. This is a good example of newly emerging strategies involving combinations of established treatment modalities.

Phase IV open-label assessment of the treatment of actinic keratosis with 3.0% diclofenac sodium topical gel (Solaraze). Nelson C, Rigel D, Smith S, et al. *J Drugs Dermatol* 2004; 3: 401–7.

This study evaluated the treatment and efficacy of diclofenac applied twice daily for 90 days with a 30-day follow-up. Of the 67 patients who completed the study, 78% had $\geq 75\%$ clearance of AKs, which improved to 85% by the 30-day follow-up. Dry skin and rash at the application site were the most common side effects of treatment.

Diclofenac sodium 3% gel for the management of actinic keratosis: 10+ years of cumulative evidence of efficacy and safety. Martin GM, Stockfleth E. *J Drugs Dermatol* 2012; 11: 600–8.

This comprehensive review draws from 17 publications beyond the initial phase 3 clinical trials that led to the approval of diclofenac sodium for the treatment of AKs. It discusses the data regarding treatment efficacy, tolerability, and performance in comparison to other topical field agents, as well as its use in combination treatment strategies.

Long-term clinical outcomes of imiquimod 5% cream vs. diclofenac 3% gel for actinic keratosis on the face or scalp: a pooled analysis of two randomized control trials. Gollnick H, Dirschka T, Ostendorf R, et al. *J Eur Acad Dermatol Venereol* 2020; 34: 82–9.

In this paper, 479 patients with 5–10 AKs treated with either imiquimod or diclofenac were followed for 3 years after treatment. The imiquimod group had lower high grade AKs, invasive SCCs, and recurrence of AKs.

Ingenol mebutate gel for actinic keratosis. Lebwohl M, Swanson N, Anderson LL, et al. *N Engl J Med* 2012; 366: 1010–9.

This multicenter, randomized, double-blind report investigated the use of 0.015% ingenol mebutate used once daily for 3 consecutive days for AKs on the face and scalp, as well as 0.05% IM used once daily for 2 consecutive days for AKs on the trunk and extremities. All analyses were conducted at day 57. The rate of complete clearance was 42% for the face/scalp group and 34% for the trunk/extremities group. Local skin reactions peaked between days 3–8 and were mild to moderate in nature. Hypertrophic or hyperkeratotic lesions were excluded from the study.

Randomized, double-blind, double-dummy, vehicle-controlled study of ingenol mebutate gel 0.025% and 0.05% for actinic keratosis. Anderson L, Schmieder GJ, Werschler WP, et al. *J Am Acad Dermatol* 2009; 60: 934–43.

Two hundred and twenty-two patients from 22 US centers with non-facial AKs were randomized to receive vehicle for 3 days, 0.025% ingenol mebutate (IM) gel for 3 days, vehicle for 1 day followed by 0.05% IM gel for 2 days, or 0.05% IM gel for 3 days. Partial clearance rate (>75% reduction in baseline AKs) as well as complete clearance rate was statistically significantly higher in all three treatment groups over baseline and these results were dose dependent. Partial and complete clearance rates were 28%/20% for the 0.025% × 3 days group, 34%/24% for the 0.05% × 2 days group, and 43%/31% for the 0.05% × 3 days cohort. The most common local skin responses seen in all groups included erythema, scaling, crusting, swelling, erosion/ulceration, vesiculation, and pigmentary changes, and were largely resolved by day 15. Patient satisfaction was high.

Efficacy and safety of ingenol mebutate gel in field treatment of actinic keratosis on full face, balding scalp, or approximately 250 cm² on the chest: a phase 3 randomized controlled trial. Hanke CW, Albrecht L, Skov T, et al. *J Am Acad Dermatol* 2020; 82: 642–50.

For this trial, patients with 5–20 AKs received 3 days of IM treatment vs vehicle. There were higher rates of complete clearance, 75% clearance, and sustained clearance in the treatment arm vs vehicle alone.

Third-Line Therapies

• Curettage	E
• Excision	E
• Ablative lasers	B
• Chemical peels	D
• Dermabrasion	D

Guidelines for the management of actinic keratoses. de Berker D, McGregor JM, et al. *Br J Dermatol* 2007; 156: 222–30.

Recalcitrant treatment-resistant AKs may be treated with curettage or surgical excision. Both techniques enable tissue to be obtained for the purposes of histological analysis. Curettage can be used alone or in conjunction with electrosurgery, cryotherapy, or chemical applications. Surgical excision is particularly useful in lesions suspected of being SCC because this technique enables the clinician to treat the lesion and establish the diagnosis.

Widespread, extensive AKs may benefit from field treatments of a physically destructive nature. These include ablative laser resurfacing, dermabrasion, and chemical peels.

Full face laser resurfacing: therapy and prophylaxis for actinic keratoses and non-melanoma skin cancer. Iyer S, Friedli A, Bowes L, et al. *Lasers Surg Med* 2004; 34: 114–9.

In this retrospective study of 24 patients with over 30 AKs on the face treated with full-face UltraPulse CO₂ laser or erbium Er:YAG laser resurfacing, the authors found that 21 patients remained lesion free for at least 1 year.

Recurrence rates and long-term follow-up after laser resurfacing as a treatment for widespread actinic keratoses on the face and scalp. Ostertag JU, Quaedvlieg PJ, Neumann MH, et al. *Dermatol Surg* 2006; 32: 261–7.

A retrospective case-control study of 25 patients who underwent laser resurfacing for widespread AKs on the scalp and/or face. Forty-four percent had no recurrences in an average follow-up period of 39 months (range 7–70 months).

Laser-assisted photodynamic therapy for actinic keratosis: a systematic review and meta-analysis. Steeb T, Schlager JG, Kohl C, et al. *J Am Acad Dermatol*. 2019; 80: 947–56.

For this analysis, seven randomized controlled trials were reviewed to conclude that laser-assisted PDT showed significantly higher clearance rates than PDT monotherapy.

Single ablative fractional resurfacing laser treatment for forearm actinic keratosis: 6-month follow-up data from an inpatient comparison between treated and untreated sites. Chen R, Wargo JJ, Williams A, et al. *Lasers Surg Med* 2020; 52: 84–7.

In this study, 30 subjects with AKs on both arms underwent a single fractionally ablative laser treatment to one forearm and AKs were recorded at several time points. There was a 62% reduction in AKs in the treated arm at 6 months after treatment.

This result makes us question results as seen in the prior study listed – does ablative laser treatment make PDT more efficient, or is it acting to directly reduce the number of AKs?

Randomized controlled trial comparing 35% trichloroacetic acid peel and 5-aminolaevulinic acid photodynamic therapy for treating multiple actinic keratosis. Holzer G, Pinkowicz A, Radakovic S, et al. *Br J Dermatol* 2017; 176: 1155–61.

In this study, 28 patients were treated with trichloroacetic acid (TCA) in one area and photodynamic therapy (PDT) on another and assessed by a blinded investigator at several time points after treatment. ALA-PDT provided significantly better clinical results than TCA.

Nonablative fractional photothermolysis for facial actinic keratoses: 6-month follow-up with histologic evaluation. Katz TM, Goldberg LH, Marquez D, et al. *J Am Acad Dermatol* 2011; 65: 349–56.

In this study, 14 patients underwent five treatments of non-ablative fractional resurfacing with 32–40% surface area coverage at 2–4-week intervals. Clinical images and biopsies were evaluated. Although clinical images had a reduced number of AKs, virtually all histologic specimens were positive for features of AK and/or SCC. It was concluded that fractional non-ablative resurfacing was not adequate therapy for AKs.

A clinical comparison and long-term follow-up of topical 5-fluorouracil versus laser resurfacing in the treatment of widespread actinic keratoses. Ostertag JU, Quaedvlieg PJ, van der Geer S, et al. *Lasers Surg Med* 2006; 38: 731–9.

A prospective randomized trial of 55 patients comparing 5-FU with Er:YAG laser resurfacing. At 3, 6, and 12 months there were significantly fewer recurrences in the laser group than in the 5-FU group. Side effects were more common in the group treated with laser resurfacing. Side effects included erythema and hypopigmentation.

Long-term efficacy and safety of Jessner's solution and 35% trichloroacetic acid vs 5% fluorouracil in the treatment of

widespread facial actinic keratoses. Witheiler DD, Lawrence N, Cox SE, et al. *Dermatol Surg* 1997; 23: 191–6.

In this prospective study, 15 patients with severe facial AKs were treated on one side of the face with a single application of Jessner's solution – a medium-depth chemical peel – and the other side with twice-daily applications of topical 5-FU 5% for 3 weeks. The authors found that both treatments resulted in a similar reduction of AKs at 12 months, with an increase in the number of AKs in both groups from 12 to 32 months. The authors concluded that both treatments were similarly efficacious in the treatment of AK, and that retreatment for recurrences might be necessary after 12 months.

Dermabrasion for prophylaxis and treatment of actinic keratoses. Coleman WP 3rd, Yarborough JM, Mandy SH. *Dermatol Surg* 1996; 22: 17–21.

In this retrospective study, 23 patients who had undergone dermabrasion for facial AKs were followed for 2–5 years. The authors found that the benefits of dermabrasion diminished with time: 1-year postdermabrasion, 22 patients remained clear of AKs. Of 13 patients who were followed up for 5 years, seven remained clear. The authors concluded that dermabrasion provided long-term clearance of AKs in some patients.

6

Actinic prurigo

Marianne de Brito, Ian H. Coulson, Tsui Chin Ling

(Synonyms: hereditary polymorphic light eruption of American Indians, Hutchinson summer prurigo, photodermatitis in North American Indians)



Actinic prurigo (AP) is a distinct photodermatosis, diagnosed on the basis of characteristic clinical features and supported by phototest results and human leukocyte antigen (HLA) typing. It has a perennial nature, although it tends to be worse in the sunnier months in countries with seasonal variation in sunlight exposure. Morphologically, it presents as a papular or mixed papulovesicular eruption during acute flares, persistent eczematized nodules, and/or dermatitic patches, scarring, dorsal nose involvement, cheilitis, and conjunctivitis. Exposed skin tends to be more severely affected than unexposed skin, but it is not unusual for covered areas, such as the buttocks, to be involved. Abnormal photosensitivity (to ultraviolet A [UVA], ultraviolet B [UVB]) is frequently severe, but when onset has been in childhood, the condition generally gradually improves, probably largely by patients learning to adapt to their photosensitivity.

MANAGEMENT STRATEGY

Diagnosing AP requires a high index of suspicion for the general dermatologist. Differential diagnoses include severe polymorphic light eruption and photoaggravated atopic dermatitis. Although differences between European and Amerindian forms of AP have been described, these are either closely related conditions or the same disease with some differences affected by population and environment. Full phototesting and HLA typing is needed to confirm the diagnosis and establish the severity of the photosensitivity. Photopatch testing may reveal coexisting sunscreen allergies and help guide the choice of suitable sunscreens.

Once the diagnosis is established, initial management consists of advice on *photoprotective* measures (behavioral, clothing, and sunscreen use) and the use of potent or very potent *topical*

corticosteroids for acute flares. *Topical tacrolimus* can also be considered, especially if prolonged treatment to the face is required. This approach alone is often insufficient. Some patients may benefit from the addition of a springtime course of narrowband (TL-01) UVB or psoralen-ultraviolet A (PUVA) phototherapy to enable skin hardening. When *phototherapy* is administered for this indication, only normally photoexposed sites need be treated. It is helpful to apply a potent topical steroid to the treated areas immediately after each exposure to reduce the risk of AP flares.

In the UK, systemic treatment is sometimes required. *Thalidomide* is usually effective, but its value is restricted by teratogenicity and the risk of irreversible peripheral neuropathy; *antimalarials* and *β -carotene* are of doubtful value. *Pentoxifylline* has anti-tumor necrosis factor (TNF)- α effects and, although listed as a third-line therapy here, may sometimes be worth considering before thalidomide because of its more attractive safety profile. Elevated serum immunoglobulin E (IgE) levels have been associated with moderate-to-severe clinical AP, suggesting involvement of the Th2-mediated inflammatory pathway. This was successfully targeted by dupilumab in a case report of a pediatric patient and raises the possibility of treatment with biologics for refractory cases in the future.

Specific Investigations

- Phototesting
- HLA typing
- IgE levels

Phototesting may reveal reduced erythmal thresholds on monochromator testing. Typical lesions are sometimes provoked with UVA or solar simulator. Up to 60% of white Caucasian AP patients may carry the HLA-DRB1*0407 subtype, but this may be negative in 40% and diagnosis may need to be supported by clinical and other phototest findings.

Actinic prurigo—a specific photodermatosis? Addo HA, Frair-Bell W. *Photodermatology* 1984; 1: 119–28.

This study showed that almost 60% of AP patients have abnormal delayed erythema on monochromator phototesting.

Phototest abnormalities tend to be more severe in AP than in polymorphic light eruption.

Actinic prurigo among the Chimila Indians in Colombia: HLA studies. Bernal JE, Duran de Rueda MM, Ordóñez CP, et al. *J Am Acad Dermatol* 1990; 22: 1049–51.

In this population, the HLA class I antigen Cw4 was more frequent in AP patients than in controls.

HLA-DR4 may determine expression of actinic prurigo in British patients. Menage H du P, Vaughan RW, et al. *J Invest Dermatol* 1996; 106: 362–7.

Actinic prurigo and HLA-DR4. Dawe RS, Collins P, O'Sullivan A, et al. *J Invest Dermatol* 1997; 108: 233–4.

An even stronger association with the HLA class II antigen HLA-DR4 was shown and, more specifically, with HLA-DRB1*0407.

Association of HLA subtype DRB1*0407 in Colombian patients with actinic prurigo. Suárez A, Valbuena MC, Rey M, et al. *Photodermatol Photoimmunol Photomed* 2006; 22: 55–8.

These associations are not a feature of polymorphic light eruption. The absence of HLA-DR4 can help to rule out the diagnosis of AP, whereas the presence of HLA-DRB1*0407 helps to rule in the diagnosis.

Actinic prurigo: clinical features and HLA associations in a Canadian Inuit population. Wiseman MC, Orr PH, MacDonald SM, et al. *J Am Acad Dermatol* 2001; 44: 952–6.

No statistically significant association of AP with HLA-DR4 (frequent in the studied population) or HLA-DRB1*0407 was detected, and another HLA type (DRB1*14) was found more commonly than expected, although it was only present in 19 of 37 AP subjects. The authors acknowledge the possibility that they were studying a different condition from AP in other populations.

Actinic prurigo in Singaporean Chinese: a positive association with HLA-DRB1*03:01. Chen Q, Shen M, Heng YK, et al. *Photochem Photobiol* 2016; 92: 355–9.

In this population the strongest association was with HLA-DRB1*03:01, although it should be noted that although a strong association was compared with controls, only six of these 14 Chinese Singaporean patients diagnosed with AP had this HLA allele.

These findings suggest we should be cautious in attempting to use HLA typing as a diagnostic test, especially in populations in which strong HLA associations have not been confirmed. The diagnosis should still be based on the characteristic constellation of clinical features.

Actinic prurigo of the lower lip – review of the literature and report of five cases. Mounsdon T, Kratochvil F, Auclair P, et al. *Oral Surg Oral Med Oral Pathol* 1988; 65: 327–32.

Follicular cheilitis – a distinctive histopathologic finding in actinic prurigo. Herrera-Geopfert R, Magana M. *Am J Dermatopathol* 1995; 17: 357–61.

Actinic prurigo cheilitis: clinicopathologic analysis and therapeutic results in 116 cases. Vega-Memije ME, Mosqueda-Taylor A, Irigoyen-Camacho ME, et al. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; 94: 83–91.

A ‘follicular cheilitis’ has been reported to be characteristic of AP. Thirty-two of 116 patients attending a dermatology clinic in Mexico City had cheilitis as their sole manifestation of disease.

Lip histopathology may be helpful diagnostically, especially in patients presenting with cheilitis without cutaneous features at presentation. Where other typical features (skin, eyes) are present, it is arguable how much lip histopathology will contribute to diagnosis.

Correlation of serum IgE levels and clinical manifestations in patients with actinic prurigo. Cuevas-Gonzalez JC, Lievanos-Estrada Z, Vega-Memije ME, et al. *An Bras Dermatol* 2016; 91: 1–23.

A case-control study of 21 patients with a clinical and histopathological diagnosis of AP and 21 controls showed elevated levels in 11 of 21 patients (compared with no controls). Those with elevated levels were more likely to have moderate-to-severe clinical lesions.

Raised serum IgE levels may correlate with AP severity, which may be of limited use diagnostically; this raises the possibility of a Th2-inflammatory pathway targeted biologic agents.

Topical photoprotection for hereditary polymorphic light eruption of American Indians. Fusaro RM, Johnson JA. *J Am Acad Dermatol* 1991; 24: 744–6.

The authors of this open study found 18 of 30 patients with hereditary polymorphic light eruption of American Indians (with described features indistinguishable from AP) to show ‘good to excellent results’ with use of a broad-spectrum sunscreen.

Although broad-spectrum sunscreens are useful, advice on other sunlight avoidance measures, including appropriate clothing and behavioral avoidance, is equally important.

Actinic prurigo deterioration due to degradation of Derma-Gard window film. Kerr AC, Ferguson J. *Br J Dermatol* 2007; 157: 619–20.

Window films that reduce the transmission of UV rays can be used as a method of environmental photoprotection. This case report describes an exacerbation of AP explained by increased transmission through such a window film as it aged. Because the technology of such window films has matured, such degradation now might be less likely, but the possibility of it should be considered.

Treatment of actinic prurigo with intermittent short-course topical 0.05% clobetasol 17-propionate: a preliminary report. Lane PR, Moreland AA, Hogan DJ. *Arch Dermatol* 1990; 126: 1211–3.

Seven out of eight patients treated with intermittent 3- to 14-day courses of topical 0.05% clobetasol 17-propionate cream or ointment cleared or markedly improved. All had previously found less potent topical steroids ineffective.

Narrow-band UVB (TL-01) phototherapy: an effective preventative treatment for the photodermatoses. Collins P, Ferguson J. *Br J Dermatol* 1995; 132: 956–63.

Six patients with AP were included in this open study. All reported at least a sixfold increase in tolerable duration of sunlight exposure, which was sustained 4 months after treatment. In one patient whose phototesting (severely abnormal before treatment) was repeated after treatment, the test results normalized.

Actinic prurigo: treatment with tacrolimus. Favorable response in two pediatric patients. Vivoda JL, Mantero N, Jaime LJ, et al. *Rev Arg Derm* 2015; 96: 30–4.

These two girls showed a good response by 10 days of treatment with tacrolimus ointment.

Treatment of actinic prurigo with tacrolimus 0.1%. Gonzalez-Carrascosa Ballesteros M, De la Cueva DP, et al. *Med Cutan Ibero Lat Am* 2006; 34: 233–6.

A 13-year-old boy with only facial involvement with AP was reported to respond rapidly to 0.1% tacrolimus ointment after failure to respond to topical corticosteroids.

Tacrolimus ointment can be helpful in treating facial AP, especially when there are concerns about topical corticosteroid adverse effects.

The quality of life of 790 patients with photodermatoses. Jong CT, Finlay AY, Pearse AD, et al. *Br J Dermatol* 2008; 159: 192–7.

Of the photodermatoses assessed in the British tertiary referral photodermatology centers participating in this study, AP was associated with the greatest health-related quality of life impairment.

First-Line Therapies

• Photoprotective measures – environmental, behavioral, clothing, sunscreen use, window UV films	C
• Potent/very potent topical corticosteroids	C
• Topical tacrolimus	E
• Narrowband (TL-01 lamp) UVB phototherapy	C

Second-Line Therapies

- PUVA photochemotherapy **C**
- Thalidomide **C**

Treatment of actinic prurigo with PUVA: mechanism of action. Farr PM, Diffey BL. *Br J Dermatol* 1989; 120: 411–8.

Five patients were treated in this open study. Clinical improvement was accompanied by an increase of UVA minimal erythral doses to within the normal range on phototesting. Corroboration that PUVA worked through a local effect was provided by before and after phototesting of areas kept covered during treatment. The UVA minimal erythema dose did not increase in these areas.

In the absence of any controlled study comparisons of PUVA and TL-01 phototherapy for this condition, PUVA should generally be reserved for those who fail to benefit from TL-01.

Thalidomide in the treatment of actinic prurigo. Londoño F. *Int J Dermatol* 1973; 12: 326–8.

Thirty-four patients were treated, with a starting dose of 300 mg thalidomide daily, gradually reducing to a minimum of 15 mg; 32 had good results while on the drug but relapsed on stopping.

Thalidomide in actinic prurigo. Lovell CR, Hawk JL, Calnan CD, et al. *Br J Dermatol* 1983; 108: 467–71.

Of 14 British patients treated with thalidomide (adult starting dose 100–200 mg daily), 13 reported improvement. One could not tolerate the drug due to dizziness. This benefit was sustained in 11 patients, of whom eight required maintenance doses of between 50 mg weekly and 100 mg daily.

Includes a review of earlier open studies reporting the use of thalidomide in AP.

Third-Line Therapies

- β -Carotene **C**
- Pentoxifylline **C**
- Tetracycline and vitamin E **C**
- Oral corticosteroids **E**
- Azathioprine **E**
- Chloroquine **E**
- Ciclosporin eye drops **E**
- Ciclosporin A **E**
- Dupilumab **E**

Hereditary polymorphic light eruption in American Indians: photoprotection and prevention of streptococcal pyoderma and glomerulonephritis. Fusaro RM, Johnson JA. *JAMA* 1980; 244: 1456–9.

Seventeen of 54 patients who participated in this open study were reported to have achieved complete photoprotection, and 16 'marked improvement'. The plasma carotene level tended to be higher in those who benefited. The authors also comment on their use of dihydroxyacetone and Lawsone cream, with apparent benefit.

The clinical features of the study patients were not reported, but the authors' introductory description of hereditary polymorphic light eruption suggests that they probably included AP.

Pentoxifylline in the treatment of actinic prurigo: a preliminary report of 10 patients. Torres-Alvarez B, Castanedo-Cazares JP, Moncada B. *Dermatology* 2004; 208: 198–201.

Clinical improvement was reported in all 10 participants in this 6-month open-label uncontrolled study.

Treatment of actinic prurigo in Chimila Indians. Duran MM, Ordóñez CP, Prieto JC, et al. *Int J Dermatol* 1996; 35: 413–6.

One group of eight patients was treated with tetracycline (1.5 g daily), and another eight with vitamin E (100 IU daily). On follow-up analysis comparing signs and itch, no difference was found between the groups. Both treatments were considered promising and the possibility of using a tetracycline–vitamin E combination therapy was raised.

These treatments need further investigation but may be worth considering if first-line therapies are inadequate and thalidomide is contraindicated or not tolerated.

The clinical features and management of actinic prurigo: a retrospective study. Lestarini D, Khoo LS, Goh CL. *Photodermatol Photoimmunol Photomed* 1999; 15: 183–7.

This is a review of the features and clinical course of 11 patients. Of three treated with systemic corticosteroids, one improved slightly. Intralesional steroids helped one. Three patients were treated with azathioprine: two appeared to benefit.

Topical cyclosporine in the treatment of ocular actinic prurigo. Ortiz-Castillo JV, Boto-de-los-Bueis A, De-Lucas-Laguna R, et al. *Arch Soc Esp Oftalmol* 2006; 81: 661–4.

In these two case reports, topical 2% ciclosporin eye drops were associated with improvement in chronic AP conjunctivitis.

Lymphocyte subtypes and adhesion molecules in actinic prurigo: observations with cyclosporin A. Umaña A, Gómez A, Durán MM, et al. *Int J Dermatol* 2002; 41; 3: 139–45.

Eighteen of 19 patients reported to have significant clinical improvement in lesions and pruritis after 2 months of treatment with ciclosporin A, sustained 6 months after cessation.

Actinic prurigo in Scandinavian adolescent successfully treated with cyclosporine A. Sitek JC. *Dermatol Reports* 2017; 9; 1: 7050.

A case report of an 11-year-old girl with typical lesions and HLA-DRB1*0407 allele refractory to photoprotection, potent steroids, and tetracyclines whose skin became clear after 4 months of ciclosporin A.

Clearance of pediatric actinic prurigo with dupilumab. Eickstaedt JB, Starke S, Krakora D, et al. *Pediatr Dermatol* 2020; 37; 6: 1176–1178.

Case report of successful treatment with dupilumab of a pediatric patient with AP with cheilitis, refractory to topical steroids and methotrexate (although with response to ciclosporin). Skin almost cleared at 8 weeks, sustained response at 7 months.

Dupilumab, an anti-IL-4 receptor antagonist, targets Th2-mediated inflammation and could be a way to avoid systemic side effects of thalidomide and ciclosporin if topical treatments are ineffective, as in this pediatric case.

Actinomycosis

Jonathan E. Blume, Daniel Caplivski



Actinomycosis is an indolent infection that may be difficult to recognize initially and is caused by an anaerobic, Gram-positive rod that is a normal human commensal. Infections are usually the result of introduction of bacteria into a normally sterile space from the oropharynx, gastrointestinal tract, or vaginal tract. The organism may be difficult to recover in the microbiology laboratory because it grows slowly and is ideally cultured under anaerobic conditions. Microscopically, it has a similar appearance to *Nocardia* spp.; however, it does not retain the modified acid-fast stain, and the colonies may have a molar-tooth appearance. Infections of the cervical region are typified by the slow induration of the skin at the angle of the jaw that progresses over several weeks or months. A mass may be palpable and, due to the slow progression and absence of systemic inflammatory symptoms, the infection can often be confused with other conditions such as malignancies. Patients may notice the discharge of small yellow grains known as *sulfur granules*. These are macroscopic colonies of the organism that may be cultured for confirmation, but their absence should not exclude the diagnosis from consideration.

MANAGEMENT STRATEGY

Actinomyces spp. are universally susceptible to *penicillin*. The severity of the illness will dictate whether the patient requires intravenous or oral formulations of the antibiotic, but the general principle is that prolonged treatments for 6 months or more are often required for cure. In patients who are penicillin allergic, the *tetracycline* class of antibiotics is a useful substitute. *Surgical removal* of the abscess may also be required to ensure complete resolution. Treatment failures are rare but may be due to coinfecting organisms from the oropharynx. In order to treat these organisms, the combination of a β -lactam antibiotic with a β -lactamase inhibitor may be sufficient. *Carbapenems* such as *imipenem*, *meropenem*, or *ertapenem* are also effective.

Clinical review: actinomycosis. Wong VK, Turmezei TD, Weston VC. *BMJ* 2011; 343: d6099.

Susceptibility of pathogenic actinomycetes to antimicrobial compounds. Lerner PI. *Antimicrob Agents Chemother* 1974; 5: 302–9.

SPECIFIC INVESTIGATIONS

Diagnostic methods for human actinomycosis. Holmberg K. *Microbiol Sci* 1987; 4: 72–8.

An excellent review of the diagnosis of actinomycosis.

The most accurate way to diagnose actinomycosis is by culture – usually a difficult task – which requires thioglycolate or brain–heart-enriched agar at 37°C under anaerobic or microaerophilic conditions. ‘Molar-tooth’ and ‘breadcrumb’ colonies may take up to 3 weeks to grow. Unfortunately, definitive identification cannot be based on colony morphology and requires the measurement of physiologic and biochemical characteristics (e.g., sensitivity to oxygen, presence of preformed enzymes).

Because cultures of *Actinomyces* spp. are often unsuccessful, observation of ‘sulfur granules’ on a peripheral smear or histology often helps make the diagnosis. The granules are bacterial colonies, which on hematoxylin and eosin staining have a basophilic central area surrounded by a zone of eosinophilic ‘clubs’. Other typical histologic findings include extensive fibrosis, chronic granulation tissue, sinus tracts, and scattered microabscesses.

Immunofluorescent staining of *Actinomyces* spp. is available and can be used on clinical material, granules, and formalin-fixed tissues. The direct immunoperoxidase technique can specifically show *Actinomyces* spp. in formalin-fixed sections via light microscopy. These techniques, as well as gene sequencing (see later), are promising diagnostic modalities given the difficulty of culture and histologic identification.

Cervicofacial actinomycosis: diagnosis and management. Oostman O, Smego RA. *Curr Infect Dis Res* 2005; 7: 170–4.

Culture isolation of *Actinomyces* spp. and microscopic visualization of Gram-positive, non-acid-fast, thin, branching filaments remain the best methods of diagnosing cervicofacial actinomycosis.

Diagnosis of pelvic actinomycosis by 16S ribosomal RNA gene sequencing and its clinical significance. Woo PCY, Fung AMY, Lau SKP, et al. *Diagn Microbiol Infect Dis* 2002; 43: 113–8.

Actinomyces odontolyticus was identified by rRNA gene sequencing. Because the 16S ribosomal RNA gene is conserved within a species, it can be used to identify a specific species of bacteria.

Cervicofacial actinomycosis: CT and MR imaging findings in 7 patients. Park JK, Lee HK, Ha HK, et al. *Am J Neuroradiol* 2003; 24: 331–3.

Findings on computed tomography (CT) and magnetic resonance imaging (MRI) may be helpful in distinguishing cervicofacial actinomycosis from malignant neoplasms, tuberculosis, and fungal infections.

First-Line Therapy

- Penicillin

C

Antimicrobial susceptibility testing of *Actinomyces* species with 12 antimicrobial agents. Smith AJ, Hall V, Thakker B, et al. *J Antimicrob Chemother* 2005; 56: 407–9.

The authors tested the susceptibility of 87 strains of *Actinomyces* to 12 different antimicrobial agents. All isolates were susceptible to penicillin and amoxicillin.

Actinomycosis. Smego RA, Foglia G. Clin Infect Dis 1998; 26: 1255–63.

The authors recommend 2 months of oral penicillin V (2–4 g/day divided every 6 hours) or a tetracycline (e.g., oral doxycycline 100 mg twice daily) for mild cervicofacial disease. For more complicated infections, parenteral penicillin G (10–20 million U/day divided every 6 hours) for 4–6 weeks followed by 6–12 months of oral penicillin V (2–4 g/day divided every 6 hours) is suggested. Tetracycline, erythromycin, clindamycin, or cephalosporins are advocated for patients allergic to penicillin.

Actinomycosis and nocardiosis. A review of basic differences in therapy. Peabody JW, Seabury JH. Am J Med 1960; 28: 99–115.

The authors review the treatment of actinomycosis and state that penicillin is the drug of choice.

Second-Line Therapies

• Amoxicillin	C
• Ceftriaxone	D
• Clindamycin	C
• Doxycycline	D
• Erythromycin	D
• Imipenem	C
• Minocycline	C
• Tetracycline	D

The use of oral amoxicillin for the treatment of actinomycosis: a clinical and invitro study. Martin MV. Br Dent J 1984; 156: 252–4.

Ten patients with cervicofacial actinomycosis were cured in less than 6 weeks with a combination of amoxicillin (500 mg four times daily) and surgery.

Actinomycosis abscess of the thyroid gland. Cevera JJ, Butehorn HF 3rd, Shapiro J, et al. Laryngoscope 2003; 113: 2108–11.

A 39-year-old woman who developed actinomycosis of the thyroid gland after tooth extraction was cured with thyroidectomy and 6 months of ceftriaxone (1 g intravenously every 12 hours).

Successful treatment of thoracic actinomycosis with ceftriaxone. Skoutelis A, Petrochilos J, Bassaris H. Clin Infect Dis 1994; 19: 161–2.

A 38-year-old patient with pulmonary actinomycosis was successfully treated with a 3-week course of daily ceftriaxone (2 g intravenously), followed by 3 months of daily oral ampicillin (no dose listed but typically given 500 mg orally every 6 hours).

Mandibular actinomycosis treated with oral clindamycin. Badgett JT, Adams G. Pediatr Infect Dis J 1987; 6: 221–2.

Clindamycin in the treatment of cervicofacial actinomycosis. de Vries J. Int J Clin Pharmacol 1974; 9: 46–8.

A 60-year-old man with cervicofacial actinomycosis that was resistant to penicillin and tetracycline responded fully to a 1-month course of clindamycin (150 mg four times a day).

Clindamycin in the treatment of serious anaerobic infections. Fass RJ, Scholand JE, Hodges GR, et al. Ann Intern Med 1973; 78: 853–9.

Four patients with cervicofacial actinomycosis and one with thoracic actinomycosis were successfully treated with a combination of intravenous (1.8–2.7 g/day) and oral (0.9–1.2 g/day) clindamycin.

Primary actinomycosis of the hand: a case report and literature review. Mert A, Bilir M, Bahar H, et al. Int J Infect Dis 2001; 5: 112–4.

A 35-year-old man with primary actinomycosis of the hand was cured with 1 month of intravenous ampicillin (12 g/day), followed by 11 months of oral doxycycline (200 mg/day).

Actinomycosis of the prostate. de Souza E, Katz DA, Dworzack DL, et al. J Urol 1985; 133: 290–1.

A case of acute prostatitis due to *Actinomyces* spp. was cured with long-term erythromycin (500 mg intravenously every 6 hours followed by 500 mg orally every 6 hours), chosen because of its excellent penetration into prostatic secretions.

Actinomycosis of the temporomandibular joint. Bradley P. Br J Oral Surg 1971; 9: 54–6.

A 58-year-old man with actinomycosis of the temporomandibular joint was cured with a 12-week course of erythromycin (500 mg six times a day).

Use of imipenem in the treatment of thoracic actinomycosis. Yew WW, Wong PC, Wong CE, et al. Clin Infect Dis 1994; 19: 983–4.

Report of eight cases of pulmonary actinomycosis and their treatment with imipenem–cilastatin. Yew WW, Wong PC, Lee J, et al. Arch Chest Dis 1994; 54: 126–9.

Seven of eight patients with pulmonary actinomycosis were successfully treated with a 4-week course of parenteral imipenem–cilastatin (500 mg intravenously every 8 hours).

Cutaneous disseminated actinomycosis in a patient with acute lymphocytic leukemia. Takeda H, Mitsunashi Y, Kondo S. J Dermatol 1998; 25: 37–40.

A patient with primary cutaneous disseminated actinomycosis was cured with a 3-month course of intravenous minocycline (2 mg/kg/day).

Antibiotic treatment of cervicofacial actinomycosis for patients allergic to penicillin: a clinical and in vitro study. Martin MV. Br J Oral Maxillofac Surg 1985; 23: 428–34.

Six patients with cervicofacial actinomycosis were cured with 8–16 weeks of oral minocycline (250 mg four times a day). There were no recurrences after 1 year.

Primary actinomycosis of the quadriceps. Langlosh JT, Lauerman WC. J Pediatr Orthop 1987; 7: 222–3.

Surgical drainage followed by a 6-week course of oral tetracycline (500 mg orally every 6 hours) cured a case of actinomycosis of the quadriceps.

Comparative in vitro susceptibilities of 396 unusual anaerobic strains to tigecycline and eight other antimicrobial agents. Goldstein EJ, Citron DM, Merriam CV, et al. Antimicrob Agents Chemother 2006; 50: 3507–13.

Tigecycline (50 mg intravenously every 12 hours, with a 100-mg loading dose) had good in vitro activity against isolates of *Actinomyces* spp.

Resistance patterns in clinical isolates of pathogenic *Actinomyces* species. Steninger C, Willinger B. J Antimicrob Chemother 2016; 71: 422–7.

β-lactam antibiotics are effective; however, rates of resistance to metronidazole suggest that alternatives should be considered in case of β-lactam allergy.

Third-Line Therapies	
• Ciprofloxacin	E
• Levofloxacin	E
• Rifampicin	E

Treatment of recalcitrant actinomycosis with ciprofloxacin. Macfarlane DJ, Tucker LG, Kemp RJ. J Infect 1993; 27: 177–80.

Treatment of pulmonary actinomycosis with levofloxacin. Ferreira D de F, Amado J, Neves S, et al. J Bras Pneumol 2008; 34: 245–8.

Treatment of pulmonary actinomycosis with rifampin. Morone N, De Castro Pereira CA, Saito M, et al. G Ital Chemioter 1982; 29: 121–4.

Pulmonary actinomycosis. Rapid improvement with isoniazid and rifampin. King JW, White MC. Arch Intern Med 1981; 141: 1234–5.

A series of single case reports responding to other antibiotic options.

8

Acute generalized exanthematous pustulosis

Sidra S. Khan, Ian H. Coulson



Acute generalized exanthematous pustulosis (AGEP) is characterized by the acute onset of numerous small, non-follicular, sterile pustules arising on a diffuse erythematous base in a febrile patient with an accompanying blood neutrophilia. Most cases occur in the context of drug ingestion (commonly within 24 hours). Rapid resolution after drug withdrawal is the usual outcome.

MANAGEMENT STRATEGY

Treatment of AGEP involves establishing the correct diagnosis coupled with the *withdrawal of any implicated medication* (Table 8.1). Pustular psoriasis is its main differential diagnosis. A comprehensive drug history and a personal or family history of psoriasis are therefore required.

Intraepidermal or subcorneal pustules in conjunction with a leukocytoclastic vasculitis, focal necrosis of keratinocytes, marked edema of the papillary dermis, and an infiltrate of eosinophils are histologic features that help distinguish AGEP from pustular psoriasis; biopsy is thus an integral facet of management.

Differentiation of AGEP from other inflammatory, toxic, or infectious conditions, such as Sneddon–Wilkinson disease (subcorneal pustular dermatosis) or, in severe cases, toxic epidermal necrolysis, is often readily apparent both clinically and histologically. The clinician should, however, be aware that erythema multiform-like targetoid lesions, mucous membrane involvement, facial edema, purpura, and vesicubullous lesions have all been documented in the context of AGEP.

Antibiotics (primarily penicillin or macrolide based) are the most frequently implicated medications. Numerous case reports have cited various other causative agents, including calcium channel blockers, non-steroidal antiinflammatory drugs (NSAIDs),

angiotensin-converting enzyme (ACE) inhibitors, and anticonvulsants (Table 8.1). Acute enterovirus infection, mycoplasma pneumonia, cytomegalovirus, parvovirus B19, spider bites, Chinese herbal compounds (ginkgo biloba), contrast media, and mercury exposure have also been reported as possible causes.

There is no specific therapy for AGEP. A skin swab establishes the sterile nature of the pustules, and drug withdrawal, if feasible, results in rapid spontaneous resolution. *Supportive therapy* is all that is required. A superficial desquamation often occurs during this time and may be treated with *simple emollients*. Several case reports cite the use of patch testing to confirm the causative medication. Recalcitrant cases have benefited from *oral prednisolone*, *ciclosporin*, and *secukinumab*.

Specific Investigations

- Detailed history
- Hematology
- Skin swab of pustule
- Microscopy, culture, Gram stain
- Skin biopsy

First-Line Therapy

- Drug withdrawal

E

Risk factors for acute generalized exanthematous pustulosis (AGEP) – results of a multinational case-control study (EuroSCAR).

Sidoroff A, Dunant A, Viboud C. Br J Dermatol 2007; 157: 6. A multinational case-control study (97 cases of AGEP and 1009 controls) that assessed the risk for different drugs causing severe cutaneous adverse reactions.

The most frequently implicated drugs were pristinamycin (a macrolide marketed in France), ampicillin/amoxicillin, quinolones, (hydroxy) chloroquine, anti-infective sulfonamides, terbinafine, and diltiazem. Infections and a personal or family history of psoriasis were not deemed to be significant risk factors for developing AGEP. Of note, the median treatment duration was 1 day for antibiotics and 11 days for all other associated drugs.

Acute generalized exanthematous pustulosis. Analysis of 63 cases.

Roujeau JC, Bioulac-Sage P, Bourseau C, et al. Arch Dermatol 1991; 127: 1333–8. A retrospective review of cases of AGEP. Almost 90% of cases were attributable to drugs, with 50% of reactions occurring within 24 hours of ingestion.

Acute generalized exanthematous pustulosis.

Manders SM, Heymann WR. Cutis 1994; 54: 194–6. Two of the three cases reported in this series were attributable to penicillin. This succinct overview of AGEP also provides the reader with useful clinicopathologic features that may help distinguish AGEP from pustular psoriasis.

Generalized pustular psoriasis or drug-induced toxic pustuloderma? The use of patch testing.

Whittam LR, Wakelin SH, Barker JNWN. Clin Exp Dermatol 2000; 25: 122–4. Patch testing to a 1% and 5% amoxicillin preparation confirmed a type 4 hypersensitivity reaction in a patient with long-standing plaque psoriasis who developed a generalized pustular eruption when treated with amoxicillin for an episode of epididymo-orchitis.

Table 8.1 Drugs and other substances reported to have caused AGEF**Drugs****Antibiotics**

Penicillins: amoxicillin, ampicillin, bacampicillin, piperidic acid, piperacillin, propicillin, tazobactam, meropenem
 Macrolides: azithromycin, erythromycin
 Quinolones: ciprofloxacin, norfloxacin, ofloxacin
 Tetracyclines: doxycycline, minocycline
 Cephalosporins: cefaclor, cefazolin, cefuroxime, cephalexin, cephadrine
 Aminoglycosides: gentamicin, isepamicin sulfate, streptomycin
 Other antibiotics
 Chloramphenicol, clindamycin, cotrimoxazole, imipenem/cilastatin, lincomycin, metronidazole, nifuroxazide, sulfamethoxazole, teicoplanin, vancomycin, daptomycin, telavancin

NSAIDs

Celecoxib, etoricoxib, ibuprofen, naproxen, nimesulide, valdecoxib
 ACE inhibitors
 Captopril, enalapril
 Calcium channel blockers
 Nifedipine, nimodipine, diltiazem

Anticonvulsants

Carbamazepine, phenobarbital, phenytoin
 Analgesia (opioid/non-opioid)
 Acetaminophen, paracetamol, morphine, codeine, dextropropoxyphene

Antiplatelets

Aspirin, ticlopidine, clopidogrel

Benzodiazepines

Clobazam, nitrazepam, tetrazepam

Antimalarials

Chloroquine, hydroxychloroquine, proguanil, pyrimethamine

Antipsychotics

Clozapine, chlorpromazine

Antifungals

Amphotericin, fluconazole, itraconazole, nystatin, terbinafine

Antivirals

Lamivudine, lopinavir, ritonavir, zidovudine

Antituberculosis drugs

Isoniazid, rifampicin

Proton pump inhibitors

Lansoprazole, omeprazole

Immunosuppressants

Azathioprine

Antidepressants

Amoxapine, sertraline

Antihistamines

Clemastine, hydroxyzine

Beta agonists and antagonists

Buphenine, fenoterol, nadolol

H₂-receptor antagonists

Cimetidine, famotidine, ranitidine

Table 8.1 Drugs and other substances reported to have caused AGEF—cont'd**Cholesterol-lowering medications**

Simvastatin, pitavastatin, fenofibrate

Corticosteroids

Dexamethasone, methylprednisolone, prednisolone

Diuretics

Furosemide, hydrochlorothiazide

Antineoplastic drugs

Gefitinib, imatinib, vemurafenib

Other drugs

Acetazolamide, allopurinol, bamifylline, bleomycin, bupropion hydrochloride, cadralazine, carbimazole, carbutamide, cytarabine, dalteparin, disulfiram, eperisone hydrochloride, eprazinone, fludione, icodextrin, interferon, metamizole, pentoxifylline, piperazine, propafenone, alprostadil, progestogens, pseudoephedrine, psoralen + UVA, quinidine, ranolazine, sulbutamine, senna, sulfasalazine, terazosin, thalidomide

Other substances

Chromium picolinate
 Diphenyl sulfone
 Contrast agents iohexol and iopamidol
 Mercury
 Pneumococcal vaccine
 Essential oil
Andrographis paniculata

A systemic reaction to patch testing for the evaluation of acute generalized exanthematous pustulosis. Mashiah J, Brenner S. Arch Dermatol 2003; 139: 1181–3.

The authors report a generalized AGEF-like reaction caused by patch tests carried out to determine the drug eliciting AGEF. Interestingly, negative results were obtained with the drug in question.

Second-Line Therapies

• Corticosteroids	E
• Ciclosporin	E

Acute generalized exanthematous pustulosis: clinical characteristics, etiologic associations, treatments, and outcomes in a series of 28 patients at Mayo Clinic, 1996–2013. Alniemi DT, Wetter DA, Bridges AG, et al. Int J Dermatol 2017; 56: 405–14.

A retrospective review of 28 patients with AGEF. Ten of the 28 were treated with oral corticosteroids and demonstrated complete resolution. Three patients went on to develop non-AGEF skin eruptions a few months after resolution of their AGEF.

Successful treatment of hydroxychloroquine-induced recalcitrant acute generalized exanthematous pustulosis with ciclosporin: case report and literature review. Yalçın B, Çakmak S, Yidirim B. Ann Dermatol. 2015; 27: 431–4.

A case report of a 67-year-old rheumatoid arthritis patient with recalcitrant AGEF secondary to hydroxychloroquine responding successfully to ciclosporin 4 mg/kg/day tapered over 2 months.

Third-Line Therapy

- Secukinumab

E

Interleukin 17 as a therapeutic target of acute generalized exanthematous pustulosis (AGEP). Gualtieri B, Solimani F, Hertl M, et al. J Allergy Clin Immunol Pract 2020; 8; 6: 2081-4.

A case report of a 63-year-old patient with terbinafine-induced AGEP that was unresponsive to prednisolone. A rapid clinical improvement was observed following a single 300 mg dose of secukinumab.

Allergic contact dermatitis and photoallergy

Rosemary L. Nixon, Claire Felmingham



Allergic contact dermatitis (ACD) is a delayed or type IV hypersensitivity reaction. It consists of a primary sensitization phase followed by secondary elicitation by haptens, leading to activation of T lymphocytes.

ACD usually appears 24–48 hours after contact with an allergen. Typically, the rash is localized to the site of contact. It may later spread to other areas. Spreading is characteristic of ACD and can help differentiate the diagnosis from that of irritant contact dermatitis. The spread of the rash can occur from transfer of the allergen (e.g., from hands to face), or as a result of an id reaction (also known as autoeczematization). Other possible routes of exposure to contact allergens include systemic, airborne, and proxy exposures.

The rash of ACD is typically pruritic and eczematous, with papules and vesicles on an erythematous base.

The location on the body at which the rash originated can assist in determining the causative allergen. For example, if the hands are affected, the causative allergen could be rubber glove accelerators. If the rash begins at the scalp and neck, perhaps paraphenylenediamine from hair dye is the culprit. ACD to nickel might occur at the left wrist from a watch, at the ears or neck from jewelry, or at the navel from a belt buckle.

Factors that increase the likelihood of sensitization include chemical factors (such as chemical size and concentration); skin factors (such as integrity of the skin exposed to the chemical); and factors pertaining to the conditions of contact (such as the duration of contact).

Photoallergens additionally require activation by UV light to cause photoallergic contact dermatitis (PACD). Organic UV absorbers and topical non-steroidal antiinflammatory agents are the two most common photoallergens. Other potential photoallergens include fragrances, antibacterials, plants, and insecticides.

MANAGEMENT STRATEGY

Identification and avoidance of offending allergens and potential cross-reacting agents is the principal management strategy for ACD. Patch testing is the gold standard for diagnosing ACD and identifying allergens. Following this, patient education regarding the diagnosis, the relevant allergen(s), and how to avoid them, is essential.

Government legislation can reduce ACD rates significantly. The European Union has introduced legislation to limit the concentration of the preservative methylisothiazolinone (MI) in personal products, to restrict nickel content in jewelry, and to reduce available chromate in cement by adding ferrous sulfate. These measures have resulted in reduced sensitization rates and a reduced number of cases of ACD to MI, nickel, and chromate, respectively.

The workplace also plays an important role in minimizing exposure to allergens, thereby reducing rates of sensitization and ACD. This can be done by modifying work environments; for example, by improving ventilation to reduce exposure to airborne substances, by substituting common allergens, and by providing and ensuring the use of appropriate personal protective equipment (PPE).

Glove use is an important component of ACD prevention and management. Glove choice will depend on the activity being performed and on the chemicals being handled. When working in a hot environment, sweating and leaching of chemicals from gloves can occur. Cotton gloves can be worn underneath rubber or leather gloves to prevent sensitization to rubber accelerators and chromate.

The initial management of ACD follows the general principles of eczema therapy. This includes avoiding skin irritants (such as water, soap, friction, and heat), using emollients or moisturizing creams, and applying topical corticosteroids to affected areas. Barrier creams have had limited success in preventing dermatitis. Topical tacrolimus and pimecrolimus have been shown to be effective. In severe cases, oral corticosteroids may be required. These are usually short courses of prednisolone 25–50 mg daily for 1 week.

If secondary infection is suspected, oral antibiotics (cephalosporins, erythromycin, or flucloxacillin) or topical antibiotics (mupirocin or fusidic acid) may be required.

ACD will usually resolve with this initial treatment, provided that the responsible allergen has been identified and avoided. However, patients may experience ongoing issues if they are inadvertently exposed to the allergen or if they develop persistent postoccupational dermatitis, a dermatitis that recurs despite absence of exposure to causative agents.

If ACD is chronic or refractory to first-line treatments, ultraviolet light therapy with narrowband ultraviolet B (UVB) or psoralen plus ultraviolet A (PUVA) can be used. Systemic immunosuppression with ciclosporin, azathioprine, and methotrexate may be considered. Acitretin may be helpful in some cases, particularly if there is hyperkeratotic palmar involvement. Alitretinoin is helpful in cases of chronic hand eczema; however, more evidence is required to determine its usefulness in treating ACD specifically.

Small case series and a retrospective chart review have suggested that dupilumab is effective in treating ACD. A phase 4 clinical trial is underway to investigate the effects of dupilumab on ACD in 20 patients.

Recent evidence suggests that there is an association between contact dermatitis and smoking. There is no strong evidence available to show that smoking cessation leads to improvement of ACD. However, smoking cessation could be a worthwhile action, especially when considering health cobenefits.

For PACD, identification and avoidance of the photoallergen is again the major treatment goal. Sun protection, with sunscreen and protective clothing, is also important. If the photoallergen is an ingredient in sunscreen, avoidance and substitution of that ingredient is recommended. Physical UV blockers such as zinc oxide or titanium dioxide are not known to cause allergic or PACD and may be useful substitutes to chemical sunscreens.

Specific Investigations

- Patch testing to appropriately diluted allergens
- Photopatch testing if PACD is suspected – duplicate sets of allergens are applied, and after 48 hours one set is exposed to 5 J/cm² UVA; results are read after a further 48 hours
- Repeat open application test (ROAT) to determine whether a reaction is significant in individuals who develop weak (1+) positive reactions to an allergen

First-Line Therapies

Allergic contact dermatitis

• Allergen avoidance and substitution	C
• Skin care education	B
• PPE	D
• Topical corticosteroids	B
• Emollients and soap substitutes	C
• Barrier creams	B
• Calcineurin inhibitors (tacrolimus, pimecrolimus)	B
• Prednisolone	D
• Antibiotics – topical and systemic	D
• Alitretinoin	A

Photoallergy

• Allergen avoidance and substitution	C
• Photoprotection	C
• Sunscreens – physical UV blockers	E

Skin care education and individual counseling versus treatment as usual in healthcare workers with hand eczema: randomised clinical trial. Ibler KS, Jemec GBE, Diepgen TL, et al. *BMJ* 2012; 345: e7822.

Two hundred and fifty-five healthcare workers with hand eczema were randomized to an intervention or control group. The intervention comprised education in skin care, individual counseling based on patch and prick testing, and assessment of occupational and domestic exposures. At the 5-month follow-up, hand eczema was significantly improved in the intervention group compared with the control group as measured both objectively and subjectively.

Determinants of epoxy allergy in the construction industry: a case-control study. Spee T, Timmerman JG, Rühl R, et al. *Contact Dermatitis* 2016; 74: 259–66.

A case-control study compared 179 German epoxy workers with diagnosed ACD to epoxy (cases) with 151 epoxy workers without such an allergy (controls). ACD to epoxies was found to be associated with unusually high levels of exposure to the chemicals (OR 2.13) and with poor compliance with personal protection, including wearing short sleeves and trousers (OR 2.38), and incorrect glove use (OR 2.12).

Effectiveness of skin protection measures in prevention of occupational hand eczema: results of a prospective randomized controlled trial over a follow-up period of 1 year. Kütting B, Baumeister T, Weistenhöfer W, et al. *Br J Dermatol* 2010; 162: 362–70.

A total of 1020 metalworkers were randomized to one of four arms: skin care (use of moisturizer), skin protection (application of protection creams before or during work), both combined, and a control group. Eight hundred subjects were retained in the study after 12 months, with a compliance range of 73.7–88.7%. Hands were examined using a quantitative skin score. The group following the regime of both skin care and skin protection demonstrated the greatest improvement.

Tacrolimus 0.1% vs. mometasone furoate topical treatment in allergic contact hand eczema: a prospective randomized clinical study. Katsarou A, Makris M, Papagiannaki K, et al. *Eur J Dermatol* 2012; 22: 192–6.

Thirty adults with chronic hand eczema and positive patch test reactions were randomized to either tacrolimus 0.1% ointment or mometasone furoate 0.1%. A significant difference was observed in both groups in all parameters between baseline and day 90 results. The results suggest tacrolimus is a favorable alternative therapy to topical corticosteroids with similar outcomes.

A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of alitretinoin (BAL4079) in the treatment of severe chronic hand eczema refractory to potent topical corticosteroid therapy. Fowler JF, Graff O, Hamedani AG. *J Drugs Dermatol* 2014; 13: 1198–204.

Five hundred and ninety-six participants were randomized to receive either treatment with 30 mg of alitretinoin, or placebo, for 24 weeks. A greater proportion of alitretinoin-treated patients achieved a physician global assessment of 'cleared' or 'almost cleared' of eczema at the end of the trial. Alitretinoin was shown to significantly improve severe chronic hand eczema.

New sunscreens confer improved protection for photosensitive patients in the blue light region. Moseley H, Cameron H, Macleod T, et al. *Br J Dermatol* 2001; 145: 789–94.

Seven patients with known photosensitivity extending into the visible (blue) region at 430 ± 30 nm were tested with new reflectant sunscreens, which use larger particle size zinc oxide and titanium dioxide as active ingredients. The mean photo protection factors at this wavelength were determined. The new sunscreens were found to provide protection for patients with sensitivity to visible light (blue light region); for example, those with chronic actinic dermatitis, compared with sunscreens using chemical UV absorbers and microfine particles, which scatter radiation.

Second-Line Therapies

Allergic contact dermatitis

• Ultraviolet light (PUVA, UVB)	B
• Azathioprine	C
• Cyclosporin	D
• Methotrexate	D
• Acitretin	E
• Low-nickel diet for nickel dermatitis	C
• Grenz ray therapy	C

Chronic eczematous dermatitis of the hands. A comparison of PUVA and UVB treatment. Rosén K, Mobacken H, Swanbeck G. *Acta Derm Venereol* 1987; 67(1): 48–54.

Thirty-five patients with chronic hand dermatitis were randomly allocated to PUVA or UVB treatment. Twenty-two of the patients had ACD. One hand was exposed to treatment; the other served as an untreated control. The treated hand cleared in all participants receiving PUVA. There was also statistically significant clinical improvement in the group treated with UVB.

Azathioprine versus betamethasone for the treatment of parthenium dermatitis: a randomized controlled study. Verma KK, Mahesh R, Srivastava P, et al. *Indian J Dermatol Venereol Leprol* 2008; 74: 453–7.

Fifty-five patients with contact dermatitis caused by airborne *Parthenium* were randomly assigned to azathioprine 100 mg daily or betamethasone 2 mg daily for 6 months in a double-blinded manner. Treatment effects appeared equal in each group; however, the group randomized to betamethasone appeared to have more adverse effects.

Oral cyclosporine inhibits the expression of contact hypersensitivity in man. Higgins EM, McLelland J, Friedmann PS, et al. *J Dermatol Sci* 1991; 2: 79–83.

Six patients with chronic contact dermatitis were treated with ciclosporin 5 mg/kg/day. Quantitative patch test reactions were diminished in all six, and responses were reduced over the whole range of allergen concentrations. In addition, the clinical manifestations of ACD resolved completely within 2–3 weeks of ciclosporin therapy.

Methotrexate use in allergic contact dermatitis: a retrospective study. Patel A, Burns E, Burkemper NM. *Contact Dermatitis* 2018; 78: 194–8.

In a retrospective chart review of 32 patients with ACD, 78% of patients showed either a partial or complete response to treatment with methotrexate (dose range: 15–30 g per week).

Open-label exploratory study of acitretin for the treatment of severe chronic hand dermatitis. Tan J, Maari C, Nigen S, et al. *J Dermatolog Treat* 2015; 26: 373–5.

In a pilot study, nine participants with severe chronic hand dermatitis were treated with 10–30 mg of acitretin daily for up to 24 weeks. Three patients withdrew from the study. In the remaining patients 33.3% achieved clear or almost clear on physician global assessment.

A double-blind study of Grenz ray therapy in chronic eczema of the hands. Lindelöf B, Wrangsjö K, Lidén S. *Br J Dermatol* 1987; 117: 77–80.

Twenty-four patients with chronic hand eczema received Grenz ray therapy (at 3 Gy) to one hand, and a simulated therapy to the other, on six occasions at 1-week intervals. A significantly better response was observed in the hands receiving Grenz ray therapy.

Third-Line Therapies

Allergic contact dermatitis

• Disulfiram	C
• Pentoxifylline	E
• Dupilumab	E

Disulfiram and low nickel diet in the management of hand eczema: a clinical study. Sharma AD. *Indian J Dermatol Venereol Leprol* 2006; 72: 113–8.

In this single-blinded controlled trial, 21 patients with chronic hand eczema and nickel sensitivity were randomly divided into a treatment group, with a low nickel diet and 4 weeks of oral disulfiram, and a control group, with a regular diet and oral placebo. Hand eczema cleared completely in 10 of 11 participants in the treatment group, and in 1 of 10 participants in the control group.

The effect of the topical application of different pentoxifylline concentrations on the patch test results of nickel-sensitive patients. Saricaoglu H, Başkan EB, Tunalı S. *Int J Dermatol* 2004; 43: 315–6.

Twenty-two volunteers with nickel-induced contact dermatitis were pretreated with three concentrations of pentoxifylline and then patch tested to nickel. Though there was some evidence of suppressed patch test results, the decrease in patch test reactions was statistically insignificant.

Effect of tobacco smoking and alcohol consumption on the prevalence of nickel sensitization and contact sensitization. Thyssen JP, Johansen JD, Menné T, et al. *Acta Derm Venereol* 2010; 90: 27–33.

In this cross-sectional study, 3460 adults underwent patch testing and answered a questionnaire on smoking status. Using an adjusted model, a statistically significant trend ($p < 0.05$) was found between smoking status and nickel sensitization.

Dupilumab treatment in two patients with severe allergic contact dermatitis caused by sesquiterpene lactones. Ruge IF, Skov L, Zachariae C, et al. *Contact Dermatitis* 2020; 83: 2: 137–9.

Two cases of recalcitrant, severe ACD to sesquiterpene lactones demonstrated an adequate response to dupilumab.

Alopecia areata

Brittany Craiglow, Danielle Peterson, Brett King



Photo courtesy of Dr Craiglow.

Alopecia areata (AA) is a common autoimmune disease characterized by non-scarring hair loss. Extent or severity of disease ranges from one or more patches of alopecia (involving the scalp and/or other hair-bearing sites) to complete scalp hair loss (referred to as alopecia totalis [AT]) or complete body hair loss (referred to as alopecia universalis [AU]). Patients with AA often experience a negative impact on quality of life and have increased rates of depression and anxiety.

MANAGEMENT STRATEGY

There are presently no FDA-approved treatments for AA. Approach to management depends on a variety of factors, including patient age, extent and duration of hair loss, and impact on quality of life. Traditional therapeutic options include topical, intralesional and systemic corticosteroids, topical immunotherapy, and systemic immunomodulatory medications. While mild patchy disease often improves with topicals and/or intralesional corticosteroids, more severe AA is less likely to respond to these treatments. Janus kinase (JAK) inhibitors have recently emerged as an effective treatment for AA, and large clinical trials are presently underway.

Intralesional corticosteroids, most commonly triamcinolone acetate, are considered first-line therapy for adult patients with limited, patchy AA. There is evidence that 2.5 mg/mL has similar efficacy to 5 mg/mL and 10 mg/mL concentrations. Injections are typically performed at 4–6-week intervals, with up to 40 mg administered per session. Side effects include skin atrophy, which is usually transient.

For patients who are unable to tolerate intralesional therapy, *topical corticosteroids* may provide some benefit. Superpotent topical corticosteroids such as clobetasol propionate are applied

twice daily to affected areas and may be followed by an eventual taper once there has been regrowth.

Topical immunotherapy with contact sensitizers, including *squaric acid dibutyl ester (SADBE)* and *diphenylcyclopropenone (DPCP)*, also called diphenylprone, induces allergic contact dermatitis, which likely works by changing the immune milieu of the hair follicle. DPCP is a more stable compound than SADBE and more widely utilized. Patients are first sensitized with 2% DPCP to a localized area (e.g., 2 cm² area on the buttock or hip) followed by weekly applications of increasing concentrations typically ranging from 0.001% to 0.1% until the patient develops mild erythema and pruritus, which is then maintained with repeated application of the same concentration solution. Side effects include generalized dermatitis and lymphadenopathy.

Janus kinase (JAK) inhibitors are an emerging treatment for patients with AA, with efficacy now described in numerous case reports, retrospective series, and open-label clinical trials. These small molecules, which variably target the JAK family of enzymes, disrupt signaling of IFN- γ and IL-15, which appear to be integral cytokines to AA pathogenesis. *Tofacitinib* and *ruxolitinib* have been most commonly used, with larger studies reporting that 50%–75% of patients experienced >50% scalp hair regrowth and 20%–66% patients experienced near-complete or complete regrowth. In adult patients, we typically start with tofacitinib 5 mg twice daily and consider increasing to 10 mg twice daily if there is not at least 25% scalp hair regrowth by 3–6 months. While JAK inhibitors are generally well tolerated, potential adverse events include serious infection, malignancy, and blood clots and therefore a thorough discussion of potential risks is important prior to initiating treatment. Large, placebo-controlled clinical trials investigating a variety of JAK inhibitors are now underway. While there have been reports of successful use of topical JAK inhibitors for AA, clinical trials have failed to show efficacy. Compounded topical preparations of tofacitinib or ruxolitinib in 1%–2% concentrations may be considered for the treatment of limited areas, such as the eyebrow regions or small areas on the scalp, or for patients in whom avoidance of systemic therapy is desired or appropriate.

Systemic corticosteroids are sometimes effective for the treatment of AA; however, there are significant risks associated with long-term treatment and relapse is common after discontinuation, and so routine use is not recommended. Pulsed therapy may be associated with less morbidity and may be useful for some patients experiencing rapidly progressive hair loss. Monthly doses of prednisone 5 mg/kg (maximum 300 mg) for 4–6 months may be considered; however, patients need to be counseled that hair growth may not be sustained.

Oral minoxidil monotherapy has been shown to lead to significant scalp hair regrowth in 18% of patients and may be synergistic with oral JAK inhibitors, and we use it commonly in the treatment of our patients, both as monotherapy and in combination with other treatments. The minoxidil dose we typically use is 2.5–5 mg once or twice daily. *Topical minoxidil* 5% is unlikely to yield improvement in AA when used as monotherapy, but it may be useful as an adjunctive therapy, such as with intralesional or topical corticosteroids or topical JAK inhibitors.

Specific Investigations

- Complete review of systems, with laboratory investigations reserved for patients with findings suggestive of comorbid disease, such as thyroid dysfunction
- Scalp biopsy is rarely needed given the characteristic clinical presentation but may be useful in cases of diffuse alopecia areata or to differentiate from scarring alopecias

First-Line Therapies

• Intralesional corticosteroids	A
• Topical corticosteroids	A
• Topical immunotherapy	B
• Oral JAK inhibitors	B

Benefit of different concentrations of triamcinolone acetonide in alopecia areata: an intrasubject pilot study. Chu TW, Aljasser M, Albarbi A, et al. *J Am Acad Dermatol* 2015; 73: 338–40.

Four patients each received six injections of saline and triamcinolone acetonide 2.5 mg/mL, 5 mg/mL, and 10 mg/mL at 6-week intervals. All three concentrations yielded similar responses and were superior to placebo.

Clobetasol propionate 0.05% under occlusion in the treatment of alopecia totalis/universalis. Tosti A, Piraccini B, Pazzaglia M, et al. *J Am Acad Dermatol* 2003; 49: 96–8.

A refractory group of 28 patients with AT/AU of 3–12 years' duration who had not responded to immunotherapy were treated on half of their scalp with 2.5 g of clobetasol propionate ointment under plastic film 6 nights per week for 6 months. Regrowth started at 6–14 weeks, and eight patients (28.5%) achieved >75% regrowth. Eleven patients developed painful folliculitis, including five of the six who withdrew from the study. At 6 months, follow-up, 18% of the 28 patients maintained complete regrowth.

Randomized double-blind placebo-controlled trial in the treatment of alopecia areata with 0.25% desoximetasone cream. Charuwichitratana S, Wattanakrai P, Tanrattanakorn S. *Arch Dermatol* 2000; 136: 1276–7.

This double-blind, controlled trial randomized 70 patients with patchy AA to either topical 0.25% desoximetasone cream or placebo twice daily for 12 weeks. At the end of 12 weeks, any patient without complete regrowth was offered intralesional triamcinolone acetonide (10 mg/mL). Complete hair regrowth was seen in 15 (57.7%) of the treatment arm compared with 11 (39.3%) in the placebo group but this was not statically significant ($p=0.28$). Among those with incomplete regrowth, 14 elected for intralesional steroid injection with 13 (92.9%) achieving complete regrowth after 1–3 monthly injections. Among those with complete regrowth, 66% had no recurrence at 6 months, follow-up.

Diphencyprone in the treatment of alopecia areata. Happle R, Hausen BM, Weisner-Menzel L. *Acta Derm Venereol* 1983; 63: 49–52.

This study demonstrated the unilateral response observed when one side of the scalp is treated with DPCP. A total of 27 patients (5 with mild alopecia, 22 with totalis) were sensitized with 2% solution of DPCP and titrated to an effective concentration (0.0001–2%). Among those, 18 (66.6%) demonstrated continuous response, five (18.5%) had initial response, and four (14.8%) had no response. Interestingly, among the five patients who demonstrated an initial response, four responded to a lower concentration of DPCP.

Topical immunotherapy with diphenylcyclopropenone in the treatment of chronic extensive alopecia areata. Sotiriadis D, Patsatsi A, Lazaridou E, et al. *Clin Exp Dermatol* 2007; 32: 48–51.

This prospective, open clinical trial included 17 patients with AT/AU and 24 with severe AA (>50% scalp involvement). After sensitization with DPCP 2% in acetone, progressively higher concentrations (from 0.001% to 0.1%) were applied once weekly for a period of 6–12 months. Significant hair regrowth was observed

in five patients with AT/AU (31.25%) and 10 patients with AA (45.4%). These results were sustained in 66.6% of patients for a 12-month follow-up period.

Topical immunotherapy with diphenylcyclopropenone of patients with alopecia areata – a large retrospective study on 142 patients with a self-controlled design. Ohlmeier MC, Traupe H, Luger TA, et al. *J Eur Acad Dermatol Venereol* 2012; 26: 503–7.

This large, retrospective review evaluated 142 patients (70% female), the majority of whom (60%) had multifocal AA. After sensitization with 2% DPCP in acetone, weekly challenges with increased concentrations (0.00001–2%) were used. Complete response (>90% hair regrowth) was seen in 51 (37.8%) patients and 20 (14.8%) patients had partial regrowth (50%–90%). Hair regrowth was inversely related to severity of disease (severe AA less responsive to DPCP) and 45.1% of patients with complete response relapsed within 3 years.

Oral ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata. Mackay-Wiggan J, Jabbari A, Nguyen N, et al. *JCI Insight* 2016; 1: e89790.

This open-label study evaluated 12 patients with moderate-to-severe AA receiving ruxolitinib 20 mg twice daily for 3–6 months with a 3-month follow-up after cessation of therapy. Nine patients (75%) demonstrated >50% regrowth. Responders experienced shedding at the cessation of therapy.

Safety and efficacy of the JAK inhibitor tofacitinib citrate in patients with alopecia areata. Crispin MK, Ko JM, Craiglow BG, et al. *JCI Insight* 2016; 1: e89776.

This multicenter, open-label, single arm trial evaluated tofacitinib 5 mg twice daily in 66 patients with severe AA (>50% scalp loss) for 3 months. A majority of patients had AU (71.2%). Twenty-one patients (32%) were significant responders (>50% change in Severity of Alopecia Tool [SALT] score), 21 patients (32%) were intermediate responders (5–50% change) and 24 patients (36%) were non-responders (<5% change) at 3 months. AA and ophiasis subtypes were more responsive than AT/AU. Duration of current episode was negatively correlated with percentage change in SALT score.

Tofacitinib for the treatment of severe alopecia areata and variants: a study of 90 patients. Liu LY, Craiglow BG, Dai F, et al. *J Am Acad Dermatol* 2017; 76: 22–8.

This retrospective study evaluated 90 patients with severe AA (>40% scalp loss) treated with tofacitinib. Of these, 75 patients (83.3%) had AU, 2 patients (2.2%) had AT, and 13 patients (14.4%) had AA. All patients started on tofacitinib 5 mg twice daily. Adjuvant therapy (300 mg prednisone monthly for 3 doses) or tofacitinib dose was increased (10 mg twice daily) if the patient had no response or the response plateaued. Clinical response (>50% SALT reduction) was seen in 77%, complete response was seen in 13 patients (20%), and moderate response (51%–90%) was seen in 25 patients (38.4%). AA subtype was more responsive than AT/AU.

Tofacitinib for the treatment of alopecia areata and variants in adolescents. Craiglow BG, Liu LY, King BA. *J Am Acad Dermatol* 2017; 76(1): 29–32.

This retrospective study evaluated 13 adolescent patients treated with tofacitinib 5 mg twice daily for median duration of 5 months. Six patients (46%) had AA, one patient (8%) had AT and six patients (46%) had AU. Nine patients (69%) experienced regrowth. The mean duration of current episode was similar

between responders and non-responders (2 years), except for one non-responder who had AU for 12 years.

Second-Line Therapies

• Oral minoxidil	B
• Topical minoxidil	B
• Anthralin	B

Evaluation of oral minoxidil in the treatment of alopecia areata. Fiedler-Weiss VC, Rumsfield J, Buys CM, et al. Arch Dermatol 1987; 123: 1488–90.

Sixty-five patients were treated with oral minoxidil 5 mg twice daily. Forty-four patients (68%) had 75%–100% hair loss, 19 patients (29%) had 25%–74% of hair loss, and two patients (3%) had 0%–24% loss. Fifty-two patients (80%) had some response to oral minoxidil. Cosmetic response was reported in 18% of patients, with the majority of responders (66.7%) having mild-to-moderate disease (<75% loss at baseline). The drug was generally well tolerated; higher sodium intake increased the risk of fluid retention.

Combination tofacitinib and oral minoxidil treatment for severe alopecia areata. Wambier CG, Craiglow BG, King BA. J Am Acad Dermatol 2019; S0190-9622(19)32688-X.

This retrospective review examined 12 patients with severe AA treated with combination tofacitinib 5–10 mg twice daily and oral minoxidil 2.5 mg dosed daily for female patients and twice daily for male patients (to minimize hirsutism in female patients). Seven patients (58%) achieved at least 75% improvement in baseline SALT score over 4–6 months of treatment with tofacitinib 5 mg twice daily in combination with oral minoxidil.

Topical minoxidil solution (1% and 5%) in the treatment of alopecia areata. Fiedler-Weiss VC. J Am Acad Dermatol 1987; 16: 745–8.

Sixty-six patients applied minoxidil 1% or 5% solution twice daily at night under white petrolatum occlusion. In the minoxidil 5% solution group, 4 of 11 patients (37%) with 25%–74% scalp hair loss at baseline and 2 of 26 patients (6%) with 75%–100% scalp hair loss were 'cosmetic responders'.

Treatment of alopecia areata by anthralin-induced dermatitis. Plewig G, Braun-Falco O. Arch Dermatol 1979; 115: 1254–5.

In this study using 0.5% and 1.0% concentrations of anthralin, the mean time to response was 11 weeks and the mean time to cosmetic response was 23 weeks (range 8–60 weeks). Cosmetic response was achieved in 29% (11/38) of patients with <75% scalp hair loss and in 20% (6/30) of patients with >75% scalp hair loss. Approximately 75% of responders maintained adequate hair growth with continued treatment.

Third-Line Therapies

• Systemic corticosteroids	B
• Ciclosporin	A
• Intralesional autologous platelet-rich plasma	C
• Sulfasalazine	C
• Methotrexate	C
• Azathioprine	C
• Excimer laser	C
• Combination treatment of simvastatin and ezetimibe	C
• Topical/compounded JAK inhibitors	A

High-dose pulse corticosteroid therapy in the treatment of severe alopecia areata. Seiter S, Ugurel S, Tilgen W, et al. Dermatology 2001; 202: 230–4.

In this prospective open study 30 patients with >30% hair loss were treated with three courses of IV methylprednisolone (8 mg/kg) on 3 consecutive days at 4-week intervals. Twelve of 18 AA patients achieved >50% regrowth. None of the four patients with AT, five with AU, or three with ophiasic AA responded. Ten patients who responded retained the growth at 10 months.

Placebo-controlled oral pulse prednisolone therapy in alopecia areata. Kar BR, Handa S, Dogra S, et al. J Am Acad Dermatol 2005; 53: 1100–1.

Forty-three patients were randomized to receive oral prednisolone 200 mg weekly (23) or placebo (20) for 3 months. All patients had more than 40% scalp hair loss, or more than 10 patches of AA, for more than 9 months. Eight of 23 in the treatment group showed more than 30% regrowth, compared with none in the placebo group. More than 60% regrowth occurred in only two patients, both within the treatment group. Side effects occurred in 55% of the treatment group, compared with 11% in the placebo group, although all were temporary.

Pulse methylprednisolone therapy for severe alopecia areata: an open prospective study of 45 patients. Friedli A, Labarthe MP, Engelhardt E, et al. J Am Acad Dermatol 1998; 39: 597–602.

This open prospective study evaluated intravenous pulsed methylprednisolone in 45 severe AA patients (> 30% hair loss) with less than 1 year's duration of recent AA episode. Twenty patients had multifocal disease, 10 had ophiasic, and 15 had AT/AU. A pulse dose of IV methylprednisolone 250 mg twice daily for 3 consecutive days was administered at 1, 3, 6, and 12 months. Patients were treated concomitantly with oral ranitidine 2 days prior to the pulse and continued a week afterwards. Among the 28 patients with regrowth, 11 patients (24%) had 100% regrowth after 6 months and 7 patients (15.5%) had 80%–90% regrowth. A majority of complete responders had patchy multifocal AA, with AT/AU and ophiasic patterns being less responsive.

Cyclosporine for moderate-to-severe alopecia areata: a double-blind, randomized, placebo-controlled clinical trial of efficacy and safety. Lai VWY, Chen G, Gin D, et al. J Am Acad Dermatol 2019; 81(3):694–701.

This double-blind, placebo-controlled trial randomized 32 patients with moderate-to-severe AA to ciclosporin 4 mg/kg daily or placebo for 12 weeks. The average duration of current episode of AA was 6.5 years. Five patients (31.3%) achieved a 50% reduction in SALT score at 3 months in the treatment arm compared to the one patient (6.3%) in the placebo, but this was not statistically significant.

A randomized, double-blind, placebo- and active-controlled, half-head study to evaluate the effects of platelet-rich plasma on alopecia areata. Trink A, Sorbellini E, Bezzola P, et al. Br J Dermatol 2013; 169: 690–4.

Forty-five subjects were randomized to platelet-rich plasma (PRP), triamcinolone acetonide 2.5 mg/mL, or placebo injected intralesionally on three occasions at monthly intervals. Both triamcinolone and PRP led to hair regrowth in AA lesions compared with placebo and compared with the untreated side of the scalp at 2, 6, and 12 months.

Treatment of persistent alopecia areata with sulfasalazine. Rashidi T, Mahd AA. Int J Dermatol 2008; 47: 850–2.

An uncontrolled prospective trial of sulfasalazine 1–3 g daily in 39 patients with AA (SALT scores not provided in the article) demonstrated regrowth of more than 60% in 25.6% of patients and a moderate response in 30.7% of patients. Of those with more than 60% response, two patients demonstrated relapse, and among moderate responders three patients relapsed.

Low-dose systemic methotrexate therapy for recalcitrant alopecia areata. Lim SK, Lim CA, Kwon IS, et al. *Ann Dermatol*. 2017; 29(3): 263–7.

This retrospective review evaluated 29 patients with AA treated with methotrexate monotherapy. At the start of the trial, 23 patients (79.3%) had 25%–49% loss, 4 patients (13.8%) had 50%–74% loss, 1 patient (3.4%) had 75%–99% loss, and 1 patient (3.4%) had AT. Patients were treated with an initial dose of methotrexate of 10 mg weekly, which was increased by 2.5 mg every 2 weeks with a maximum dose of 17.5 mg weekly for a mean duration of 28.1 weeks (range 12–74 weeks). Complete regrowth (100%) was seen in 14 patients (48.3%) and with 75%–99% regrowth in 12 patients (41.4%). Patients with a disease duration (>24 months) demonstrated no response to methotrexate.

Long-term follow-up of the efficacy of methotrexate alone or in combination with low doses of oral corticosteroids in the treatment of alopecia areata totalis or universalis. Chartaux E, Joly P. *Ann Dermatol Venereol* 2010; 137: 507–13.

In 33 patients with AT or AU, complete regrowth was achieved in 8 of 14 patients (57%) who took methotrexate 15–25 mg once weekly and in 12 of 19 patients (63%) who took methotrexate in combination with prednisone 10–20 mg daily. Recurrence of AA occurred in 57% of responders after a decrease in the methotrexate dose or after stopping treatment.

Efficacy and tolerability of methotrexate in severe childhood alopecia areata. Royer M, Bodemer C, Vabres P, et al. *Br J Dermatol* 2011; 165: 407–10.

In this retrospective study of 14 children aged 8–18 with AA, five experienced a clinically relevant therapeutic response. The treatment was administered once weekly with a mean maximal dose of 18.9 mg weekly (0.38 mg/kg) and a mean duration of treatment of 14.2 months.

The authors have subsequently reported that response was maintained in two of the five responders at 6 and 4.3 years after treatment.

Could azathioprine be considered as a therapeutic alternative in the treatment of alopecia areata? A pilot study. Farshi S, Mansouri P, Safar F, et al. *Int J Dermatol* 2010; 49: 1188–93.

A total of 20 patients with minimum 6 months' history of AA were included in this pilot study. Azathioprine was taken at a dose of 2 mg/kg of body weight. The mean regrowth was 52.3% and the mean hair loss before treatment was 72.7%, compared with 33.5% after 6 months of treatment.

Treatment of alopecia areata with simvastatin/ezetimibe. Latouf C, Jimenez JJ, Tosti A, et al. *J Am Acad Dermatol* 2015; 72: 359–61.

A series of 29 patients with AA were treated with simvastatin 40 mg and ezetimibe 10 mg daily. Nineteen completed 24 weeks treatment, and 14 of these were considered responders (20% hair regrowth). Five out of seven responders who discontinued the treatment relapsed, whereas five out of seven who continued for a further 24 weeks maintained the response.

Alopecia areata (AA) and treatment with simvastatin/ezetimibe: experience of 20 patients. Loi C, Starace M, Piracini BM. *J Am Acad Dermatol* 2016; 74: e99–100.

No convincing response was observed in this study, which seems to have sampled a more severely affected population.

Unsuccessful treatment of alopecia areata with simvastatin/ezetimibe: experience in 12 patient. Freitas Gouveia M, Trüeb RM. *Skin Appendage Disord* 2017; 3(3): 156–60.

This prospective observational study evaluated 12 patients (75% female) taking simvastatin/ezetimibe 40/10 mg daily in addition to their ongoing therapy for AA over the course of 6 months. No response was seen in eight (67%) patients, two (24%) had transient regrowth, and two (24%) had <20% regrowth.

Ruxolitinib cream for the treatment of patients with alopecia areata: a 2-part, double-blind, randomized, vehicle-controlled phase 2 study. Olsen EA, Kornacki D, Sun K, et al. *J Am Acad Dermatol* 2020; 82(2): 412–9.

In this 24-week study of ruxolitinib 1.5% cream (applied twice daily) in patients with 25%–100% scalp loss there was no significant difference (defined as 50% SALT score reduction) between the ruxolitinib 1.5% cream and vehicle treatment groups.

11

Amyloidosis

William Y.-M. Tang, Loi-Yuen Chan



Amyloid is an altered, insoluble protein folded in β -pleated sheets, which is deposited extracellularly. Amyloid can accumulate in one or many organs, thereby causing dysfunction. The common amyloid entities are AL (amyloid light chain), AA (amyloid associate), ATTR (transthyretin), and β_2 -microglobulin.

Systemic amyloidosis consists of primary systemic amyloidosis (AL amyloidosis), secondary systemic amyloidosis (AA amyloidosis), dialysis-associated amyloidosis (β_2 -microglobulin), and senile systemic amyloidosis. Skin changes such as petechiae, ecchymoses, waxy papules and plaques, nail dystrophy, and, rarely, blisters may occur. Management of systemic amyloidosis is complex. Treatment of any skin lesions depends on treating the underlying systemic amyloidosis and is beyond the scope of this chapter.

Cutaneous amyloidosis may be primary or secondary. The latter refers to deposition of amyloid within skin tumors such as seborrheic keratosis, porokeratosis, pilomatricoma, and basal cell carcinoma. Primary localized cutaneous amyloidosis is characterized by the deposition of amyloid in the skin without involving any internal organ. It occurs more commonly in Southeast Asian, Chinese, Middle Eastern, and South American people. There are three types of primary localized cutaneous amyloidosis: lichen amyloidosis; macular amyloidosis (keratinic amyloid in both types, derived from degenerated keratinocytes); and nodular amyloidosis (AL amyloid, derived from immunoglobulin light chains). *Biphasic amyloidosis* refers to co-occurrence of macular and lichen amyloidosis in a patient. Approximately 10% of cases of primary localized cutaneous amyloidosis appear to be familial with autosomal inheritance. Mutation in oncostatin M receptor (OSMR) and interleukin-31 receptor A (IL31RA) genes have been reported.

Lichen amyloidosis is a persistent eruption of multiple red-brown hyperkeratotic papules often affecting extensor aspects of extremities, especially the pretibial surfaces. The male-to-female ratio varies among studies from 2:1 and 1:2. Pruritus is present in 60–90% of primary localized cutaneous amyloidosis lesions and the intensity can be quite severe. Small-fiber neuropathy and increased IL-31 receptor expression might play a role in pruritus.

Macular amyloidosis is characterized by an eruption consisting of small, dusky-brown or grayish pigmented macules distributed symmetrically over the upper back and upper arm. It has a reticulated or rippled pattern. Itch is variable, and patients seek medical advice for aesthetic issues.

Nodular amyloidosis is the rarest subtype of primary localized cutaneous amyloidosis. It is characterized by single or multiple waxy, firm, brown or pink nodules involving the legs, head, trunk, arms, and genitalia. It is usually asymptomatic.

Both lichen and macular amyloidosis run a benign course. However, for primary localized nodular amyloidosis, an estimated 7% risk of progression to systemic amyloidosis has been reported. Further, a case of primary localized nodular amyloidosis associated with CREST and Sjögren syndrome was also reported.

MANAGEMENT STRATEGY

Pruritus and unsightly presentation are common in localized cutaneous amyloidosis. Currently, effective treatment of cutaneous amyloidosis is lacking. *Antihistamines* and *topical corticosteroids* are commonly prescribed.

Phototherapy (ultraviolet B or PUVA [psoralen and ultraviolet A]) has been used to treat lichen amyloidosis successfully for relief of pruritus. Oral retinoid (*acitretin* or *alitretinoin*) either used alone or in combination with phototherapy is an effective treatment. Laser treatments reported to be successful in treating cutaneous amyloidosis include carbon dioxide laser, pulsed-dye laser (PDL), and neodymium:yttrium aluminum garnet (Nd:YAG) laser.

Dermabrasion has been successful in treating lichen and nodular amyloidosis. This improves cosmesis and alleviates pruritus but brings accompanying procedural pain and possible skin atrophy. There is an anecdotal report that dermabrasion of lichen amyloidosis under tumescent anesthesia reduced procedural pain.

Other treatment choices include tacrolimus, transcutaneous electrical nerve stimulation (TENS), capsaicin, tocotrienate, *amitriptyline*, and *methotrexate*.

Specific Investigations

- Skin biopsy
- Dermoscopy

All forms of amyloidosis have similar histological findings. On light microscopy, amyloid is characteristically a pink, amorphous material. Special stains, such as Congo red and crystal violet, can highlight the amyloid deposit. Amyloid can be metachromatically stained red by crystal violet staining of an aqueous mount of the specimen. Congo red staining of amyloid shows apple-green birefringence under polarized light microscopy. There are two major dermoscopic patterns characteristic of primary localized cutaneous amyloidosis. The most common dermoscopic finding is a central hub, either white or brown, surrounded by various configurations of pigmentation. For cases of lichen amyloidosis with prominent hyperkeratosis, the central hub is replaced by a scar-like morphology.

First-Line Therapies

- Sedating antihistamines **E**
- Topical high-potency corticosteroids **E**

Although there are no specific studies evaluating the efficacy of antihistamines and topical corticosteroids for treating cutaneous amyloidosis, they are considered first-line therapies. Sedating antihistamines and high-potency steroids help in the relief of pruritus and thinning of lesions.

Second-Line Therapies

- Phototherapy/photochemotherapy **D**
- Oral retinoids **D**
- Laser **D**
- Tacrolimus **E**
- TENS **D**

Successful treatment of lichen amyloidosis with combined bath PUVA photochemotherapy and oral acitretin. Grimmer J, Weiss T, Weber L, et al. Clin Exp Dermatol 2007; 32: 39–42.

Two male patients with lichen amyloidosis over the extensor surfaces of the lower legs were treated with bath PUVA three to four times per week for 11 weeks, plus oral administration of acitretin 0.5 mg/kg/day for 7 months. There was almost complete resolution of skin lesions in both patients. No relapse was observed for 8 months after discontinuation of treatment.

An alternative treatment model: the combination therapy of narrow band ultraviolet B phototherapy and tacrolimus ointment 0.1% in biphasic amyloidosis. Kalkan G, Markoç F, Bas Y. J Pak Med Assoc 2014; 64(5): 579–82.

A 26-year-old woman with biphasic amyloidosis received tacrolimus 0.1% plus narrow band ultraviolet B treatment. Significant improvement was seen at the end of 8 weeks, with remission of pruritus and flattening of papules.

Successful treatment of lichen amyloidosis with oral alitretinoin. Tietze JK, Heppt MV, Flaig MJ, et al. J Eur Acad Dermatol Venereol 2016; 30(5): 884–5.

A 66-year-old patient with biopsy-confirmed lichen amyloidosis, who failed treatments with topical steroids, tacrolimus ointment, emollients, PUVA therapy, and dimethyl sulfoxide (DMSO), was treated with oral alitretinoin 30 mg QD. The pruritus improved and hyperkeratotic papules flattened within 1 month of therapy. The treatment continued for a further 6 months but was then stopped by the patient. The skin condition remained stable over the next 4 months but then deteriorated. Re-implementation of alitretinoin improved the pruritus and the skin lesions. The effect of alitretinoin was attributed to its strong antiinflammatory and immune-modulatory effects.

Alitretinoin treatment of lichen amyloidosis. Koh WS, Oh EH, Kim JE, et al. Dermatol Ther 2017; 30(6).

A 49-year-old woman with atopic dermatitis and biopsy-proven lichen amyloidosis had been treated by oral ciclosporin, antihistamine, and topical steroids without response. A 6-month course of alitretinoin 30 mg daily produced marked improvement in thickness and color of the papules without aggravation of her dermatitis. It was proposed that alitretinoin increases the production of IL-4, thereby exerting an inhibitory effect on growth

of mast cells, and consequently decreasing pruritogenic IL-31, accounting for its antipruritic effect.

Lichen amyloidosis improved by 0.1% topical tacrolimus. Castaneda-Cazares JP, Lepe V, Moncada B. Dermatology 2002; 205: 420–1.

One patient with lichen amyloidosis was treated with tacrolimus 0.1% ointment twice daily. Resolution of pruritus was noted after 2 weeks of therapy and marked improvement of plaque thickness was observed after 2 months.

Transcutaneous electrical nerve stimulation for reduction of pruritus in macular amyloidosis and lichen simplex. Yüsek J, Sezer E, Aksu M, et al. J Dermatol 2011; 38: 546–52.

Eight patients with macular amyloidosis and eight with lichen simplex were treated with high-frequency TENS thrice weekly for 4 weeks, 30 minutes' duration, to areas with most intense itching. All patients with macular amyloidosis and six (75%) with lichen simplex had relief of their pruritus.

Efficacy of different modes of fractional CO₂ laser in the treatment of primary cutaneous amyloidosis: a randomized clinical trial. Esmat SM, Fawzi MM, Gawdat HI, et al. Lasers Surg Med 2015; 47: 388–95.

Twenty-five patients with primary cutaneous amyloidosis (16 macular amyloidosis and nine lichen amyloidosis) were treated by fractional CO₂ laser using superficial ablation and deep rejuvenation to equal areas of randomly assigned lesions after the application of a topical anesthetic cream. Each patient received four sessions with 4 weeks intervals. Both modes yielded significant reduction of pigmentation, thickness, itching, and amyloid deposit. The superficial ablation was better tolerated by patients.

Successful treatment of lichen amyloidosis using a CO₂ surgical laser. Norisugi O, Yamakoshi T, Shimizu T. Dermatol Ther 2014; 27: 71–3.

Two male patients with lichen amyloidosis on their legs unresponsive to topical corticosteroids were treated with CO₂ laser twice a month, using a setting of 10–15 W with a 0.12-second pulse duration, 0.36-second rest duration, and a 5-mm laser spot size. The papules gradually flattened and there was marked reduction of the itching as assessed by the visual analog score (VAS). No complications of the treatment were noted.

Pulsed dye laser for the treatment of macular amyloidosis: a case report. Barsky M, Buka RL. Cutis 2014; 93(4): 189–92.

A 57-year-old man with recalcitrant macular amyloidosis was treated with three treatment sessions of 595-nm PDL (7.5 J/cm², 30/10 millisecond epidermal cooling, 6-mm spot size) at 2-week intervals. Improvement of lesions was noted with each treatment.

532-nm and 1064-nm Q-switched Nd:YAG laser therapy for reduction of pigmentation in macular amyloidosis patches. Ostovari N, Mohtasham N, Oadras MS, et al. J Eur Acad Dermatol Venereol 2008; 22: 442–6.

Twenty patients with histologically confirmed macular amyloidosis were treated with Q-switched Nd:YAG laser with 532 nm in a part of their plaques and with 1064 nm in another part of their plaques. Assessment of efficacy was done by colorimetric scores and digital photographs before laser therapy and 8 weeks after treatment. Both lasers were effective in reducing pigmentation, with the 532 nm more effective; 90% of cases treated by 532 nm had a good or very good response. For the 1064-nm-treated patches, 60% of cases had a good or very good response.

Third-Line Therapies

- Capsaicin
- Tocoretinate
- Amitriptyline
- Methotrexate

E
D
E
E

Successful treatment of lichen amyloidosis using capsaicin 8% patch. Zeidler C, Metze D, Ständer S. *J Eur Acad Dermatol Venereol* 2016; 30(7): 1236–8.

Two male patients with longstanding lichen amyloidosis not responding to topical corticosteroid and systemic antihistamine were treated with an 8% capsaicin patch applied once directly over the itchy area for 60 minutes. Pruritus subsided totally the next day and the improvement lasted for at least 2–3 months. The mechanism of action is due to capsaicin inducing regrowth of anatomically normal nerves and restoring normal neuronal function over the treated areas.

Clinical effect of tocoretinate on lichen and macular amyloidosis. Terao M, Nishida K, Murota H, et al. *J Dermatol* 2011; 38(2): 179–84.

Tocoretinate is a synthetic esterified compound of retinoic acid and tocopherol that is used for treating skin ulcers and improving skin manifestations of scleroderma, morphea, and hypertrophic scars. Ten patients (seven men and three women) with lichen amyloidosis and macular amyloidosis were treated with once-daily topical tocoretinate ointment. The outcome was very good for four, good for two, moderate for two, and poor for two. Normalization of epidermal differentiation via decreased expression

of involucrin and keratins 1 and 10 shown in vivo was thought to be beneficial in the treatment of amyloidosis.

Itch in familial lichen amyloidosis: effective treatment with amitriptyline in two cases. Yew YW, Tey HL. *Dermatol Ther* 2014; 27: 12–5.

Two Chinese male patients with lichen amyloidosis had extensive, pruritic, and hyperkeratotic papules affecting the shins. In both patients, the pruritus was not improved with potent topical steroids and oral antihistamines. Amitriptyline was started at a dose of 10 mg every other night, resulting in significant reduction of itch score and Dermatology Life Quality Index score assessed 3 weeks after commencement of treatment. Itch was well controlled at 8 months and 6 months, respectively. Side effects were minimal. However, the lesions of lichen amyloidosis remained unchanged. The action of amitriptyline may be related to inhibition of the reuptake of 5-HT and noradrenaline in the brainstem and spinal cord and the inhibition of voltage-dependent sodium and potassium channels in peripheral nerves.

Methotrexate for the treatment of recalcitrant primary localized cutaneous amyloidosis: a case series. Stull CM, Tey HL, Yosipovitch G. *Acta Derm Venereol* 2018; 98(9): 900–1.

Two Chinese males (57 years old and 71 years old) with 30 years' history of primary localized cutaneous amyloidosis failing to respond to multiple prior treatments. Significant reduction of itch and resolution of lesions were seen after methotrexate treatment (15 mg weekly for 4 weeks and 10 mg weekly for 8 weeks, respectively). The authors proposed methotrexate as a viable treatment option for longstanding refractory primary localized cutaneous amyloidosis that failed to respond to other treatment modalities.

Androgenetic alopecia

Rodney Sinclair, Wei-Liang Koh



In androgenetic alopecia (AGA), genetically predisposed scalp hair follicles miniaturize in response to androgens. AGA manifests clinically as male pattern hair loss (MPHL) in men and female pattern hair loss (FPHL) in women. Men develop bitemporal recession, diffuse thinning over the frontal scalp, and vertex balding. In women, especially those with long hair, the first symptoms are recurrent episodes of increased hair shedding and a reduction in ponytail volume. These symptoms may precede the visible diffuse thinning over the mid-frontal scalp by many years. The main hormone implicated is dihydrotestosterone (DHT), which is derived from testosterone after activation by 5 α -reductase type II sited at the hair follicle outer root sheath (ORS). In females, factors other than androgens (e.g., estrogens imbalance) may also play a role.

The severity of MPHL is most commonly graded by the Hamilton–Norwood scale. Men who experience early onset hair loss tend to progress more rapidly. In these men, early treatment is likely to have the greatest impact on hair growth. The severity of FPHL is most commonly scored using the Sinclair scale, a validated five-point photographic grading system based on part width.

The diagnosis is usually established clinically, through history and physical examination, including trichoscopy. Differential diagnoses include acute and chronic telogen effluvium, diffuse alopecia areata, and cicatricial alopecia (in particular frontal fibrosing alopecia). Blood tests may be indicated to exclude potential contributory cofactors such as thyroid dysfunction, iron deficiency anemia, or polycystic ovary syndrome. AGA may be associated with metabolic syndrome. Scalp biopsy is only required when a clinical diagnosis cannot be made confidently. In AGA, trichoscopy shows an increased proportion of single hair follicular units, miniaturized vellus-like hairs, and variable hair shaft diameters.

The goals of treatment are to identify and manage any possible triggering factors or comorbidities; reduce hair shedding; arrest progression of the hair loss; and where possible regrow scalp hair.

Specific Investigations

- Full blood count
- Ferritin
- Thyroid function test
- Female androgen screen:
 - Free serum testosterone
 - Sex hormone-binding globulin
 - Dehydroepiandrosterone sulfate (DHEA-S)
 - Prolactin
 - Luteinizing hormone/follicle-stimulating hormone
- Consider metabolic syndrome screening (fasting glucose/lipids)
- Trichoscopy
- Serial photographic documentation
- Scalp biopsy (only if diagnosis is in doubt)

Towards a consensus on how to diagnose and quantify female pattern hair loss – The ‘Female Pattern Hair Loss Severity Index (FPHL-SI)’. Harries M, Tosti A, Bergfeld W, et al. *Eur Acad of Dermatol and Venereol* 2016; 30: 667–76.

This scale looks at three components (Sinclair hair shedding scale, Sinclair hair density scale, and trichoscopy findings) and assigns points for a score range of 0–20 points. Calculation of the severity index can be performed rapidly in an office setting to establish a baseline and to monitor a patient’s progress. Early FPHL can be detected even before the patient developed Ludwig stage I hair loss, and treatment can then be instituted.

MANAGEMENT STRATEGY

A multimodality treatment approach is most likely to increase the chances of treatment success.

Male Pattern Hair Loss

There are two medications currently approved by the US Food and Drug Administration (FDA) for the treatment of MPHL: topical *minoxidil* (2% solution, 5% solution, and 5% foam formulations), and *finasteride* 1 mg once daily. Low-level laser light therapy medical devices also have FDA 510(k) clearance for the treatment of AGA. All other medical treatment options discussed below are used off-label. Treatments need to be continued indefinitely for continued effect.

Topical minoxidil is an effective therapy for AGA, with minimal side effects (e.g., irritant contact dermatitis, which is more likely with solution compared to foam). Minoxidil is converted by sulfotransferase in the ORS of hair follicles into its active metabolite, minoxidil sulfate. Minoxidil prolongs anagen duration, shortens telogen duration, and reverses hair follicle miniaturization. Inter-individual differences in the percutaneous absorption and sulfotransferase levels account for the variable clinical response. For men, the recommended dose of minoxidil 5% solution (50 mg/mL) is 1 mL twice daily. Peak hair growth is seen between 26 and 52 weeks. Some clinical improvement is noted after 2 years of continuous use in 40%–60% of patients. The vertex responds better than the frontal scalp. Continued use is necessary for sustained efficacy, and patients may experience a significant hair shedding

2–3 months after stopping treatment. For topical minoxidil 5% foam, the recommended usage is half a capful twice daily.

Minoxidil has also been used orally off-label. It has a higher patient treatment adherence rate compared to topical application. It is particularly useful for patients who develop contact dermatitis to topical minoxidil. Doses of 0.25–5 mg once daily have been evaluated in various studies for both MPHL and FPHL and found to be useful. Potential side effects are dose-related and include postural dizziness, palpitations, fluid retention, and hypertrichosis. Finasteride is a 5 α -reductase type II isoenzyme competitive inhibitor that is FDA-approved for the treatment of MPHL. Finasteride 1 mg daily reduces serum DHT by 71.4% and scalp DHT by 64.1% after 6 weeks in one study, while serum DHT is reduced by 68.4% after 52 weeks in another. On the other hand, finasteride 5 mg daily reduces serum DHT by 72.2% and scalp DHT by 69.4% after 6 weeks in one study, while serum DHT is reduced by 73% and scalp DHT by 41% after 24 weeks in another. Its actions include reversal of hair follicle miniaturization and prolonging anagen duration. Continuous use for 2 years arrests hair loss in over 95% of men, with 66% achieving moderate hair regrowth and 5% marked hair regrowth. Following discontinuation of finasteride, patients' hair counts return to baseline within 1 year. Finasteride is generally well tolerated. Sexual side effects such as decreased libido, erectile dysfunction, and decreased seminal fluid volume have been reported in 1.5% of men while on treatment, which usually reverse within 3 months of treatment cessation. Other less common side effects include gynecomastia and depression. Dutasteride has also been used off-label to treat MPHL. Dutasteride is a type I and type II 5 α -reductase isoenzyme inhibitor with greater suppression of DHT production than finasteride. Serum DHT is reduced by 92% and scalp DHT by 51% with dutasteride 0.5 mg daily for 24 weeks. In a meta-analysis, dutasteride has been shown to be more effective than finasteride in MPHL treatment. Dutasteride also produces greater adverse sexual side effects than finasteride.

Female Pattern Hair Loss

Topical minoxidil is the FDA-approved treatment for FPHL. Women may use the 2% solution twice daily, or 5% foam or solution once daily. Clinical improvement is seen in up to 80% of patients. Topical minoxidil is well tolerated. Potential side effects include facial hypertrichosis, scalp pruritus, palpitations, postural dizziness, or headaches in women with low blood pressure. While oral minoxidil has been used to treat pre-eclampsia in pregnancy in doses up to 100 mg daily, use of topical minoxidil to treat hair loss is generally not recommended for women while pregnant. Oral minoxidil has also been used off-label to treat FPHL in doses of 0.25–5 mg daily. It is particularly useful for women who develop scalp irritation with topical minoxidil and for women with long hair who find it difficult to adhere to topical therapy.

A number of oral antiandrogens have also been used off-label to treat FPHL. These agents appear to be more effective in women with hyperandrogenism. Androgen receptor antagonists used include spironolactone, cyproterone, flutamide, and bicalutamide. The 5 α -reductase inhibitors finasteride and dutasteride have also been used to treat FPHL; however, they appear to be less effective than androgen receptor antagonist agents. Antiandrogens and 5 α -reductase inhibitors could potentially feminize an unborn male fetus and caution is required when using in women with childbearing potential. Spironolactone has been shown to arrest progression of FPHL in over 90% of women, with approximately 30% having hair regrowth. This can be given at

a dose of 100–200 mg once daily. Potential side effects include breast tenderness, menstrual irregularities, headaches, decreased libido, polyuria, and hyperkalemia. There is no need for routine monitoring of serum potassium levels in a healthy female with no kidney disease. Cyproterone acetate has been used at a dose of 50–100 mg once daily for the first 10 days of the menstrual cycle in premenopausal women and continuously or for 3 weeks per month in postmenopausal women. Potential side effects include weight gain, breast tenderness, and decreased libido. Flutamide is a potent antiandrogen that can be used at doses of 50–250 mg for the treatment of FPHL not responding to other medical treatment modalities. Rare but severe cases of hepatotoxicity have been reported; hence, regular monitoring of liver function tests is mandatory. Other potential side effects include diarrhea and hot flushes. Bicalutamide is an antiandrogen in the same family as flutamide but is less likely to cause hepatotoxicity and has fewer other side effects. Effective doses used include 10–50 mg once daily.

Finasteride has been used off-label in the treatment of FPHL. Studies in premenopausal and postmenopausal women have reported effective dosing between 1.25 mg and 5 mg once daily. Potential side effects include decreased libido and risk of teratogenicity.

Hair restoration surgery is effective in patients who do not respond satisfactorily to medical therapy and in whom the hair loss is advanced. Skilled hair transplant surgeons can create a natural hair line and achieve a cosmetically significant increase in hair density. The technique requires substantial additional training and there is significant doctor to doctor variation in the quality of the outcome.

Other possible adjunctive treatments include *platelet-rich plasma* (PRP) treatment, *low-level laser light therapy*, *microneedling*, *fractional lasers*, *topical prostaglandin analogs*, and *Stemoxidine*. Further research is required to understand the true potential of these modalities. Keratin fiber camouflage powders, hairpieces, and wigs are also helpful for camouflage.

First-Line Therapies for MPHL

• Topical minoxidil	A
• Finasteride	A
• Oral minoxidil	C

Second-Line Therapy for MPHL

• Dutasteride	A

First-Line Therapies for FPHL

• Topical minoxidil	A
• Oral minoxidil	B
• Spironolactone	B
• Cyproterone acetate	B
• Flutamide	B
• Bicalutamide	C
• Finasteride	B

The effectiveness of treatments for androgenetic alopecia: a systematic review and meta-analysis. Adil A, Godwin M. J Am Acad Dermatol 2017; 77: 136–141.e5.

Meta-analysis showed a mean difference of +12.41 hairs/cm² in the topical minoxidil 2% twice-daily group compared with placebo treatment in women. The treatments that showed a

mean difference in hair count for men are finasteride 1 mg daily (+18.37 hairs/cm²), low-level laser light therapy (+17.66 hairs/cm²), topical minoxidil 5% twice daily (+14.94 hairs/cm²), and topical minoxidil 2% twice daily (+8.11 hairs/cm²). All these treatments were superior to placebo ($p < .00001$).

Effectiveness and safety of low-dose oral minoxidil in male androgenetic alopecia. Jimenez-Cauhe J, Saceda-Corralo D, Rodrigues-Barata R, et al. *J Am Acad Dermatol* 2019; 81: 648–9.

In this retrospective review of 41 males with AGA who received oral minoxidil at 2.5–5 mg daily (16 patients received as monotherapy) over a minimum of 6 months, 90.2% of patients had clinical improvement (26.8% with marked improvement) while the remaining 9.8% showed stabilization. For the oral minoxidil monotherapy subgroup, six out of 16 patients had marked improvement. Mild and well-tolerated side effects include hypertrichosis in 10 patients, lower limb edema in two patients, and shedding in one patient.

Minoxidil 1mg oral versus minoxidil 5% topical solution for the treatment of female-pattern hair loss: a randomized clinical trial. Ramos PM, Sinclair RD, Kasprzak M, et al. *J Am Acad Dermatol* 2020; 82: 252–3.

In this first study of its kind, females between 18 and 65 years of age with FPHL were randomized to receive oral minoxidil 1 mg or topical minoxidil 5% once daily for 24 weeks. The primary end point was change in total hair density in parietal area from baseline to week 24. The increase was by 12% in the oral minoxidil group versus 7.2% in the topical minoxidil group, with an overlap in their 95% confidence intervals. For the oral minoxidil group, 4% had pretibial edema and 27% had hypertrichosis. For the topical minoxidil group, 19% had scalp pruritus and 4% had hypertrichosis. Cases of hypertrichosis were mild and well tolerated. There was no hypotension-related event. Oral minoxidil can be considered if a patient cannot tolerate, or is poorly compliant to, topical minoxidil.

Female pattern hair loss: a pilot study investigating combination therapy with low-dose oral minoxidil and spironolactone. Sinclair RD. *Int J Dermatol* 2018; 57: 104–9.

This is an observational pilot study of 100 women with FPHL treated with combination minoxidil 0.25 mg and spironolactone 25 mg oral capsule once daily, followed prospectively for 12 months. Mean reduction in hair loss severity score by Sinclair staging was 0.85 at 6 months and 1.3 at 12 months. Mean reduction in hair shedding score using a six-point visual analog scale was 2.3 at 6 months and 2.6 at 12 months. Mild side effects were seen in eight patients and included postural hypotension, hypertrichosis, and urticaria. This combination treatment appears to be safe and effective for the treatment of FPHL.

The efficacy and safety of dutasteride compared with finasteride in treating men with androgenetic alopecia: a systematic review and meta-analysis. Zhou Z, Song S, Gao Z, et al. *Clin Interv Aging* 2019; 14: 399–406.

This systematic review and meta-analysis looked at three randomized, controlled trials (total 576 men), comparing dutasteride with finasteride. The mean change in total hair count, investigator's assessment of global photographs for the vertex and frontal views, panel global photographic assessment for the vertex and frontal views, and subjects' assessment were significantly better for the dutasteride group (0.5–2.5 mg daily) compared to the finasteride group (1–5 mg daily) after 6 months of treatment. With regard to side effects, there was no significant difference between

dutasteride and finasteride in altered libido, erectile dysfunction, and ejaculation disorders. Long-term efficacy and tolerance were not assessed. Selection and publication bias might have affected study results.

The efficacy and use of finasteride in women: a systematic review. Hu AC, Chapman LW, Mesinkovska NA. *Int J Dermatol* 2019; 58: 759–76.

In this systematic review evaluating the use of finasteride in various conditions, with regard to female pattern hair loss treatment, higher doses of finasteride (1.25–5 mg/day) seem to be more effective for improving hair loss. Lower doses of finasteride at 1 mg/day do not seem to be efficacious.

Androgens in women: hormone-modulating therapies for skin disease. Azarchi S, Bienenfeld A, Lo Sicco K, et al. *J Am Acad Dermatol* 2019; 80: 1509–21.

This is a comprehensive review of the current hormone-modulating therapies for the management of androgen-mediated cutaneous disorders, including FPHL. The level of evidence and strength of recommendations for spironolactone, flutamide, finasteride, and dutasteride were presented.

Safety of oral bicalutamide in female pattern hair loss: a retrospective review of 316 patients. Ferial Ismail F, Meah N, de Carvalho LT, et al. *J Am Acad Dermatol* 2020 [Epub ahead of print].

This retrospective study included 316 females, with a mean age of 48.96 years (range 15–85 years), receiving bicalutamide 10–50 mg once daily for a mean duration of 6.216 months (range 2–69 months) as monotherapy (8 patients) or associated with oral minoxidil (308 patients) and spironolactone (172 patients). Based on photographs, comparison by three independent dermatologists, the mean Sinclair stage at baseline was 2.77. The mean reduction in Sinclair stage was 0.18 at 3 months, 0.47 at 6 months, 0.56 at 9 months, 0.68 at 12 months, and 0.80 at 2 years. The most common adverse effect was mild elevation of liver transaminases in nine (2.85%) patients.

Second-Line Therapies for FPHL/Third-Line Therapies for MPHL

• Hair transplant surgery	A
• Low-level laser light therapy	A
• Platelet-rich plasma	A
• Microneedling	B
• Fractional laser	B
• Topical prostaglandin analogs	A
• Topical Stemoxydine	B

Old friend or new ally: a comparison of follicular unit transplantation and follicular unit excision methods in hair transplantation. Gupta AK, Love RP, Harris JA. *Dermatol Surg* 2020 [Epub ahead of print].

This article gives a good overview with regard to follicular unit excision and follicular unit transplantation, comparing the pros and cons between the two techniques and when to choose one over the other.

Platelet-rich plasma as a treatment for androgenetic alopecia. Gupta AK, Cole J, Deutsch DP, et al. *Dermatol Surg* 2019; 45:1262–73.

The authors performed a meta-analysis to evaluate the effectiveness of PRP as treatment for AGA. The standardized mean difference (SMD) in hair density in patients treated with PRP injections was 0.58 (medium effect) in favor of PRP treatment when compared with baseline (10 studies, pooled $n=165$, $p < .00001$). The SMD was 0.51 (medium effect) in favor of PRP treatment when compared with placebo treatment (6 studies, pooled $n=99$, $p < .0004$). The authors conclude that PRP is beneficial in AGA treatment and recommended that three monthly sessions of PRP be used followed by a 3–6-month maintenance period.

Comparative effectiveness of low-level laser therapy for adult androgenic alopecia: a system review and meta-analysis of randomized controlled trials. Liu KH, Liu D, Chen YT, et al. *Lasers Med Sci* 2019; 34: 1063–69.

In this meta-analysis, quantitative analysis showed a significant increase in hair density for those treated with low-level laser therapy (LLLT) vs. sham group (standardized mean difference (SMD) 1.316, 95% CI 0.993–1.639). Subgroup analysis showed LLLT increases hair growth in both genders, in both comb- and helmet-type devices and in short- (<20 weeks) and long-term (>20 weeks) treatment course. Paradoxically, the subgroup analysis also revealed a more significant increase in hair growth for LLLT versus sham in the low-frequency treatment group (<60 minutes per week) than in the high-frequency group (>60 minutes per week). The explanation remains unclear. The authors conclude that LLLT represents a potentially effective treatment for both MPHL and FPHL, and that the type of LLLT device and LLLT treatment course duration did not affect hair growth effectiveness.

Microneedling for the treatment of hair loss? Fertig RM, Gamret AC, Cervantes J, et al. *J Eur Acad Dermatol Venereol* 2018; 32: 564–9.

This review article summarizes the current literature on microneedling and its role in treatment of hair loss. For AGA, there are a total of five studies (case series to controlled studies) involving microneedling, but mainly in conjunction with other therapies. Microneedling as adjunctive therapy may have a beneficial effect in improving hair density, although further studies are required to refine a standard treatment protocol. Microneedling may help hair regrowth by triggering neovascularization and stimulating the release of growth factors and expression of Wnt proteins. In addition, microneedling can help facilitate penetration of topically applied medications.

Laser-assisted hair regrowth: fractional laser modalities for the treatment of androgenic alopecia. Dabek RJ, Austen WG Jr, Bojovic B. *Plast Reconstr Surg Glob Open* 2019; 7: e2157.

The authors evaluated nine original studies looking at the effect of fractional lasers on hair growth in AGA. Four different types of lasers were identified (fractional ablative CO₂ laser, fractional ablative erbium:YAG laser, fractional non-ablative Er glass laser, fractional non-ablative thulium laser). Only the non-ablative Er glass and thulium lasers have been shown to be effective for hair growth as monotherapy. The fractional ablative CO₂ laser has been shown to be effective in one human study, in conjunction with the use of topical growth factors. Common side effects were mild transient pain and pruritus. In the studies reviewed, the number of treatment sessions ranged from 5 to 15, with a frequency of once weekly to 30-day intervals. The ideal treatment frequency and duration are yet to be determined. Mechanisms of action leading to hair regrowth are likely similar to the effects of microneedling.

A randomized double-blind placebo-controlled pilot study to assess the efficacy of a 24-week topical treatment by latanoprost 0.1% on hair growth and pigmentation in healthy volunteers with androgenetic alopecia. Blume-Peytavi U, Lönnfors S, Hillmann K, et al. *J Am Acad Dermatol* 2012; 66: 794–800.

In this randomized, double-blind, placebo-controlled study, 16 men with mild AGA (Hamilton II–III) were included. Latanoprost 0.1% and placebo were applied daily for 24 weeks on two comparable minizones on the frontotemporal scalp. Measurements on hair growth, density, diameter, pigmentation, and anagen/telogen ratio were performed at intervals. At 24 weeks, an increased hair density (+22% in the entire study population) on the latanoprost-treated site was observed and this was significantly higher compared with baseline and placebo.

Oral presentation: Stemoxydine, a hair kenogen phase shortener, leading to increased hair density. Reygagne P. *Int J Trichology* 2014; 6(3): 113–39.

Stemoxydine, a prolyl-4-hydroxylase competitive inhibitor, has been found in three double-blind, vehicle-controlled, randomized trials involving healthy males aged 18–55 with AGA Grade III to IV (two intraindividual studies on 16 and 23 males, respectively, with 5 days a week application, and one interindividual study on 100 men with daily application) to significantly increase hair density after a 3-month treatment period (additional 4% increase compared to control). Additionally, a significant decrease in the percentage of hairs in kenogen phase was found in one study. Kenogen is a subphase within telogen and may lead to empty follicles. No skin intolerance was recorded in all three studies. The author suggested that Stemoxydine could act as a kenogen phase shortener in AGA, leading to an increase in visible scalp hair density.

Angiolymphoid hyperplasia with eosinophilia

William Y.-M. Tang, Loi-Yuen Chan



Angiolymphoid hyperplasia with eosinophilia (ALHE), also known as epithelioid hemangioma, is an uncommon disease. ALHE is a benign vascular proliferation of unknown etiology with a characteristic component of epithelioid endothelial cells.

Recent literature review shows that ALHE usually affects patients in their third to fourth decade with approximately an equal male to female ratio. Cutaneous lesions present as single or multiple cutaneous papules or subcutaneous nodules, sometimes with inflammatory features. The ear and periauricular area, face, and scalp are most commonly affected. Peripheral blood eosinophilia is noted in 10%–20%. Regional lymphadenopathy is observed in 5%–10%. Although considered benign in nature, the etiology of ALHE is unknown. Neoplastic proliferation of vascular tissue, arteriovenous shunting, or reactive hyperplasia of vascular tissue secondary to trauma (such as ear piercing), infection (human T-lymphotropic virus [HTLV] or herpes virus 8), renin, or hyperestrogenic states have all been proposed as causal factors. ALHE may cause symptoms such as cosmetic disfigurement, bleeding, itch, and pain. It has been associated with various lymphoproliferative conditions, supporting the contention that it may represent a monoclonal T-cell process.

The differential diagnoses of ALHE include Kimura disease, pyogenic granuloma, lymphocytoma cutis, insect bite, sarcoidosis, Kaposi sarcoma, and angiosarcoma. ALHE and Kimura

disease are generally regarded as separate clinicopathological entities. Kimura disease is a chronic inflammatory condition of unknown etiology often affecting young Asian men, and typically presenting as cervical lymphadenopathy and subcutaneous nodules in the head and neck region. However, coexistence of ALHE and Kimura disease in the same patient has been reported.

MANAGEMENT STRATEGY

Spontaneous remission is rare in ALHE. *Complete surgical excision* is preferred for persistent lesions. Recurrence may occur if excision is incomplete. *Laser therapy and radiofrequency ablation* are alternative surgical options. *Cryotherapy*, inexpensive and easily available, is a conventional treatment although reports on its efficacy are lacking. Other treatments reported effective include *topical and intralesional corticosteroids*, *propranolol*, *topical imiquimod*, *topical tacrolimus*, *isotretinoin*, *methotrexate*, *suplatast tosilate*, *intralesional interferon- α_{2b}* , *thalidomide*, and *photodynamic therapy*. Whatever treatment method, recurrence and incomplete resolution remain frequent. Although treatment failure is lowest with excision, it is still noted in about 40.8%.

Specific Investigations

- Histopathology
- Dermoscopy
- Imaging

Histopathological features of ALHE are characterized by a proliferation of blood vessels of varying sizes lined by plump endothelial cells. These histiocytoid endothelial cells show abundant eosinophilic or clear cytoplasm and large vesicular nuclei. The cells are mostly cuboidal with occasional 'hobnailing', which is related to the presence of cytoplasmic vacuoles in these cells, causing cytoplasmic protrusion into lumina. There is also an accompanying perivascular lymphocytic and eosinophilic infiltrate.

Dermoscopy may help to differentiate ALHE from other vascular tumors such as angiosarcoma or Kaposi sarcoma. Under polarized light, ALHE shows polymorphous vascular pattern composed of dotted and linear vessels with a regular distribution over a pale-reddish to light-pink background.

The location and extent of underlying vascular anomalies may be assessed by angiography, angio-computed tomography, and angio-magnetic resonance imaging.

First-Line Therapies

• Surgery	D
• Laser therapy	D
• Corticosteroid, topical or intralesional	E

Epidemiology and treatment of angiolymphoid hyperplasia with eosinophilia (ALHE): a systematic review. Adler BL, Krausz AE, Minuti A, et al. *J Am Acad Dermatol* 2016; 74: 506–12.

After reviewing 416 studies detailing 908 patients, the authors concluded that surgical excision was the best option, albeit suboptimal, with a treatment failure rate of 40.8%, defined as incomplete resolution of disease or recurrence after treatment. Pulsed dye lasers, or other lasers, may represent other reasonable therapeutic options. The treatment failure rates for different lasers ranged from 50% to 66.7%.

Facial angiolymphoid hyperplasia with eosinophilia: sustained remission following treatment with carbon dioxide laser. Ali FR, Madan V. Clin Exp Dermatol 2016; 41: 96–8.

A 35-year-old woman presented with biopsy-proven ALHE lesions on her left temple, which had developed during pregnancy 5 years previously. Ablation with CO₂ laser (15W, 4-mm spot, 10600 nm) was undertaken in three sessions over the course of 8 months, with an excellent clinical response. There was no recurrence after 30 months.

Combined pulsed dye and CO₂ lasers in the treatment of angiolymphoid hyperplasia with eosinophilia. Sagi L, Halachmi S, Levi A, et al. Lasers Med Sci 2016; 31(6): 1093–6.

The authors reported combination of pulsed dye laser and CO₂ laser in treating 14 patients with ALHE. All patients exhibited clinical response after a mean of 2.4 ± 0.4 treatment sessions. They did not recommend surgery for risk of recurrence or development of new lesions and that further surgical excision would result in a new scar.

Angiolymphoid hyperplasia with eosinophilia treated with vascular laser. Alcántara González J, Boixeda P, Truchuelo Díez MT, et al. Lasers Med Sci 2011; 26: 285–90.

The sequential laser combines 595-nm pulsed dye laser (PDL) with 1064-nm Nd:YAG targeting structures at different dermal levels using two different wavelengths. Greater effectiveness and lower recurrence rates are possible with the Nd:YAG laser, which allows the destruction of deeper vessels than PDL. Three patients with ALHE were treated with this sequential laser system. Complete resolution was observed in two of them 3 years after their last treatment; the other patient showed a marked improvement.

Second-Line Therapies

• Propranolol	E
• Imiquimod	E
• Tacrolimus	E
• Isotretinoin	E
• Radiofrequency ablation	E

Propranolol: a novel treatment for angiolymphoid hyperplasia with eosinophilia. Horst C, Kapur N. Clin Exp Dermatol 2014; 39: 810–2.

A 32-year-old woman presented with multiple ALHE lesions in the left periauricular area and scalp vertex. She was started on oral propranolol 40 mg daily. Within 6 weeks, several lesions had decreased in size and all were less erythematous. Propranolol was subsequently stopped within a few months of initiating treatment. Propranolol targets the vascular proliferative element of ALHE. It is also effective in decreasing the vasculature of hemangiomas of infancy.

There are a few reports successfully utilizing topical timolol in combination with other therapies for ALHE.

Angiolymphoid hyperplasia with eosinophilia treated successfully with imiquimod. Isohisa T, Masuda K, Nakai N, et al. Int J Dermatol. 2014; 53: e43–4.

A 49-year-old woman with multiple ALHE lesions in her left postauricular area and external auditory canal was treated with 5% imiquimod cream five times per week. The pruritus improved markedly within 2 weeks. By 22 weeks of treatment, the small lesions had almost completely regressed. The authors suggested that topical imiquimod should be considered for treatment of ALHE because of its excellent cosmetic results and safety record, especially for those with multiple lesions. The underlying

mechanism may be related to the immunomodulating and anti-angiogenic effect of imiquimod.

A case of angiolymphoid hyperplasia with eosinophilia successfully treated with tacrolimus ointment. Mashiko M, Yokota K, Yamanaka Y, et al. Br J Dermatol 2006; 154: 803–4.

A 33-year-old Japanese woman with ALHE over her left ear for a year was treated with 0.1% tacrolimus ointment twice daily. The lesions disappeared within 4 months. Continuous application resulted in no recurrence in 9 months. The underlying mechanism may be due to tacrolimus ointment reducing eosinophil counts in tissue and suppressing eosinophil function.

In another recent report,¹ a patient with periauricular ALHE showing only a partial response to topical corticosteroids was treated with topical tacrolimus. Complete resolution of the lesions was achieved.

Angiolymphoid hyperplasia with eosinophilia: efficacy of isotretinoin? El Sayed F, Dhaybi R, Ammouy A, et al. Head Face Med 2006; 2: 32.

The authors report a 32-year-old man with multiple pruritic lesions of ALHE treated with isotretinoin 0.5 mg/kg/day for 1 year with complete resolution of one of the two scalp nodules. Two lesions on the cheeks and two in the preauricular region that decreased in size, but did not totally resolve, were surgically removed. The success of isotretinoin was due to its antiangiogenic properties via a reduction of vascular endothelial growth factor production by keratinocytes.

Angiolymphoid hyperplasia with eosinophilia treated with a novel combination technique of radiofrequency ablation and sclerotherapy. Khunger N, Pahwa M, Jain RK. Dermatol Surg 2010; 36: 422–5.

Three patients with ALHE were treated with radiofrequency ablation (RFA) after intralesional sclerotherapy with 3% polidocanol. Lesions were mostly treated with cutting plus coagulation mode with an intensity of 4U. One to four sessions of treatment were required to achieve complete response. No recurrence was seen after follow-up period of 6 months to 2 years. The synergistic effect is due to sclerosants treating the deeper vascular component while RFA ablates the lesion.

Angiolymphoid hyperplasia of external ear treated with intralesional radiofrequency ablation. Yadav D, Singh S, Bhari N, et al. BMJ Case Rep 2018 Apr 20. doi: 10.1136/bcr-2017-223447.

The authors reported a single setting of intralesional radiofrequency ablation using 18-G intravenous cannula to treat a 21-year-old woman with multiple ALHE lesions in the right concha. There was near complete flattening of the lesion after 2 weeks and no recurrence at 3 months' follow-up.

Third-Line Therapies

• Methotrexate	E
• Suplatast tosilate	E
• Interferon- α_{2b}	E
• Thalidomide	E
• Photodynamic therapy	E

Angiolymphoid hyperplasia with eosinophilia treated with low-dose methotrexate. Alaidarous A, Bouissou X, Mazereeuw-Hautier J, et al. J Am Acad Dermatol 2015; 1(6): 342–4.

A 31-year-old woman with multiple infiltrative ALHE lesions on the right neck regressed with prednisolone 30 mg daily but recurred shortly upon tapering the dose. She then responded to pulsed dye laser and remained symptom free for 6 years. She then relapsed but this time she failed to respond to pulsed dye laser. Methotrexate (MTX) was started at 15 mg per week for 12 months. She showed significant improvement. The MTX dose was then tailed down and stopped after 10 months. No recurrence was seen in the subsequent 4 months' follow-up. The clinical response was attributed to the antiinflammatory and antiangiogenic effect of methotrexate.

In another report,² a 14-year-old Caucasian female with biopsy-confirmed ALHE presented with a left eyelid swelling, which was shown by computed tomography (CT) to be an infiltrative mass in the left superotemporal orbit. The lesion shrank with high-dose prednisolone, but it was not possible to tail down to daily 20 mg. Methotrexate was added to the treatment regime and stepped up to 20 mg weekly. The steroid was successfully tapered off, after which the patient still remained symptom free. CT scan 6 months after cessation of methotrexate showed only small residual disease.

Angiolymphoid hyperplasia with eosinophilia on the leg successfully treated with T-helper cell 2 cytokine inhibitor suplatast tosilate. Bito T, Kabashima R, Sugita K, et al. *J Dermatol* 2011; 38: 300–2.

Suplatast tosilate is a Th2 cytokine inhibitor that inhibits T-helper cell production of IL-4 and IL-5. This results in reduced eosinophil infiltration and suppression of IgE production in B cells. A 63-year-old man with ALHE on the right calf was treated with suplatast tosilate both orally and topically. The lesions dramatically improved after 4-week administration and completely disappeared 4 months after the beginning of the treatment. No recurrence was observed even 15 months later.

An earlier report on a 32-year-old man with ALHE was successfully treated with suplatast tosilate 300 mg/day.³

Angiolymphoid hyperplasia with eosinophilia responding to interferon-alpha 2B. Oguz O, Antonov M, Demirkesen C. *J Eur Acad Dermatol Venereol* 2007; 21: 1277–8.

Interferon- α is a potential treatment in benign angioproliferative disorders. Local intralesional injection of interferon- α_{2b} was reported effective for a 27-year-old female with occipital lesions of ALHE. Recurrence of lesions 9 years later was noted but this time the response to repeated interferon- α_{2b} treatment was poor.

In another report,⁴ intralesional interferon- α_{2a} caused almost complete resolution of lesions in one patient. However, recurrence of lesions was noted about 1 year after the last injection and no response occurred with the second course of injection.

Successful management of refractory angiolymphoid hyperplasia with eosinophilia with thalidomide. Rongioletti F, Cecchi F, Pastorino C, et al. *J Eur Acad Dermatol Venereol* 2016; 30: 527–9.

A 58-year-old woman with multiple ALHE lesions on occipital area unresponsive to oral propranolol, cryotherapy, topical and systemic steroids, and topical tacrolimus was put on thalidomide 50 mg twice a day for 2 months, then three times daily for 4 months, with progressive decolorization, flattening, and regression of the lesions. After 6 months of therapy, the lesions almost resolved; however, she developed neuropathy, necessitating the discontinuation of thalidomide. No new lesions were noted at 3 months' follow-up. The action of thalidomide is considered to be due to its antiangiogenic, antiinflammatory, and antitumor effects.

Angiolymphoid hyperplasia with eosinophilia: good response to photodynamic therapy. Sotiriou E, Apalla Z, Patsatsi A, et al. *Clin Exp Dermatol* 2009; 34: e629–31.

Photodynamic therapy (PDT) causes suppression of tumor growth by damaging endothelial cells in the tumor neovasculature. A 60-year-old woman with multiple ALHE lesions on the forehead was treated with two sessions of aminolevulinic acid (ALA) PDT, with a 2-week interval: 20% 5-ALA cream occluded from light for 4 hours, followed by exposure to red light (570–670 nm, dose 80 J/cm²) from a non-coherent light source.

Marked improvement, though not complete regression, was achieved 8 weeks after treatment and maintained at 4 months posttreatment. The moderate response achieved in this study could be due to poor penetration of the photosensitizer to the deep part of the lesion.

Combination of electrocoagulation and photodynamic therapy for angiolymphoid hyperplasia with eosinophilia in the external ear. Wu L, Li F, Shi W, et al. *Photodiagnosis Photodyn Ther* 2019; 27: 449–51.

The authors used combined electrocoagulation and PDT to treat a 21-year-old woman and a 55-year-old man. Both presented with more than 1-year history of red, itchy papules and nodules in the posterior auricular area and external auditory canal that persisted despite topical or intralesional corticosteroids and laser therapy. Each received one electrocoagulation to remove the superficial lesions followed immediately by PDT. Each patient received three PDT sessions with an interval of 7–10 days. The lesions completely regressed with no recurrence seen after 12 months' follow-up.

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14

Angular cheilitis

Jessica Shiu, Jennifer K. Chen, Janellen Smith



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Angular cheilitis is a chronic, reactive, inflammatory condition of the oral commissures characterized by atrophy, fissures, crusting, erythema, and scaling. The etiology is often multifactorial, and causes may be mechanical (intertrigo), infectious, nutritional, hormonal, or inflammatory. Angular cheilitis may be a sign of systemic disease.

MANAGEMENT STRATEGY

Successful therapy is based on identifying and correcting any underlying condition(s). The presence of dentures, palatal erythema, and/or edema may suggest candidiasis and denture stomatitis. A pale, depapillated, atrophic tongue suggests iron deficiency. A tender depapillated tongue suggests folate or vitamin B₁₂ deficiency. An eczematous dermatitis of the lower face suggests a staphylococcal infection (infectious eczematoid dermatitis). A history of allergic contact dermatitis may suggest an allergy.

Unilateral lesions are usually short lived and induced by mechanical factors. This has also been reported to be a manifestation of plasma cell cheilitis. Bilateral lesions tend to be chronic and caused by infection or nutritional deficiency and are more likely to be associated with an underlying disease process.

Maceration of the commissural epithelium and adjacent skin is a common, non-infectious cause of mechanical angular cheilitis. Trauma from dental flossing, habitual lip-licking, and excessive salivation all contribute. Periods of oral hydration and then dryness disrupt epithelial integrity, causing fissuring of the commissures. This provides an ideal environment for low-grade candidiasis and infectious eczematoid dermatitis. Other mechanical factors are ill-fitting dentures, loss of vertical dimension of the jaws, sagging skin folds, xerostomia, and perioral dermatitis.

Infectious and systemic causes must be investigated. Angular cheilitis is frequently present in patients with HIV disease, where 10% may have localized candidiasis. Highly active antiretroviral

therapy (HAART) may decrease this incidence. Both *Candida albicans* and *Staphylococcus aureus* can colonize the fissures. Anemia, nutritional deficiencies, Down syndrome, acrodermatitis enteropathica, pemphigus vulgaris, diabetes mellitus, orofacial granulomatosis, and Crohn disease may be present.

Recurrence of angular cheilitis may be prevented by eliminating offending organisms from their reservoirs. Denture stomatitis, candidiasis, and nasal colonization by staphylococci should be investigated. *Topical imidazole creams* after meals and at bedtime may treat candidiasis, whereas *topical mupirocin* is valuable in treating staphylococcal colonization. Dentures should be removed from the mouth nightly and cleansed well before reinsertion in the morning. *New dentures* may restore facial contours, increasing the vertical dimension of the jaws and face. *Injection of fillers* into the commissures may alleviate causative mechanical factors.

Specific Investigations

- Culture or wet mount to evaluate for candidiasis
- Culture for bacteria
- For refractory or recurrent cases, laboratory evaluation should include a complete blood cell count; iron panel; vitamin B, folate, and zinc levels; glucose; hemoglobin A_{1c}; and HIV testing
- Patch testing

Angular cheilitis, part 1: local etiologies. Park KK, Brodell RT, Helms SE. *Cutis* 2011; 87: 289–95.

Angular cheilitis, part 2: nutritional, systemic, and drug-related causes and treatment. Park KK, Brodell RT, Helms SE. *Cutis* 2011; 88: 27–32.

A discussion of the multifactorial nature and evaluation of angular cheilitis.

Epidemiology and etiology of denture stomatitis. Gendreau L, Loewy ZG. *J Prosthodont* 2011; 20: 251–60.

Angular cheilitis. Scully C, Bagan J-V, Eisen D, et al., eds. *Dermatology of the Lips*. Oxford: Isis Medical, 2000; 68–73.

Nickel-induced angular cheilitis due to orthodontic braces. Yesudian PD, Memon A. *Contact Dermatitis* 2003; 48: 287–8.

First-Line Therapies

- Topical miconazole, ketoconazole, or nystatin cream two or three times daily for 2–3 weeks **D**
- Topical polymyxin B or mupirocin ointments, three to four times daily until resolution **D**
- Remove dentures nightly and cleanse overnight with chlorhexidine 2% solution or sodium hypochlorite 0.02% solution. Rinse and air-dry before reinsertion. *Please note that chlorhexidine and nystatin inactivate each other and therefore should not be used together* **D**

Oral candidiasis and angular cheilitis. Sharon V, Fazel N. *Dermatol Ther* 2010; 23: 230–42.

A review of topical and systemic therapy of candidiasis. The authors also recommend prophylaxis with chlorhexidine 0.12% mouthwash in recurrent cases.

Diseases of the lips. Rogers RS III, Bekic M. Semin Cutan Med Surg 1997; 16: 325–36.

Discussion of the evaluation and treatment of angular cheilitis. Evren BA, Uludamar A, Iseri U, et al. Arch Gerontol Geriatr 2011; 53: 252–7.

Discussion of the association between socioeconomic status, oral hygiene practice, denture stomatitis, and oral status in the elderly.

Treatment of angular cheilitis: a narrative review and authors' clinical experience. Cabras M, Gambino A, Broccolletti R, et al. Oral Diseases 2019; 26(6): 1107–15.

Review of recent topical and surgical therapies used in angular cheilitis; most recommendations are based on case reports and case series.

Second-Line Therapies

- Systemic antifungal therapy (fluconazole), 50–100mg daily, 100–200mg three times a week, or 150mg weekly until resolution **E**
- Amphotericin B cream, three to four times daily for 7–14 days **E**

Oral candidiasis and angular cheilitis. Sharon V, Fazel N. Dermatol Ther 2010; 23: 230–42.

Reviews the treatment of candidiasis, especially in the immunocompromised patient.

Third-Line Therapies

- Filler injections **E**
- Prosthodontic evaluation and treatment **E**
- Chewing gum with xylitol or chlorhexidine acetate and xylitol **B**
- Gentian violet 0.5% solution twice daily **E**
- Photodynamic therapy **E**
- Topical ozonized olive oil twice daily **E**

Collagen implant in management of perleche (angular cheilosis). Chernosky ME. J Am Acad Dermatol 1985; 12: 493–6.

Soft tissue augmentation may be used to decrease the depth of the fold at the oral commissures, thus decreasing salivary stasis.

Prosthodontic management of angular cheilitis and persistent drooling: a case report. Lu DP. Compend Contin Educ Dent 2007; 28: 572–7.

The effects of medicated chewing gums on oral health in frail older people: a 1-year clinical trial. Simons D, Brailsford SR, Kidd EA, et al. J Am Geriatr Soc 2002; 50: 1348–53.

A controlled, double-blind trial of 111 dentate patients in residential homes showed significant reductions in angular cheilitis in patients using chlorhexidine acetate/xylitol gums. Patients chewed two pellets for 15 mins twice daily for 2 weeks.

Oral candidiasis and angular cheilitis. Sharon V, Fazel N. Dermatol Ther 2010; 23: 230–42.

Antimicrobial photodynamic therapy to treat chemotherapy-induced oral lesions: report of three cases. Rocha BA, Filho MRM, Simoes A. Photodiagnosis Photodyn Ther 2016; 13: 350–2.

Efficacy of ozonized olive oil in the management of oral lesions and conditions: a clinical trial. Kumar T, Arora N, Puri G, et al. Contemp Clin Dent 2016; 7(1): 51–4.

Clinical trial looking at 50 patients with oral lesions – 10 of those with angular cheilitis reported cure but the study was lacking in adequate controls and clinical and microbiologic details. Patients massaged the oil in affected areas for 1 min twice daily until resolution or for a maximum of 6 months' duration.

Antiphospholipid syndrome

Julia S. Lehman, Mark D.P. Davis



Antiphospholipid syndrome (APS; Hughes syndrome) is associated with recurrent venous and arterial thrombosis in the presence of circulating antibodies against phospholipid-binding proteins. Diagnostic criteria for APS require that patients experience clinical features such as vascular thrombosis (venous or arterial) or pregnancy morbidity (e.g., three or more unexplained consecutive spontaneous abortions before the 10th week of gestation with exclusion of other causes). In addition, patients must harbor at least one serum antiphospholipid (aPL) antibody (i.e., lupus anticoagulant, anticardiolipin, anti- β_2 -glycoprotein 1) on two or more occasions over a 12-week period. Despite the misconception that the presence of circulating aPL antibodies is sufficient for a diagnosis of APS, it is important that patients are not diagnosed with APS based on isolated laboratory test findings, as no laboratory test for APS is entirely specific.

Although cutaneous manifestations of APS are not part of the diagnostic criteria, they may represent the initial presentation of APS. Cutaneous signs result from thrombo-occlusion of the cutaneous vasculature and may include livedo reticularis or racemosa, livedoid vasculopathy (atrophie blanche), anetoderma, superficial thrombophlebitis, or ulceration. Patients with Sneddon syndrome, a condition characterized by cerebrovascular disease in patients with livedo reticularis, may have persistently positive serum aPL. Whether Sneddon syndrome represents a subset of APS is controversial.

MANAGEMENT STRATEGY

While APS may represent a primary condition, it is important to exclude a secondary coagulopathy. Therefore, an investigation into underlying causes or other contributing factors, such as infection, prothrombotic medications (such as oral contraceptives), primary hematologic coagulopathies (e.g., factor V Leiden, prothrombin G20210A gene mutation), and connective tissue diseases (e.g., systemic lupus erythematosus [SLE]), is warranted. Patients should be offered subspecialty referral where available.

Because patients with APS are at increased risk for recurrent thromboembolism, the goal of therapy is thromboprophylaxis. Non-pharmacologic interventions include reduction of other prothrombotic risk factors, such as prolonged immobility and oral contraceptive use. Pharmaceutical interventions should be guided by the patient's age and comorbidities, pregnancy status, presence of correctable prothrombotic factors, and coagulation history. In patients with persistently elevated aPL antibodies but no history of thrombosis (thereby not meeting consensus criteria for APS), aspirin has **not** been shown to be effective in preventing future thromboembolic events. In patients with definitive APS and a history of venous thromboembolism, the mainstay of treatment is long-term warfarin therapy. The optimal duration of warfarin therapy has not been established. Based on limited available data, indefinite treatment with warfarin reduces risk for recurrent thromboembolism without an elevated risk for hemorrhagic complications, compared with treatment discontinuation after 6 months. Decisions regarding termination of warfarin therapy should be individualized. Long-term heparin use is discouraged because of the risk of heparin-induced osteopenia. Early reports of oral direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) are inconclusive, and one randomized controlled study indicated significantly more frequent adverse events in patients treated with rivaroxaban compared with warfarin. Additional randomized controlled studies are ongoing.

Placement of an inferior vena cava filter may be required in patients with recurrent venous thromboembolism to prevent pulmonary embolism.

In patients with APS who have experienced arterial thromboembolism or have developed recurrent thrombosis despite achieving target international normalized ratio (INR) on warfarin, other treatment options must be pursued. These modalities, such as rituximab, intravenous immunoglobulin, and plasmapheresis, address circulating pathogenic antibodies directly rather than the resultant coagulopathy.

In patients with SLE and APS, hydroxychloroquine has been shown to reduce aPL antibody levels and to have intrinsic anticoagulative properties. Potential future APS therapies may include mTOR inhibitors, factor Xa inhibitors, oral direct thrombin inhibitors, and statins. Correction of reversible prothrombotic factors, such as oral contraceptive use and smoking, is advisable.

Warfarin is contraindicated in pregnancy, a particularly high-risk state for patients with APS. Women with APS should be treated with aspirin before conception. Low-molecular-weight heparin may be introduced thereafter.

In patients with acute thrombosis, monitored intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin, with or without subsequent initiation of warfarin, is standard therapy. Thrombolytic medications (e.g., streptokinase, tissue plasminogen activator [tPA]) or percutaneous or surgical interventions may be necessary in life- or limb-threatening thrombotic events. Catastrophic antiphospholipid syndrome (CAPS), the rapid

development (<1 week) of widespread thromboses with end-organ damage (involving ≥ 3 organs, systems, or tissues), requires intensive multidisciplinary interventions to halt disease progression and to reverse end-organ damage. *Plasma exchange* may have a role in the treatment of CAPS.

Specific Investigations

- Inquiry into history of thromboembolism, pregnancy morbidity, and medication use
- aPL antibodies (i.e., lupus anticoagulant, anticardiolipin IgG and IgM antibodies, anti- β_2 -glycoprotein 1 antibodies)
- Coagulopathy screen (i.e., INR, partial thromboplastin time [PTT], protein C, protein S, antithrombin III, prothrombin G20210A gene mutation, antiprothrombin antibodies, factor V Leiden, homocysteine level)
- Screen for underlying prothrombotic disease state (hematology, fasting blood glucose, fasting lipid profile, connective tissue serology, HIV testing, hepatitis serology, malignancy evaluation) and other risk factors, as directed by clinical evaluation

International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). Miyakis S, Lockshin MD, Atsumi T, et al. *J Thromb Haemost* 2006; 4: 295–306.

Consensus guidelines require a history of thromboembolism and documentation of elevated aPL antibodies on at least two occasions separated by at least 12 weeks for definitive diagnosis of APS.

Controversies and unresolved issues in antiphospholipid syndrome pathogenesis and management. Baker WF Jr, Bick RL, Fareed J. *Hematol Oncol Clin North Am* 2008; 22: 155–74.

Thorough investigation into underlying (and potentially correctable) conditions is recommended.

First-Line Therapies

• Observation (persistent aPL elevation but no thromboembolic events)	A
• Long-term warfarin, target INR 2.0–3.0	A
• Correction of reversible prothrombotic factors	B
• Long-term warfarin, target INR >3.0 (recurrent or arterial thrombosis)	B
• Low-molecular-weight heparin and low-dose aspirin (pregnancy)	B
• Heparin followed by warfarin (acute thrombosis)	C
• Hydroxychloroquine with low-dose aspirin (SLE)	D
• Thrombolytic therapy or percutaneous/surgical intervention (critical thrombosis)	E
• Reduction of prothrombotic risk factors, such as prolonged immobilization	E

Aspirin for primary thrombosis prevention in the antiphospholipid syndrome. Erkan D, Harrison MJ, Levy R, et al. *Arthritis Rheum* 2007; 56: 2382–91.

A randomized, double-blind, placebo-controlled trial of aspirin versus placebo in asymptomatic patients with persistently positive aPL antibodies found no benefit of aspirin in primary thromboprophylaxis.

A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome. Crowther MA, Ginsberg JS, Julian J, et al. *N Engl J Med* 2003; 349: 113–8.

A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome. Finazzi G, Marchioli R, Brancaccio V, et al. *Thromb Haemost* 2005; 3: 848–53.

These two randomized, double-blind trials comparing high-intensity warfarin (target INR 3.0–4.0) and moderate-intensity warfarin (target INR 2.0–3.0) in patients with APS found no significant difference in preventing secondary thrombosis between the two treatment regimens.

A systematic review of secondary thromboprophylaxis in patients with antiphospholipid antibodies. Ruiz-Irastorza G, Hunt BJ, Khamashta MA. *Arthritis Rheum* 2007; 57: 1487–95.

In several cohort studies of patients with APS, INR at the time of recurrent thromboembolism on warfarin was <3.0 in 86%. The authors propose that the target INR should be >3.0 in patients with recurrent or arterial thrombosis.

Treatment of antiphospholipid antibody syndrome (APS) in pregnancy: a randomized pilot trial comparing low-molecular-weight heparin to unfractionated heparin. Stephenson MD, Ballen PJ, Tsang P, et al. *J Obstet Gynaecol Can* 2004; 26: 729–34.

In a randomized trial, 28 women with APS received low-dose aspirin and either low-molecular-weight heparin or unfractionated heparin before conception or early in pregnancy. Pregnancy was successful in nine of 13 (69%) women treated with low-molecular-weight heparin and low-dose aspirin and in four of 13 (31%) women treated with unfractionated heparin and low-dose aspirin.

In addition, the obstetrics literature tends to favor low-molecular-weight over unfractionated heparin because of its superior safety profile.

Second-Line Therapies

• Long-term low-molecular-weight heparin (recurrent thrombosis)	D
• Rituximab (SLE)	D
• Hydroxychloroquine (SLE)	E
• Intravenous immunoglobulin (IVIg) (in pregnancy)	E

Rituximab usage in systemic lupus erythematosus-associated antiphospholipid antibody syndrome: a single-center experience. Wang CR, Liu MF. *Semin Arthritis Rheum* 2016; 46(1): 102–8.

A series of six patients with APS treated with rituximab suffered no relapse of thrombosis with a mean follow-up period of over 3 years.

Evidence-based management of thrombosis in the antiphospholipid antibody syndrome. Petri M. *Curr Rheum Rep* 2003; 5: 370–3.

Hydroxychloroquine appears to reduce aPL antibody titers and the risk for recurrent thrombosis in patients with SLE.

An excellent evidence-based review of APS treatments.

A multicenter, placebo-controlled pilot study of intravenous immune globulin (IVIG) treatment of antiphospholipid syndrome during pregnancy. Branch DW, Peaceman AM, Druzin M, et al. *Gen Obstet Gynecol* 2000; 182: 122–7.

In this pilot study of 16 pregnant women with APS, patients were randomized to receive IVIG or placebo. All patients also received heparin and low-dose aspirin. A trend toward decreased fetal growth restriction was observed in the IVIG group compared with the placebo group, but differences were not statistically significant.

Third-Line Therapies

• Plasma exchange (pregnancy)	D
• Placement of inferior vena cava (IVC) filter (medically refractory, recurrent venous thromboses)	D
• Direct oral anticoagulants	D
• Statins (recurrent venous thromboses)	E
• IVIG (recurrent venous thromboses)	E
• Sirolimus (APS-related arterial vasculopathy)	E

Plasma exchange in the management of high risk pregnant patients with primary antiphospholipid syndrome. A report of 9 cases and a review of the literature. Ruffatti A, Marson P, Pengo V, et al. *Autoimmunity Rev* 2007; 6: 196–202.

Nine patients with APS and triple-positive aPL antibodies were treated with plasma exchange for secondary prophylaxis during pregnancy. The authors found that combined plasma exchange and IVIG therapy contributed to favorable pregnancy outcomes in high-risk patients.

Insertion of inferior vena cava filters in patients with the antiphospholipid syndrome. Zifman E, Rotman-Pikielny P, Berlin T, et al. *Semin Arthritis Rheum* 2009; 38: 472–7.

Ten patients with APS who experienced recurrent thrombosis despite warfarin therapy received IVC filters. One patient had a documented pulmonary embolus (PE) after intervention, and two died suddenly of unknown causes (PE could not be excluded). The authors state that the results were suggestive of a protective effect of IVC filters in refractory APS.

Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. Cohen H, Hunt BJ, Efthymiou M, et al. *Lancet Haematol* 2016; 3: e426–36.

This randomized, controlled trial comparing rivaroxaban 20 mg daily with warfarin showed that rivaroxaban was non-inferior. No new thromboses were noted with either treatment.

Incidence of a first thromboembolic event in symptomatic carriers of high-risk antiphospholipid antibody profile: a multicenter prospective study. Pengo V, Ruffatti A, Legnani C, et al. *Blood* 2011; 118: 4714–8.

This randomized controlled trial comparing rivaroxaban 20 mg daily with warfarin showed increased overall events (i.e., thromboses, hemorrhage, death) and arterial events in patients treated with rivaroxaban. No patients experienced venous thromboembolism in the study.

Though some small reports demonstrate benefit of IVIG when used as an additive therapy for secondary prophylaxis, large, well-designed studies are lacking.

The NF- κ B specific inhibitor DHMEQ prevents thrombus formation in a mouse model of antiphospholipid syndrome. Nishimura M, Nii T, Trimova G, et al. *J Nephropathology* 2013; 2: 114–21.

Catastrophic Antiphospholipid Syndrome

• Anticoagulation, systemic corticosteroids, and plasmapheresis or IVIG	D
• Eculizumab	E

Catastrophic antiphospholipid syndrome (CAPS): proposed guidelines for diagnosis and treatment. Asherson RA, Espinosa G, Cervera R, et al. *J Clin Rheumatol* 2002; 8: 157–65.

Based on experience from 130 cumulative cases of CAPS, the authors recommend heparin, systemic corticosteroids, and plasmapheresis in the treatment of CAPS.

Catastrophic antiphospholipid syndrome presenting with multiorgan failure and gangrenous lesions of the skin. Incalzi RA, Gemma A, Moro L, et al. *Angiology* 2008; 59: 517–8.

A 38-year-old woman with CAPS triggered by abrupt withdrawal of systemic corticosteroids recovered completely after treatment with immunosuppressive and antibiotic treatment combined with plasmapheresis.

Brief report: induction of sustained remission in recurrent catastrophic antiphospholipid syndrome via inhibition of terminal complement with eculizumab. Shapira I, Andrade D, Allen SL, et al. *Arthritis Rheum* 2012; 64: 2719–23.

First report of eculizumab's efficacy in CAPS. Larger studies are ongoing.

Aphthous stomatitis

Maryam Liaqat, Justin J. Green



Recurrent aphthous stomatitis (RAS) is the most common cause of oral ulceration, affecting 5–25% of the population. It is characterized by the recurrence of one or more painful, shallow, sharply margined ulcerations with a fibrinous base and surrounding erythematous halo on mobile oral mucosa. Three main types include minor, major, and herpetiform aphthae, which differ in size, duration, number, potential for scarring, and location of ulcerations. The etiology remains unclear; however, genetic predisposition (with at least 40% of patients having a positive family history), nutritional deficiencies, infections, hormonal alterations, immunodeficiency, and environmental agents have been implicated. It is important to differentiate aphthae from other causes of mucosal ulcers. The differential diagnosis would include viral and bacterial infections (herpes simplex virus [HSV], Epstein-Barr virus, cytomegalovirus, varicella zoster virus, Coxsackie virus, syphilis, gonorrhea, tuberculosis), erythema multiforme, lichen planus, autoimmune bullous diseases (pemphigus vulgaris and cicatricial pemphigoid), contact dermatitis, chronic ulcerative stomatitis, and trauma. Malignancy and systemic vasculitis must also be considered in lesions that are not self-resolving.

MANAGEMENT STRATEGY

The therapeutic approach to aphthae is dependent on the frequency of recurrence, duration, and severity of symptoms. In addition, underlying hematologic abnormalities, nutritional deficiencies, and medications should be considered as causative agents, as well as systemic disorders such as Crohn disease, Behçet disease, mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome, cyclic neutropenia, Sweet syndrome, reactive arthritis, HIV infection, and autoinflammatory syndromes such as periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome (PFAPA syndrome). Stress is also thought to play a role in exacerbation of the disease. Unfortunately, because there is no curative treatment to date, the emphasis of treatment is on measures that may afford symptomatic relief and decrease occurrence, without causing significant adverse effects.

Topical corticosteroids are the mainstay of therapy. For milder disease, corticosteroids such as *fluocinonide* can be used. Superpotent corticosteroids such as *clobetasol* or *halobetasol* are appropriate for more severe episodes. Most practitioners suggest the use of topical therapy after meals. These can be applied in equal parts with an occlusive agent such as *Orabase* for better adherence. Drug delivery can be enhanced by cotton-tip applications for 30 seconds and avoidance of eating and drinking for 30 minutes after application. Initial concentrations of 3–10 mg/mL of *intralesional triamcinolone acetonide* are helpful for major aphthae. Repeat injections over 2- to 4-week intervals are suggested. *Dexamethasone elixir* 0.5 mg/5 mL three times daily used as a mouthwash or *beclomethasone dipropionate* aerosol spray can target ulcers on the soft palate or oropharynx. Elixirs can be combined with *sucralfate* or *Kaopectate* to improve adhesion to ulceration. When used for less than 3 weeks, systemic absorption and hypothalamic-pituitary-adrenal axis suppression are unlikely.

RAS that elicits severe pain may require intermittent *systemic corticosteroid therapy*. Prednisone 1 mg/kg (40–60 mg) daily can be given with a 2-week taper or as 'burst therapy' for shorter periods. Concomitant therapy with topical corticosteroids may be helpful. *Thalidomide* 50–200 mg daily is the most effective steroid-sparing agent. It is also the only Food and Drug Administration (FDA)-approved treatment for major aphthae in HIV-positive patients. *Dapsone* 100 mg daily, *pentoxifylline* 400 mg three times daily, and *clofazimine* 100 mg daily may also lead to suppression of aphthae. Oral *rofecoxib* 50 mg on the first day and 25–50 mg per day on the following days or oral *tinidazole* 1 g per day may have some benefit. *Anti-tumor necrosis factor (TNF)-α* therapies may be effective in recalcitrant cases. The use of oral phosphodiesterase-4 inhibitor apremilast in treatment of recalcitrant RAS has also been proposed. Those patients who require suppressive therapy but cannot tolerate the side effects of systemic agents can try medications such as *topical ciclosporin* rinse 500 mg/5 mL three times daily, or *interferon-α_{2a}* 1200 IU daily as a 1-minute rinse and swallow.

Application of *amlexanox 5% paste* four times daily has been shown to reduce aphthous ulcer healing time, and the application of amlexanox OraDisc four times daily to prodromal areas of the buccal mucosa has shown promise in the prevention of recurrent minor aphthous ulceration.

Lidocaine gel or spray, *dyclonine*, *diphenhydramine* (12.5/5 mL), or *benzocaine* are helpful for pain reduction. Patients must avoid desensitization of the entire oral vault, which may lead to self-induced trauma. A compounded *anesthetic mouthwash* (aluminum hydroxide-magnesium hydroxide, diphenhydramine, and lidocaine) has better mucosal adherence. Systemic *nonsteroidal antiinflammatory drugs (NSAIDs)*, *sucralfate suspension*, 0.2% *chlorhexidine gluconate* mouthwash, *triclosan*, or *tetracycline suspension* (250 mg/5 mL) may provide pain relief and reduce healing time, although these are less effective than potent topical corticosteroids. Bioadhesives, such as *carboxymethylcellulose*, provide a protective film and may reduce healing time. Use of laser therapies, including CO₂ laser, Nd:YAG, and low-level light therapies in RAS, has also been shown to improve symptoms caused by consumption of food, beverages, and brushing of teeth.

Trigger avoidance can be useful. Predisposing factors include food (nuts, chocolate, tomatoes, citrus fruits, and spices), alcohol and carbonated beverages, trauma, menstruation, and stress. A *food diary* may be of value in identifying an offending agent. Certain medications, such as β-blockers, NSAIDs, and antioxidants, as well as sensitivity to sodium lauryl sulfate found in toothpaste, may contribute to the recurrence of aphthae. *Hormonal therapy* may alleviate RAS associated with menstruation. *Reassurance* of

the benignity of this condition is paramount, and *relaxation techniques* or *biofeedback* can be discussed if stress is found to be a significant trigger.

Specific Investigations

- Complete blood count
- Vitamins B₁, B₂, B₆, and B₁₂; folate, zinc, and iron levels
- Culture/polymerase chain reaction of aphthae to exclude HSV
- Consider HIV testing

Aphthous ulcers. Messadi DV, Younai F. *Dermatol Ther* 2010; 23: 281–90.

Review article containing the summary of possible etiologies and clinical presentations of aphthae, differential diagnosis, and treatment options.

Oral mucosal disease: recurrent aphthous stomatitis. Scully C, Porter S. *Br J Oral Maxillofac Surg* 2008; 46: 198–206.

Review article highlighting possible etiologies and differential diagnosis of RAS. This article recommends checking complete blood count, folate, iron studies, and B₁₂, as well as excluding infections or systemic diseases that may include aphthae-like ulcerations, namely Behçet disease and HSV.

Haematological deficiencies in patients with recurrent aphthosis. Compilato D, Carroccio A, Calvino F, et al. *J Eur Acad Dermatol Venereol* 2010; 24: 667–73.

Thirty-two patients with RAS and 29 healthy controls were subjected to hematologic investigations. Deficiencies were noted in 56.2% of RAS patients and in 7% of controls. All patients with a negative family history of RAS showed complete remission after replacement therapy, whereas patients with a family history of RAS showed reduction in frequency and severity. The authors recommended that routine screening for serum iron, folic acid, and vitamin B₁₂ deficiencies should be performed.

First-Line Therapies

• Vitamin and mineral deficiency replacement	A
• Topical corticosteroids	A
• Amlexanox 5% paste	A
• Intralesional corticosteroids	B
• Tetracycline suspension	A
• Antimicrobial mouth rinses	A
• Sucralfate	A
• Hydroxypropyl cellulose/carboxymethylcellulose	C
• Herbal supplements	D

Urban legends: recurrent aphthous stomatitis. Baccaglini L, Lalla RV, Bruce AJ, et al. *Oral Dis* 2011; 17: 755–70.

Review article examining several myths about aphthous ulcerations, with specific emphasis of literature review of treatments in the last 6 years. The authors concluded that low-dose topical tetracyclines and amlexanox showed possible benefit.

Topical corticosteroids in recurrent aphthous stomatitis. Systematic review. Quijano D, Rodriguez M. *Acta Otorrinolaringol Esp* 2008; 59: 298–307.

This is a systematic review of published literature evaluating the effectiveness of topical corticosteroids in treating RAS. The

authors were able to show a trend toward reduced healing times and decreased pain but commented on the lack of high-quality experiments in the literature.

Efficacy and safety of dexamethasone ointment on recurrent aphthous ulceration. Lui C, Zhou Z, Lui G, et al. *Am J Med* 2012; 125: 292–301.

This study is a randomized, double-blind, placebo-controlled, parallel, multicenter clinical trial, which showed that dexamethasone 0.1% ointment three times a day for 5 days safely reduced the size and duration of aphthae compared with placebo.

Amlexanox for the treatment of recurrent aphthous ulcers. Bell J. *Clin Drug Investig* 2005; 25: 555–6.

A review of four double-blind, randomized controlled trials (RCTs) indicating that amlexanox 5% paste up to four times per day significantly reduced ulcer size compared with placebo.

Double-blind trial of tetracycline in recurrent aphthous ulceration. Graykowski EA, Kingman A. *J Oral Pathol* 1978; 7: 376–82.

A suspension of tetracycline 250 mg/5 mL was used four times daily in patients with RAS. The suspension was held in the mouth for 2 minutes and then swallowed. This study found that tetracycline therapy significantly reduced ulcer duration, size, and pain, but did not alter the recurrence rate.

Other studies using tetracycline or its derivatives (topically or orally) have drawn similar conclusions.

Chlorhexidine gluconate mouthwash in the management of minor aphthous ulceration: a double-blind, placebo-controlled cross-over trial. Hunter L, Addy M. *Br Dent J* 1987; 162: 106–10.

This crossover study included 38 patients who used 0.2% chlorhexidine gluconate mouthwash three times daily for 6 weeks. The total number of days with ulcers was significantly reduced, and the interval between successive ulcers was increased.

Gel and mouthwash formulations of 0.1% chlorhexidine have also been efficacious. Chlorhexidine mouthwash can stain teeth.

Effect of an antimicrobial mouth rinse on recurrent aphthous ulcerations. Meiller TF, Kutcher MJ, Overholser CD, et al. *Oral Surg Oral Med Oral Pathol* 1991; 72: 425–9.

A 6-month double-blind study compared Listerine antiseptic and a hydroalcoholic control used as a vigorous mouthwash twice daily. The duration of ulcers and pain severity were significantly reduced in the Listerine group. Both the Listerine group and the control group experienced a reduced incidence of ulcers.

Mouth rinses containing triclosan reduce the incidence of recurrent aphthous ulcers (RAU). Skaare AB, Herlofson BB, Barkvoll P. *J Clin Periodontol* 1996; 23: 778–81.

In a double-blind crossover study, 0.15% triclosan mouthwash caused a significant reduction in the number of ulcers during the experimental period. Compared with the 7.8% ethanol and triclosan formulation, the efficacy of the mouthwashes was reduced when propylene glycol or a higher concentration of ethanol (15.6%) was used as a solubilizing agent.

Sucralfate suspension as a treatment of recurrent aphthous stomatitis. Rattan J, Schneider M, Arber N, et al. *J Intern Med* 1994; 236: 341–3.

Sucralfate applied four times daily to ulcers was found to be superior to antacid (aluminum hydroxide and magnesium

hydroxide) and placebo with regard to duration of pain, reduction in healing time, response to first treatment, and duration of remission. The 2-year prospective, randomized, double-blind, placebo-controlled, crossover trial included 21 patients unresponsive to conventional therapy.

A randomized, placebo-controlled, double-blind study of sucralfate applied four times daily to oral and genital ulcerations of Behçet disease resulted in reduced frequency, healing time, and pain in oral ulcerations, and reduced healing time and pain in genital ulcers.

Performance of a hydroxypropyl cellulose film former in normal and ulcerated mucosa. Rodu B, Russell CM. Oral Surg Oral Med Oral Pathol 1988; 65: 699–703.

Zilactin, which contains hydroxypropyl cellulose, led to pain relief after an acidic challenge followed by rechallenge.

Orabase, which contains carboxymethylcellulose, has been beneficial in trials when combined with topical corticosteroids, possibly due to its adhesive properties.

Topical insulin-liposomal formulation in management of recurrent aphthous ulcers: a randomized placebo-controlled trial. El-Wakeel NM, Dawoud MHS. J Invest Clin Dent 2019; 10: e12437.

Eighty participants with minor aphthous ulcers were randomly divided to receive either topical insulin-liposomal gel or placebo gel (once daily) for 6 days. Test group showed a significant decrease by time in pain score.

Second-Line Therapies

• Oral corticosteroids	A
• Colchicine	A
• Thalidomide	A
• Dapsone	A
• Zinc sulfate	A
• Low-level laser therapy	B
• Omega 3	B
• Apremilast	B

Systemic interventions for recurrent aphthous stomatitis (mouth ulcers). Brocklehurst P, Tickle M, Glenny AM, et al. Cochrane Database Syst Rev 2012; 9: CD005411.

This review article includes a total of 25 trials, 22 of which were placebo controlled and eight made head-to-head comparisons. A total of 21 interventions were assessed. The interventions included immunomodulators such as clofazimine, colchicine, prednisone vs. an uncertain category, which included homeopathy, tetracycline, vitamin B₁₂, and propolis. The main conclusions were that no single treatment was found to be effective; therefore, no recommendations regarding best systemic intervention for RAS were made. The reviewers' primary concern was the methodologic rigor of the trials and the high risk of bias.

Systemic treatment in severe cases of recurrent aphthous stomatitis: an open trial. Mimura MA, Hirota SK, Sugaya NN, et al. Clinics 2009; 64: 193–8.

An open, 4-year clinical trial of 21 patients with RAS treated with thalidomide (100 mg/day), dapsone (100 mg/day), colchicine (1.5 mg/day), and pentoxifylline (400 mg three times a day). Thalidomide was the most efficient and well tolerated. Dapsone and colchicine provided good results; however, dapsone was not well tolerated. Pentoxifylline was mildly effective.

Comparison of colchicine versus prednisolone in recurrent aphthous stomatitis: a double-blind randomized clinical trial. Pakfetrat A, Mansourian A, Momen-Heravi F, et al. Clin Invest Med 2010; 33: E189–95.

In this double-blind RCT, 34 patients with RAS were split into two groups: prednisolone 5 mg daily or colchicine 0.5 mg daily for 3 months. Both medications were equally effective in reducing pain, recurrence, size, and number of aphthae, although colchicine had a higher rate of side effects.

Clinical, historic, and therapeutic features of aphthous stomatitis: literature review and open trial employing steroids. Vincent SD, Lilly GE. Oral Surg Oral Med Oral Pathol 1992; 74: 79–86.

'Burst therapy' with prednisone 40 mg once daily for 5 days, followed by 20 mg every other day for 1 week, in addition to topical triamcinolone acetonide 0.1–0.2% four times daily, led to complete or partial control of aphthae in 12 of 13 patients.

Effects of colchicine treatment on mean platelet volume and the inflammatory markers in recurrent aphthous stomatitis. Seçkin HY, Bütün I, Baş Y, et al. J Dermatolog Treat 2016; 27(4): 389–91.

RAS is associated with increased inflammatory markers. Fifteen male and 45 female RAS patients who were taking colchicine were investigated retrospectively. The whole blood parameters of the patients were observed before starting colchicine treatment and in the third month of colchicine treatment. It was determined that colchicine lowers the levels of neutrophil-lymphocyte ratio, white blood cell count, and red cell distribution width. Furthermore, no changes were seen on mean platelet volume, platelet-lymphocyte ratio, and hemoglobin.

Thalidomide for the treatment of oral aphthous ulcers in patients with human immunodeficiency virus infection. Jacobson JM, Greenspan JS, Spritzler J, et al. National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group. N Engl J Med 1997; 336: 1487–93.

Fifty-seven HIV-positive patients were included in this double-blind, randomized, placebo-controlled study of thalidomide 200 mg daily versus placebo as therapy for oral aphthous ulcers in HIV-infected patients. Sixteen of 29 patients in the thalidomide group (55%) had complete healing of their aphthous ulcers after 4 weeks, compared with only two of 28 patients in the placebo group (7%).

Refractory aphthous ulceration treated with thalidomide: a report of 10 years' clinical experience. Cheng S, Murphy R. Clin Exp Dermatol 2012; 37: 132–5.

Retrospective review of 15 patients treated with thalidomide after failing topical and oral steroids. Out of 15 patients, 14 showed improvement with thalidomide; however, nine patients showed a decline in their nerve conduction study, independent of dose. Despite these findings only three patients stopped the medication, and the patient with the largest decline in nerve conduction (80%) opted to continue thalidomide rather than risk recurrence of the ulcers.

The therapeutic and prophylactic role of oral zinc sulfate in management of recurrent aphthous stomatitis (RAS) in comparison with dapsone. Sharquie KE, Najim RA, Al-Hayani RK, et al. Saudi Med J 2008; 29: 734–8.

In this double-blind, placebo-controlled study of 45 patients with RAS, patients were treated with zinc sulfate 150 mg twice

daily, dapsone 50 mg twice daily, and glucose 250 mg daily as placebo. Results showed that both zinc sulfate and dapsone had significant therapeutic effects in decreasing ulcer size. They concluded that zinc sulfate had much more rapid and sustained action.

Recurrent aphthous stomatitis and pain management with low-level laser therapy: a randomized controlled trial. Albrektson M, Hedström L, Bergh H. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2014; 117: 590–4.

This study is a randomized, single-blinded, placebo-controlled trial conducted with low-level laser therapy (wavelength, 809 nm; power, 60 mW; pulse frequency, 1800 Hz; duration, 80 seconds per treatment; dose, 6.3 J/cm²) in 40 patients with RAS. Improvement was assessed with visual analog scale (VAS) and patients' experience of eating, drinking, and brushing teeth. Compared with placebo there was a statistically significant decrease in VAS score, as well as the other symptoms noted.

Efficacy of omega-3 in treatment of recurrent aphthous stomatitis and improvement of quality of life: a randomized, double-blind, placebo-controlled study. El Khouli AM, El-Gendy EA. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2014; 117: 191–6.

A parallel-design, double-blind, placebo-controlled study was conducted on 50 participants divided into treatment to receive omega-3 (1 g three times daily) and control group for 6 months. Results indicated a significant reduction in the number of ulcer outbreaks, the average level of pain, and the duration of ulcer episodes per month starting in the third month of treatment.

Apremilast in treatment-refractory recurrent aphthous stomatitis. Kolios Antonios GA. *N Engl J Med* 2019; 381: 1975–7.

A retrospective series of five patients with RAS who were treated with apremilast (standard induction followed by a dose of 30 mg twice daily) for 2–24 months (mean, 11.4 months). A complete response (PGA [Physician Global Assessment] score of 0) was observed in four of the five patients, and the fifth patient had a PGA score of 1 (almost clear).

Apremilast is FDA approved for the treatment of the oral ulcers associated with Behçet disease. A multicenter, randomized placebo-controlled trial showed apremilast decreased pain, decreased number of ulcers, and increased proportion of patients with ulcer-free complete response.

Third-Line Therapies

• Pentoxifylline	A
• Clofazimine	B
• Ascorbate (vitamin C)	C
• Vitamin B ₁₂	A
• Topical ciclosporin	D
• Oral interferon- α_{2a}	C
• CO ₂ laser	D
• Penicillin G potassium troches	A
• TNF- α inhibitors	D
• Silver nitrate	B
• Montelukast	A

A randomized, double-blind, placebo-controlled trial of pentoxifylline for the treatment of recurrent aphthous stomatitis. Thornhill MH, Baccaglini L, Theaker E, et al. *Arch Dermatol* 2007; 143: 463–70.

Twenty-six patients were randomized to pentoxifylline 400 mg three times daily or placebo. Patients taking pentoxifylline had less pain, smaller ulcers, fewer ulcers, and more ulcer-free days, but this was not statistically significant. However, smaller median ulcer size in the treatment group was statistically significant. Adverse events were common and included dizziness, headaches, gastrointestinal symptoms, and fatigue.

According to the study, patients taking the active drug stated that if it were shown to be effective in the treatment of aphthous ulcers, they would not want to use it because of the side effects.

Topical cyclosporine for oral mucosal disorders. Eisen D, Ellis CN. *J Am Acad Dermatol* 1990; 23: 1259–64.

Four of eight patients with severe aphthous stomatitis obtained nearly complete suppression of ulcers during an 8-week course of topical ciclosporin 500 mg/5 mL, swish and rinse three times daily.

Chronic recurrent aphthous stomatitis: oral treatment with low-dose interferon alpha. Hutchinson VA, Angenend JL, Mok WL, et al. *Mol Biother* 1990; 2: 160–4.

Oral administration of interferon- α_{2a} (1200 IU daily) resulted in remissions of aphthae within 2 weeks of initiating therapy compared with no improvement in the placebo group. The placebo group was then treated similarly with interferon- α_{2a} leading to complete remission of their aphthae.

Treatment of recurrent aphthous stomatitis with Er,Cr:YSGG laser irradiation: a randomized controlled split mouth clinical study. Yilmaz HG, Albaba MR. *J Photochem Photobiol B* 2017; 170: 1–5.

A randomized, controlled split mouth clinical study aimed to investigate the efficacy of Er,Cr:YSGG laser irradiation on pain reduction and healing rate of RAS. Forty patients were enrolled. In the placebo group, RAS lesions were irradiated with the same device without laser emission. Laser application may be appropriate to reduce pain and also accelerate the healing of RAS.

Managing aphthous ulcers: laser treatment applied. Colvard M, Kuo P. *J Am Dent Assoc* 1991; 122: 51–3.

Pain alleviation was observed in 16 of 18 patients after CO₂ laser therapy of minor aphthae.

Evaluation of penicillin G potassium troches in the treatment of minor recurrent aphthous ulceration in a Chinese cohort: a randomized, double-blinded, placebo and no-treatment-controlled, multicenter clinical trial. Zhou Y, Chen Q, Meng W, et al. *Oral Surg Oral Med Oral Radiol Endod* 2010; 109: 561–6.

A randomized, double-blinded, control trial in 258 non-penicillin-allergic Chinese patients was performed with subjects split between placebo, treatment, and no-treatment groups. Patients treated with penicillin G potassium troches showed significant objective decreased ulcer size and subjective decrease in pain.

Efficacy and safety of TNF- α inhibitors in refractory primary complex aphthosis: a patient series and overview of the literature. Sand FL, Thomsen SF. *J Dermatolog Treat* 2013; 24: 444–6.

In this case series, a total of 18 patients were treated with etanercept, adalimumab, infliximab, or golimumab for frequent recurrent oral and genital aphthae or continuous aphthous stomatitis. Of these patients, 16 had complete or almost complete clearance of the aphthosis, whereas five had adverse reactions.

Treatment of recurrent aphthous stomatitis with clofazimine. de Abruë MA, Hirata CH, Pimentel DR, et al. Oral Surg Oral Med Oral Pathol Radiol Endod 2009; 108: 714–21.

In this randomized, controlled, partially blinded study, clofazimine (100 mg daily for 30 days, then 100 mg every other day) and colchicine (0.5 mg three times a day) were investigated for 6 months in the treatment of RAS. Patients taking clofazimine showed significant improvement to colchicine at the second, third, fifth, and sixth months of therapy.

The effect of ascorbate on minor recurrent aphthous stomatitis. Yasui K, Kurata T, Yashiro M, et al. Acta Paediatr 2010; 99: 442–5.

In this study, 16 patients with minor RAS were given daily vitamin C (2000 mg/m²) for 3 months. Treatment was then discontinued for 3 months and then restarted for another 3 months. Patients experienced a significant decrease in stomatitis during treatment months compared with months without treatment.

Effectiveness of vitamin B₁₂ in treating recurrent aphthous stomatitis: a randomized, double-blind, placebo-controlled trial. Volkov I, Rudoy I, Freud T, et al. J Am Board Fam Med 2009; 22: 9–16.

In this randomized, double-blind, placebo-controlled trial, 58 patients with RAS were split into treatment groups of 1000 mcg of sublingual vitamin B₁₂ and placebo. No patients had baseline B₁₂ levels less than 150 pg/mL. The treatment group had significantly fewer outbreaks than the controls, regardless of baseline B₁₂ level.

Of note, there have also been several studies in the literature negating the benefits of vitamin replacement.

Silver nitrate cautery in aphthous stomatitis: a randomized controlled trial. Alidaee MR, Taheri A, Mansoori P, et al. Br J Dermatol 2005; 153: 521–5.

Ninety-seven patients with painful minor aphthae were randomized to receive one stick application of silver nitrate cautery or placebo. After 1 day, a statistically significant reduction in severity of pain was shown. Silver nitrate did not prolong or shorten healing time examined after 7 days. No side effects were noted.

The authors note that the treatment is simple and cost effective for patients, with few recurrences.

Pilot study on recurrent aphthous stomatitis (RAS): a randomized placebo-controlled trial for the comparative therapeutic effects of systemic prednisone and systemic montelukast in subjects unresponsive to topical therapy. Femiano F, Buonaiuto C, Gombos F, et al. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010; 109: 402–7.

In this double-blind, randomized, placebo-controlled trial of 60 patients with minor RAS, patients were split equally into treatment groups of prednisone 25 mg daily tapered over 2 months, 10 mg montelukast daily for 1 month, then every other day for the second month, and cellulose (placebo). Both interventions significantly reduced number of lesions and pain relief compared with placebo; however, prednisone was more effective than montelukast. This suggests montelukast may be a safer alternative to prednisone.

Successful management of refractory pediatric-onset complex aphthosis with lenalidomide. Kalampokis I, Rabinovich CE. J Clin Rheumatol 2014; 20: 221–3.

A severe case of pediatric-onset complex aphthosis treated with lenalidomide for nearly 3 years with significant subjective and clinical improvement and no adverse effects.

Atopic dermatitis

Jennifer Mancuso, Lawrence F. Eichenfield



Atopic dermatitis (AD) is a chronic, relapsing, and intensely pruritic dermatosis that develops most commonly during early infancy and childhood and is, in most cases, associated with a personal or family history of atopy (allergic rhinitis, asthma, or eczema). It is associated with abnormalities in skin barrier function and immune dysregulation. Skin involvement ranges from acute weeping and crusted areas of eczema to papular lesions or lichenified plaques. Management involves education on appropriate skin care and avoidance of triggers, topical therapies, phototherapy, and systemic agents, including newer biologics and small molecules as well as traditional immunosuppressive medications.

MANAGEMENT STRATEGY

Successful AD therapy considers the patient's age and needs, the extent and localization of AD at presentation, and the overall disease course. Other factors to consider include previous response to treatment, disease persistence, frequency of flares, and susceptibility to, and past history of, infection (especially those due to *Staphylococcus aureus* and herpes simplex virus). The goals of management are to educate patients and caregivers about the disease, promote excellent skin care, reduce the degree and frequency of flares, minimize signs and symptoms, monitor medication quality/quantity of use, and, if possible, modify the overall disease course and impact on comorbidities.

Interventional Education

Education concerning chronic disease management is a core part of therapy. Learning modalities beyond in-office disease

education may be useful, including handouts, internet-based written materials, instructional videos, and other media. Comprehensive multispecialty 'eczema clinics' offer intensive education as a component of long-term AD management. This model, with its longer appointments, focused educational curricula, patient support networks, and the ability to elicit patient and family feedback, parallels strategies shown to be effective for managing asthma, diabetes, and other chronic diseases. Shared decision making – where therapeutic options and the rationales for recommending them, along with weighing the risks and benefits, are discussed with patients to arrive at therapeutic strategies – is an evolving method thought to improve patient outcomes (e.g., www.eczemacenter.org; www.nationaleczema.org; www.eczema.org).

Skin Care

Excellent skin care remains a cornerstone of management. Emollients improve the xerosis and skin barrier dysfunction associated with AD and may improve pruritus and spare the use of prescription antiinflammatory medications. With little evidence to recommend the use of one emollient or moisturizer over another, patient and caregiver preference should be considered, with product selection based on the premise that 'an emollient that is applied works better than one that remains on a shelf.' Very occlusive ointments may not be tolerated during the summer months or in humid climates because of interference with the function of eccrine sweat ducts and the induction of folliculitis; in these situations, a cream may be a more practical choice. It is best to avoid preparations that contain topical sensitizers such as fragrance, neomycin, benzocaine, etc. Emollients and moisturizers should be applied after any topical pharmacologic therapies to allow active medications to penetrate the skin with full effect.

The value of bathing and the frequency with which it should be undertaken remain controversial, though most experts believe that daily bathing with application of emollients to follow is well tolerated and may be beneficial. The chief benefits of bathing include cleansing, removing irritants and allergens, debridement of infected eczema, improved penetration of topical therapies, and skin hydration (when post bath emollients are used to 'lock in' moisture). Bathing without use of emollients may dry the skin and disrupt the stratum corneum. Recent data demonstrate twice daily soaking baths followed by immediate application of an occlusive moisturizer (soak-and-seal method) is superior at improving disease severity in moderate-to-severe pediatric AD over twice-weekly soak-and-seal baths.

Loss of function mutations in the filaggrin gene can lead to increased transepidermal water loss and an increased risk of developing AD, as well as asthma, allergies, and herpes simplex virus infections. Data regarding transepidermal water loss suggest that the frequency of application of emollients or moisturizers may be more important than timing the application to coincide strictly with bathing (the traditional 'soak-and-seal' approach); this finding remains to be confirmed in larger, more controlled studies.

Wet wraps with topical corticosteroids are a useful tool in the intensive treatment of severe AD and/or disease that is refractory to standard topical therapies. They may increase skin hydration, serve as an effective mechanical barrier to scratching, and act as an occlusive layer that promotes penetration of topical corticosteroids into the skin, thereby increasing the amount of medication delivered to the most severely affected areas. Temporary systemic

bioactivity of the corticosteroids and potential hypothermia are concerns.

Topical Therapies

Topical corticosteroids remain the first-line therapy for inflammation and pruritus associated with AD that are unresponsive to good skin care and moisturizers. Variations in corticosteroid-prescribing habits (e.g., quantity, frequency, and duration of therapy) are common even among dermatologists. Some clinicians start treatment with higher potency topical corticosteroid preparations in order to induce remission, followed by a relatively quick tapering down of potency as the dermatitis improves. Alternatively, other clinicians use short bursts of higher potency corticosteroids followed by moisturizers alone until relapse occurs. Another treatment regimen advocates more prolonged treatment with less potent steroid preparations. For persistent or frequently flaring eczema, use of moderate-to-higher potency topical corticosteroid (TCS) to induce remission followed by several times a week 'proactive' treatment to recurring areas is commonly utilized. Drug-specific FDA indications and an expanding body of clinical trial data should help guide clinicians when educating and instructing patients on TCS usage.

Non-steroid topicals, including topical calcineurin inhibitors (TCIs) tacrolimus and pimecrolimus, and phosphodiesterase (PDE)-4 inhibitor crisaborole, have the important advantage of not being associated with skin atrophy. Current indications for TCI use are as 'second-line therapy for the short-term and non-continuous chronic treatment' of mild-to-moderate AD (pimecrolimus) or moderate-to-severe AD (tacrolimus) in non-immunocompromised adults and children 'who have failed to respond adequately to other topical prescription treatments for AD, or when those treatments are not advisable.' Patients who are especially likely to benefit include those in whom the clinical course of AD is marked by steroid tachyphylaxis (versus simple non-compliance), disease persistence, and/or frequent flares, which would otherwise result in an almost continuous need for TCS treatment. TCIs may also be specifically indicated in sensitive thin skin areas, such as around the eye, face, neck, and genital area where local safety and systemic absorption are of special concern.

The safety and efficacy of tacrolimus and pimecrolimus have been studied in multiple short (6 weeks) and long-term (longer than 2 years) clinical trials. Data from these trials demonstrate that pimecrolimus reduces the number and severity of flares, extends the period between major flares, and reduces pruritus and other cutaneous signs associated with AD. Prospective studies spanning up to 10 years have investigated the clinical use of TCI in pediatric populations and have suggested that the use of TCI is not associated with systemic immunosuppression or an increased risk of cancer of any type, including skin cancer and lymphoma; nor does it appear to affect the delayed-type hypersensitivity response. In most countries, regulatory agencies do not recommend the use of TCI in patients under 2 years of age. Pimecrolimus cream 1% and tacrolimus ointment 0.03% is indicated for adults and children aged 2–15 years, whereas tacrolimus ointment 0.1% is indicated only for adults.

'Proactive' treatment with intermittent TCS or TCI is recommended for disease maintenance for persistent or frequently flaring disease. Long-term, intermittent maintenance use of tacrolimus ointment in patients with stabilized AD has been shown to significantly increase the period between disease exacerbations and the total number of disease-free days compared with vehicle.

Despite the frequency of use, the incidence of side effects in these studies was generally low and most commonly included transient application-site stinging.

Phosphodiesterase (PDE)-4 inhibitors are a newer class of therapy for AD. Studies have shown the topical agent crisaborole to be an effective therapy for AD and it is indicated in patients 3 months of age and older with mild-to-moderate AD. Similar to the TCIs, studies have demonstrated crisaborole to be safe for long-term use without risk of skin atrophy. The incidence of side effects is low, with application-site pain being the most common but often transient effect.

Careful supervision, combined with appreciation of the risk-benefit profiles of moisturizers, topical corticosteroids, TCIs, and topical PDE-4 inhibitors, allows for individualized and optimized patient care. Treatment should be readily adjusted on an 'as-needed' basis that takes advantage of available therapeutic modalities. For children with severe flares, this may mean using short-term bursts of mid- to high-potency topical steroids – with or without wet wraps – instead of relying on long-term use of less potent agents. Close reexamination of the patient at regular intervals to evaluate the efficacy and tolerability of local and systemic therapies is warranted. Once control of a flare is achieved, topical corticosteroids can be tapered to a lower-potency agent and/or from daily to intermittent (e.g., twice- or thrice-weekly) application. Transition to, or incorporation of, non-steroid agents may also be considered. There is a positive risk-to-benefit ratio of proactive, scheduled (biweekly), topical antiinflammatory agents applied to frequently relapsing areas in preventing AD flares. During quiescent periods, therapy should shift to a less intense regimen with a focus on maintenance and proper skin care at its core. The use of TCIs or topical PDE-4 inhibitor monotherapy to control flare recurrence while limiting patients' extended exposure to corticosteroids is supported by some physicians.

Other Treatment Considerations

Total avoidance of environmental aeroallergens is almost impossible and may not significantly influence AD; however, avoidance of known triggers is a reasonable approach. Food allergy is more common in children with AD than without and, in a subset of individuals, clinically relevant food allergy may exacerbate atopic dermatitis. US national guidelines for food allergy recommend that evaluation for milk, egg, peanut, wheat, and soy food allergies are considered in children less than 5 years old with moderate-to-severe AD if the child has a reliable history of an immediate reaction after ingestion of any of these foods, or the child has persistent AD in spite of optimized management and topical therapy. In addition, recent national guidelines recommend that children in the first year of life with severe AD and/or egg allergy have early evaluation with serum immunoglobulin E (IgE) or skin prick tests and also recommend early feeding of peanuts as a method to decrease development of peanut allergy. Specific serum IgE and skin prick tests have high rates of false positives and poor predictive value for food allergy diagnosis, and severely restrictive diets based on positive tests rather than true allergy can be harmful and may result in nutritional deficiencies. Thus, positive IgE testing should be verified through controlled food trials or other means unless there is a reliable history of an immediate allergic reaction after ingestion of a specific food. Maternal dietary restrictions during pregnancy and lactation are not considered to have a significant role in the development of AD and are generally not recommended.

Although they do not appear to have direct effects on the pruritus associated with AD, sedating systemic antihistamines such as hydroxyzine and diphenhydramine may be useful in improving sleep in flaring patients. This practice has not been evaluated rigorously in large, randomized, double-blind, placebo-controlled trials, and the drowsiness that may be associated with daytime use is a legitimate concern for school-age children. Second-generation, non-sedating antihistamines are less useful in managing AD, but may benefit patients with allergic triggers and, with chronic use, are suggested in some studies to reduce the rate of progression to other atopic disease (the atopic march). It is important to note that topical antihistamines are not recommended because of potential cutaneous sensitization.

Studies have shown reduced nocturnal melatonin secretion associated with sleep disturbance and more severe AD disease. Melatonin is a hormone important in sleep regulation that is secreted by the pineal gland, and supplementation with oral melatonin has been used to treat insomnia and jet lag. A randomized control trial showed that melatonin supplementation was associated with a decrease in sleep-onset latency as well as small improvements of the severity of AD compared to placebo.

Patients may have sudden exacerbations of AD due to overgrowth of *Staphylococcus aureus* – honey-colored crusting, folliculitis, and pyoderma are signs of overt infection. Topical and/or oral antibiotic therapy – typically of short duration to avoid the development of bacterial resistance – may be useful. Skin cultures and sensitivity testing can be considered before initiating treatment, as methicillin-resistant *S. aureus* (MRSA) may be an important pathogen in some patients. Recurrent, deep-seated *S. aureus* infections should raise the possibility of an immunodeficiency syndrome such as hyper-IgE syndrome or dedicator of cytokinesis 8 (DOCK8) deficiency.

The addition of antiseptics to bath water, for example, diluted bleach baths ('like swimming in pool water'), may help reduce the number of local skin infections and the need for systemic antibiotics in AD patients with heavily colonized and/or superinfected skin, although there is controversy about its effectiveness and mechanism of action. A bleach bath can be prepared by mixing one-quarter to one-half a cup of sodium hypochlorite 6% solution (chlorine liquid bleach) in a bathtub full of lukewarm water, or a solution made of one teaspoon of bleach per half gallon of water; the goal is to create a modified Dakin-like solution with a final bleach concentration that approximates 0.005%. Standardly soaking or spraying the mixed solution onto the skin for 5–10 min, with or without a rinse with fresh water, is followed by patting dry and applying topical therapy and/or emollient/moisturizer. For added convenience, newer formulations of bleach-like products are specially formulated and available as body washes, sprays, or gels.

Eczema herpeticum may be easily misdiagnosed as bacterial superinfection and presents a serious risk in patients with widespread AD. Patients can present with multiple vesiculopustular lesions and painful 'punched-out' erosions that fail to respond to oral antibiotics. Document herpes infection before treatment via culture and/or direct fluorescent antibody, and initiate antiviral therapy as soon as possible. Intravenous treatment is indicated in cases of severe disseminated eczema herpeticum. Oral acyclovir (or equivalent dosage of other anti-herpetic medications) may be useful with herpes simplex confined to the skin; for adults 400 mg three times daily for 10 days or 200 mg four times daily for 10 days usually provides a sufficient dosage.

Antifungal therapy may reduce the severity of AD lesions exacerbated by *Pityrosporum* species, particularly in the seborrheic

areas of the skin and scalp. Patients with documented dermatophyte infection or IgE antibodies to *Pityrosporum* may benefit from a trial of topical or systemic antifungal therapy.

Due to the immunologic and microbiologic relationships between the skin, gut, and airways, there has been great interest in probiotics. As the findings to date on their utility in preventing or modifying AD are conflicting, the long-term significance of probiotics in the treatment of atopic dermatitis warrants further investigation.

Although the exact mechanism of action is unknown, phototherapy in AD is thought to suppress proinflammatory cytokines (such as IL-2 and IL-12) and induce T-cell apoptosis. Broadband ultraviolet (UV) B, broadband UVA, narrowband UVB (311 nm), UVA1 (340–400 nm), and combined UVA-B phototherapy have been reported to be useful for widespread or recalcitrant disease. Photochemotherapy with psoralen and UVA light may be indicated in severe cases. Multiple treatments are usually required to be effective, and this can be inconvenient for patients and their families, depending on location and accessibility to a suitable light source. Side effects can include skin pain, erythema, pruritus, and pigment changes. Likewise, UV radiation may increase the long-term risk of premature skin aging and cutaneous malignancies. Shielding and appropriate eye protection may help minimize unnecessary exposure.

Systemic Therapies

There are rapid changes in therapeutic options for systemic treatment of AD with the approval of specific biologic agents and the study of multiple new biologic and other agents.

Systemic corticosteroids are often prescribed for acute AD exacerbations, though there are limited data on efficacy or comparative data with other medications. The temptation to use systemic corticosteroids can be significant, given the dramatic clinical improvement that can occur. The propensity to flare with abrupt discontinuation of treatment and the well-known associated systemic side-effect profile, however, suggest that systemic corticosteroids should be reserved for 'crisis cases' – and, even then, used with the intent to bridge to another systemic agent or phototherapy.

Dupilumab is a fully human IgG4 monoclonal antibody and acts as an antagonist to the IL-4 receptor α , targeting IL-4 and IL-13, and has been shown to be efficacious in treating moderate-to-severe AD. It is currently FDA approved for patients 6 years of age and older with moderate-to-severe AD. It also has received FDA approval for asthma in individuals 12 years and older, chronic rhinosinusitis with nasal polyps in adults 18 years and older, and is in clinical trials for eosinophilic esophagitis. Dupilumab for adults and pediatric patients 60 kg or greater is administered as a loading dose of 600 mg given by subcutaneous injection, followed by a maintenance dose of 300 mg every 2 weeks. The recommended dosing for other pediatric patients is 15 to <30 kg: 600 mg loading dose and 300 mg q4 weeks; 30 to <60 kg: 400 mg loading dose and 200 mg q4 weeks. Dupilumab has been shown to significantly improve clinical and patient-oriented outcomes including EASI (Eczema Area and Severity Index), SCORAD (SCORing Atopic Dermatitis), DLQI (Dermatology Life Quality Index), and itch Numeric Rating Scale scores. Concomitant use of topical steroids with dupilumab provides further benefit and several studies demonstrate the efficacy of combination therapy. One study showed the efficacy of dupilumab with concomitant topical steroid in treating adults with AD with an inadequate response or intolerance to ciclosporin.

The safety profile of dupilumab is superior when compared to the immunosuppressants listed below, and laboratory monitoring is not required. There were no significant serious safety concerns in phase III clinical trials; common adverse effects in clinical trials included rhinosinusitis, upper respiratory tract infections, and skin infections; however, these occurred with similar frequency between treatment and placebo groups. One study showed that dupilumab is associated with a decreased risk of skin infections and eczema herpeticum in adults with moderate-to-severe AD. Most studies have shown higher rates of noninfectious conjunctivitis incidence in dupilumab-treated patients with AD than in placebo groups. This adverse effect may be managed with topical lubricants or in conjunction with Ophthalmology with topical eye-drop corticosteroids, tacrolimus, ciclosporin, or lifitegrast.

Ciclosporin is a calcineurin inhibitor that blocks activation of T lymphocytes and reduces the transcription of cytokines, including IL-2, shown to be involved in the pathogenesis of AD. It may be used as a short-term treatment or as a bridge between other steroid-sparing alternatives. Ciclosporin is typically dosed at 2.5–5 mg/kg/day, and a response may be seen in 2–3 weeks. Alternatively, some experts prefer dosing ciclosporin microemulsion at 3 mg/kg/day in children, or 150 mg (low dose) or 300 mg (high dose) in adults, as the microemulsion offers more predictable absorption. Flares can occur after discontinuation of therapy; therefore, gradual tapering or use of another immunosuppressive for maintenance therapy should be considered. The safety, efficacy, and risks of ciclosporin are well documented in both adults and children, and treatment with this agent is associated with reduced skin disease and an improved quality of life. Hypertension and renal toxicity, as well as concerns about malignancy, are limitations to long-term therapy. Continuous therapy beyond 1 year is not recommended, and it is unknown how many short courses may be given safely. Blood pressure, complete blood cell count, renal and hepatic function tests, magnesium, and uric acid should be monitored.

Methotrexate is a folic acid analog that inhibits dihydrofolate reductase and interferes with DNA synthesis and lymphocyte proliferation leading to antiinflammatory effects; however, its greatest advantage may be that the relatively low doses used for skin disease appear less immunosuppressive than other AD systemic therapies. An open-label, prospective, 24-week trial of adults with AD demonstrated a response plateau at approximately 12 weeks with little additional improvement at doses greater than 15 mg weekly. Alternatively, some experts dose methotrexate at 2.5 mg daily for 4 days per week. A retrospective review of children showed that AD was well controlled with effective dosing of 0.5–0.8 mg/kg/week (either as a single weekly dose or divided 3 or 4 days/week). There is a long history of methotrexate use in pediatric and adult inflammatory disease. Nausea and liver function abnormalities/hepatotoxicity may limit dosing. Pulmonary toxicity may be another potential concern. It is unclear what role folic acid supplementation plays in the treatment of AD with methotrexate.

Azathioprine, a 6-mercaptopurine analog that inhibits purine synthesis and demonstrates cytotoxic and immunosuppressive properties, can be an effective monotherapy for AD. Marrow suppression and liver toxicity are major concerns; blood cell counts and liver function tests should be monitored closely. One in 300 individuals is homozygous for low metabolic activity alleles that correlate with higher risk of bone marrow suppression; azathioprine should be dosed according to thiopurine methyltransferase (TPMT) genotype/levels. Dosing in children and adults is

generally 2.5 mg/kg/day in patients with normal TPMT activity and adjusted to lower doses for carriers of mutant alleles and/or definite intermediate TPMT levels (e.g., 1.0 mg/kg/day). Higher doses, up to 5 mg/kg/day, have been utilized in children. Very low or absent TPMT activity indicating homozygous TPMT mutations may be associated with life-threatening myelotoxicity. Drug hypersensitivity and gastrointestinal disturbances have been reported. An increased risk of malignancy is recognized with long-term use to prevent transplant rejection or manage inflammatory bowel disease.

Mycophenolate mofetil (MMF) has a moderately good safety profile and represents a possible therapeutic alternative for severe, refractory AD. It is an inhibitor of inosine monophosphate dehydrogenase involved in de novo purine synthesis and has been used as an immunosuppressant in organ transplantation. Several adult studies have demonstrated efficacy at doses up to 2 g daily. A retrospective review of MMF as monotherapy in 14 pediatric AD patients showed it to be safe and effective at doses of 40–50 mg/kg/day in younger children (presumably due to increased surface area-to-volume ratios) and 30–40 mg/kg/day in adolescents, with maximal effect after 8–12 weeks of therapy. Patients should be monitored for leukopenia and anemia, and drug levels may be increased in the setting of renal insufficiency. MMF has been loosely linked to herpes retinitis, dose-related bone marrow suppression, and increased infection. Further prospective controlled studies are needed for this promising therapy.

The field of AD therapies has entered a new era in which novel topical and systemic agents are rapidly being developed, including biologics and small molecules that selectively target atopic dermatitis-causing pathways. While dupilumab is the prototype of AD-targeted therapies, many others are emerging in clinical trials. Novel topical therapies include topical Janus kinase (JAK) inhibitors and aryl hydrocarbon agonists, among others. Evolving systemic therapies for AD include oral Janus kinase (JAK) inhibitors, including baricitinib, abrocitinib, upadacitinib, anti-IL-13 biologics including lebrikizumab and tralokinumab, anti-IL-22 monoclonal antibody fezakinumab, and anti-IL-31 biologics including nemolizumab, among others.

Referral, Quality of Life Issues, and Educational Resources

Referral to a pediatric dermatologist or an adult dermatologist/AD specialist may help with comprehensive management of skin care and barrier repair, and consideration of systemic therapies. Allergy testing is not generally a first-line referral recommendation in the routine evaluation and treatment of uncomplicated AD. However, consultation with an allergist can be useful when proper skin care alone is not effective and/or when the clinical picture hints strongly at specific allergic triggers. Referral to immunology or gastroenterology is warranted if underlying systemic infections are frequent or when eosinophilic gastroenteritis/esophagitis becomes a concern in younger children with concomitant failure to thrive. Patch testing may be considered to exclude a coexisting contact allergen to, for example, a steroid or emollient constituent in recalcitrant disease.

Emotional stress can exacerbate AD in some patients who may respond to frustration, anxiety, embarrassment, or other psychologically stressful events with a perceived increase in pruritus and subsequent scratching. This may be particularly important in the adolescent population, where even very mild skin

disease may be considered 'disfiguring.' AD has been shown to be associated with several mental health comorbidities including attention-deficit hyperactivity disorder, anxiety, and depression. Psychosocial evaluation and counseling should be considered in families where emotional triggers appear to function as obstacles to disease management, or where quality of life is clearly affected. Therapeutic education has been shown to be beneficial in managing AD and may be accomplished through extended in-office discussion, written handouts, eczema 'school programs,' and/or web resources, which include video training modules (e.g., www.eczemacenter.org). Families may also benefit from support groups such as the US National Eczema Association (www.nationaleczema.org) and the UK National Eczema Society (www.eczema.org).

Hospitalization

Erythrodermic AD patients, those with suspected widespread superinfection, or those with severe recalcitrant disease may benefit from hospitalization.

Specific Investigations

In selected cases only:

- Skin biopsy: especially in adult onset AD and when cutaneous T-cell lymphoma is being considered as an alternative diagnosis
- Quantification of IgE, IgA, IgM, and IgG levels
- Specific serum IgE assays for food or environment allergens and oral food challenges
- Patch testing for allergic contact dermatitis: allergic contact dermatitis may be both an alternative diagnosis and exacerbator of AD
- Bacterial cultures and sensitivities
- HIV enzyme-linked immunosorbent assay (ELISA) screening

Translating atopic dermatitis management guidelines into practice for primary care providers. Eichenfield LF, Boguniewicz M, Simpson E, et al. *Pediatrics* 2015; 136: 554–65.

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Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. Eichenfield LF, Tom WL, Chamlin SL, et al. *J Am Acad Dermatol* 2014; 70: 338–51.

Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. Eichenfield LF, Tom WL, Berger TG, et al. *J Am Acad Dermatol* 2014; 71: 116–32.

Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. Sidbury R, Davis DM, Cohen DE, et al. *J Am Acad Dermatol* 2014; 71: 327–49.

Guidelines of care for the management of atopic dermatitis: section 4. Prevention of disease flares and use of adjunctive therapies and approaches. Sidbury R, Tom WL, Bergman JN, et al. *J Am Acad Dermatol* 2014; 71: 1218–33.

This comprehensive set of guidelines discusses the management of AD – from diagnosis to treatment and prevention – in both adult and pediatric populations.

Current guidelines for the evaluation and management of atopic dermatitis: a comparison of the Joint Task Force Practice Parameter and American Academy of Dermatology guidelines. Eichenfield LF, Ahluwalia J, Waldman A, et al. *J Allergy Clin Immunol*. 2017; 139(4S): S49–57.

This review highlights the basic principles of AD management and therapies from the distinct perspectives of the allergist and dermatologist.

Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. Boyce JA, Assaad A, Burks AW, et al. *J Allergy Clin Immunol* 2010; 126: S1–58.

This includes consensus definition for food allergy and discussion of comorbid conditions and IgE-mediated and non-IgE-mediated reactions to food.

Addendum guidelines for the prevention of peanut allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases-Sponsored Expert Panel. Togias A, Cooper SF, Acebal MLA, et al. *Pediatr Dermatol* 2017; 34: e1–21.

This paper presents guidelines for infants at various risk levels for the development of peanut allergy, including the highest-risk group, and infants with severe AD and/or egg allergy. Topics addressed include the definition of risk categories, appropriate use of testing (specific IgE measurement, skin prick tests, and oral food challenges), and the timing and approaches for introduction of peanut-containing foods.

Head-and-neck dermatitis: diagnostic difficulties and management pearls. Maarouf M, Saberian C, Lio PA, et al. *Pediatr Dermatol* 2018; 35: 748–53.

This article reviews head-and-neck dermatitis, including diagnostic gaps, differential diagnosis, and management techniques.

First-Line Therapies

• Education	A
• Emollients*	A
• Topical corticosteroids	A
• Proactive therapy	A
• Wet wraps	B

*The choice of using an emollient or a barrier cream should be made based on personal preference

Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: multicentre, randomized controlled trial. Staab D, Diepgen T, Fartasch M, et al. *Br Med J* 2006; 332: 933–8.

A comparison of children with AD whose parents had received 6 weeks of intensive AD education versus those children whose parents received no education. The investigators taught age-appropriate interventions to the parents. Patients in the 'treatment' group demonstrated significantly improved subjective quality-of-life scores and objective measures of eczema severity over the 12-month period.

Psychological and educational interventions for atopic eczema in children. Ersser SJ, Latter S, Sibley A, et al. *Cochrane Database Syst Rev* 2007; 3: CD004054.

Emollients improve treatment results with topical corticosteroids in childhood atopic dermatitis: a randomized comparative study. Szczepanowska J, Reich A, Szepietowski JC. *Pediatr Allergy Immunol* 2008; 19: 614–8.

A randomized study of 52 patients aged 2–12 years found that the use of emollients can significantly improve xerosis and pruritus during corticosteroid treatment of AD and helped maintain clinical improvement after discontinuation of therapy.

Quantitative assessment of combination bathing and moisturizing regimens on skin hydration in atopic dermatitis. Chiang C, Eichenfield LF. *Pediatr Dermatol* 2009; 26: 273–8.

A crossover study in five pediatric patients with AD and five patients with healthy skin in whom objective parameters of cutaneous hydration status were assessed after various combinations of bathing and moisturizing regimens. This study found that bathing without moisturizer may compromise skin hydration. Bathing followed by moisturizer application provides modest hydration benefits, though less than that of simply applying moisturizer alone.

Frequent versus infrequent bathing in pediatric atopic dermatitis: a randomized clinical trial. Cardona ID, Kempe EE, Lary C, et al. *J Allergy Clin Immunol Pract* 2020; 8: 1014–21.

This randomized clinical trial demonstrates that twice-daily soaking baths followed by immediate application of an occlusive moisturizer (soak-and-seal method) is superior at improving disease severity in moderate-to-severe pediatric AD over twice-weekly soak-and-seal baths, with a greater than 30% SCORAD (SCORing Atopic Dermatitis index) improvement.

Scoping systematic review of treatments for eczema. Nankervis H, Thomas KS, Delamere FMC, et al. *NIHR Journals Library* 2016; 4: 1–528.

A systematic review of 287 trials covering 92 different AD interventions.

Topical corticosteroids for atopic eczema: clinical and cost effectiveness of once-daily vs. more frequent use. Green C, Colquitt JL, Kirby J, et al. *Br J Dermatol* 2005; 152: 130–41.

A systematic review found no clear differences in outcomes between once-daily and more frequent application of topical corticosteroids.

Topical agents for the treatment of atopic dermatitis. Eichenfield LF, Luger T, Papp K, et al. *J Drugs Dermatol* 2020; 19: 50–64.

This literature review summarizes the efficacy and safety data of topical AD therapies, and specifically states that the published clinical studies for crisaborole demonstrate its efficacy and safety profile. It also states that comparison among different therapies is difficult due to differing methodologies across clinical trials.

A systematic review of the safety of topical therapies for atopic dermatitis. Callen J, Chamlin S, Eichenfield LF, et al. *Br J Dermatol* 2007; 156: 203–21.

This review of topical therapies for AD found that although some systemic exposure to topical steroids does occur, physiologic changes appear to be uncommon, and systemic complications are rare when medications are used properly.

Efficacy and safety of wet-wrap dressings in children with severe atopic dermatitis: influence of corticosteroid dilution. Wolkerstorfer A, Visser RL, De Waard van der Spek FB, et al. *Br J Dermatol* 2000; 143: 999–1004.

In children with severe refractory AD, 5%, 10%, and 25% dilutions of fluticasone propionate 0.05% cream proved highly efficacious, irrespective of dilution, when applied under wet-wrap dressings. Improvement occurred mainly during the first week, and the only significant adverse effect was folliculitis.

Wet dressing therapy in conjunction with topical corticosteroids is effective for rapid control of severe pediatric atopic dermatitis: experience with 218 patients over 30 years at Mayo Clinic. Dabade TS, Davis DM, Wetter DA, et al. *J Am Acad Dermatol* 2012; 67: 100–6.

Intensive inpatient treatment (with wet dressings and topical corticosteroids) was highly effective in controlling severe and recalcitrant atopic dermatitis.

Second-Line Therapies

• Topical immunomodulators	A
• Against routine antimicrobial use	A
• Against routine antihistamines/anxiolytics use	A
• Avoidance of true IgE-mediated triggers	A
• Topical phosphodiesterase inhibitors	A
• Dupilumab (moderate-to-severe disease)	A

Efficacy and safety of crisaborole ointment, a novel, non-steroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. Paller AS, Tom WL, Lebwohl MG, et al. *J Am Acad Dermatol* 2016; 75: 494–503.e6.

Crisaborole's safety and efficacy were established through two phase III clinical trials. The studies included 1522 randomized patients; 1016 received crisaborole ointment and 506 received vehicle twice daily for 28 days. At the completion of the study, a statistically significant ≥ 2 grade improvement in Investigator's Static Global Assessment (ISGA) score ($p=0.038$ for center 1 and $p<0.001$ for center 2) was noted. Application-site pain was the most common adverse effect, present in 4.4% of crisaborole-treated and 1.2% of vehicle-treated patients. However, 77.6% of patients had resolution of this symptom within 1 day of onset.

Safety and efficacy of pimecrolimus cream in atopic dermatitis: a 5-year randomized trial. Sigurgeirsson B, Boznanski A, Todd G, et al. *Pediatrics* 2015; 135: 597–606.

This is a 5-year-long randomized control trial of pimecrolimus 1% cream compared with TCS. After 5 years, >85% of patients achieved overall and facial treatment success. In addition, safety of this treatment modality was demonstrated.

A meta-analysis of the efficacy and tolerability of proactive treatment with TCS versus TCI. Schmitt J, von Kobyletzki L, Svensson A, et al. *Br J Dermatol* 2011; 164: 415–28.

This meta-analysis suggests that topical fluticasone propionate (relative risk=0.46) may be more efficacious in preventing disease flares than topical tacrolimus (relative risk=0.78).

0.03% Tacrolimus ointment applied once or twice daily is more efficacious than 1% hydrocortisone acetate in children with moderate-to-severe atopic dermatitis: results of a randomized double-blind controlled trial. Reitamo S, Harper J, Bos JD, et al.; European Tacrolimus Ointment Group. *Br J Dermatol* 2004; 150: 554–62.

This study, involving 624 children aged 2–15 years with moderate-to-severe AD, demonstrated that tacrolimus 0.03% ointment applied

once or twice daily resulted in a significantly greater reduction in modified Eczema Area and Severity Index (mEASI) scores than hydrocortisone acetate 1% ointment applied twice daily ($p < 0.001$).

Intermittent therapy for flare prevention and long-term disease control in stabilized atopic dermatitis: a randomized comparison of 3-times-weekly applications of tacrolimus ointment versus vehicle. Breneman D, Fleischer AB Jr, Abramovits W, et al. *J Am Acad Dermatol* 2008; 58: 990–9.

A double-blind study in which 197 clinically clear patients with a history of moderate-to-severe AD were randomized to three-times-weekly topical tacrolimus or vehicle for 40 weeks; tacrolimus ointment was associated with significantly more flare-free days than vehicle and a significantly longer time until relapse.

Topical calcineurin inhibitors and malignancies in AD patients. Legendre L, Barnette T, Mazereeuw-Hautier J. *J Am Acad Dermatol* 2015; 72: 992–1002.

A systematic review of the long-term safety of topical corticosteroids and TCIs in pediatric AD patients.

No evidence of increased cancer incidence in children using topical tacrolimus for atopic dermatitis. Paller AS, Fölster-Holst R, Chen SC, et al. *J Am Acad Dermatol* 2020; 1: S0190-9622 304 98-9.

In this prospective, longitudinal, international observational cohort study of 8000 children with AD treated with tacrolimus ointment, malignancies were observed at the expected rate for the age- and sex-matched general population.

Systematic review of published trials: long-term safety of topical corticosteroids and topical calcineurin inhibitors in pediatric patients with atopic dermatitis. Siegfried EC, Jaworski JC, Kaiser JD, et al. *BMC Pediatr* 2016; 16: 75.

A systematic review of the literature included multiple tacrolimus trials for pediatric AD.

The study included over 5800 patients and did not note any cases of lymphoma.

Long-term efficacy and tolerability of tacrolimus 0.03% ointment in infants: a 2-year open-label study. Mandelin JM, Rubins A, Remitz A, et al. *Int J Dermatol* 2012; 51: 104–10.

Tacrolimus 0.03% ointment was associated with substantial clinical improvement of AD in infants aged <2 years. Treatment tolerability was similar to that seen in older children.

Staphylococcus aureus: colonizing features and influence of an antibacterial treatment in adults with atopic dermatitis. Bath-Hextall FJ, Birnie AJ, Ravenscroft JC, et al. *Br J Dermatol* 2010; 163: 12–26.

Twenty-six studies involving 1229 participants were included. The authors failed to find any evidence that commonly used anti-staphylococcal interventions are clinically helpful in AD that is not clinically infected.

An evidence-based review of the efficacy of antihistamines in relieving pruritus in atopic dermatitis. Klein PA, Clark RA. *Arch Dermatol* 1999; 135: 1522–5.

This review of 16 AD-associated antihistamine trials found that the majority of studies were flawed in terms of sample size or study design.

Managing sleep disturbances in children with atopic dermatitis. Patel D, Levoska M, Shwayder T. *Pediatr Dermatol* 2018; 35: 428–33.

This article reviews the benefits and limitations of therapeutic agents used to manage sleep disturbance in pediatric patients with AD.

An assessment of the use of antihistamines in the management of atopic dermatitis. He A, Feldman SR, Fleischer AB Jr. *J Am Acad Dermatol* 2018; 79: 92–6.

This article suggests that there is no high-level evidence to suggest that non-sedating antihistamines reduce itch in AD or that sedating antihistamines provide benefit in controlling AD symptoms with the exception of sleep and AD comorbidities, including allergic rhinitis.

Melatonin supplementation for children with atopic dermatitis and sleep disturbance: a randomized clinical trial. Chang YS, Lin MH, Lee JH, et al. *JAMA Pediatr* 2016; 170: 35–42.

This double-blind, placebo-controlled crossover study found melatonin supplementation to be a safe and effective way to improve both sleep-onset latency and disease severity in pediatric AD. In 48 children treated with melatonin, the SCORAD index decreased by 9.1 compared with the placebo group ($p < 0.001$) and the sleep-onset latency shortened by 21.4 min after melatonin treatment compared with placebo ($p = 0.02$). No adverse event was reported throughout the study.

Two phase 3 trials of dupilumab versus placebo in AD. Simpson EL, Bieber T, Guttman-Yassky E, et al. *New Eng J Med* 2016; 375: 2335–48.

This two-center, double-blind, randomized, controlled trial compared dupilumab weekly and biweekly with placebo in 671 adults with moderate-to-severe AD not controlled by topical therapies. Dupilumab weekly and biweekly both resulted in an Investigator's Global Assessment (IGA) score reduction of two points or more in 36% of patients versus 10% in the placebo control group. Additionally, there was a significant improvement in AD severity observed in those receiving dupilumab compared with placebo based on a >75% change in EASI score ($p < 0.001$). Dupilumab therapy was also associated with a statistically significant improvement in other clinical end points, including reduction in pruritus, symptoms of anxiety and depression, and improvement in quality of life. Side effects occurring more frequently in the dupilumab therapy groups than in the placebo groups included injection-site reactions (8%–19% versus 6%) and conjunctivitis (3%–5% versus $\leq 1\%$).

Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. Beck LA, Thaçi D, Hamilton JD, et al. *N Engl J Med* 2014; 371: 130–9.

In this study, four separate randomized, double-blind, placebo-controlled trials were performed to assess the safety of dupilumab and found that patients treated with dupilumab had marked and rapid improvement in all evaluated measures of AD disease activity. Adverse events were more frequent in the placebo group and were not dose limiting.

A clinician's guide to the recognition and management of dupilumab-associated conjunctivitis. Agnihotri G, Shi K, Lio PA. *Drugs R D* 2019; 19: 311–8.

This article provides a useful approach on management of conjunctivitis, which is one of the most common side effects of dupilumab. It suggests that mild conjunctivitis may be managed by the dermatologist with warm compresses and eye drops, including artificial tears and antihistamine drops. Moderate-to-severe

conjunctivitis should be managed by an ophthalmologist with topical eye drops with corticosteroids, tacrolimus, ciclosporin, or, potentially, lifitegrast.

Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). de Bruin-Weller M, Thaçi D, Smith CH, et al. *Br J Dermatol* 2018; 178: 1083–101.

In this study of 318 adult patients with inadequate response to, intolerance of, or for whom ciclosporin was contraindicated, dupilumab plus topical corticosteroids significantly improved signs and symptoms of AD and quality of life.

Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. Simpson EL, Paller AS, Siegfried EC, et al. *JAMA Dermatol* 2019; 156: 44–56.

This study of 240 adolescents aged 13–17 demonstrated that dupilumab significantly improved AD signs, symptoms, and quality of life, with an acceptable safety profile.

Third-Line Therapies

• Dust mite reduction	A
• Phototherapy	B
• Azathioprine	B
• Ciclosporin	B
• Methotrexate	B
• Mycophenolate mofetil	C
• Systemic corticosteroids	B

Prescribing practices for systemic agents in controlling pediatric AD. Totri CR, Eichenfield LF, Logan K, et al. *J Am Acad Dermatol* 2017; 76: 281–5.

The TREAT survey included 133 dermatologists from the Society for Pediatric Dermatology. Of these participants, 86.5% used systemic treatments for severe pediatric AD. Ciclosporin (45.2%), methotrexate (29.6%), and mycophenolate mofetil (30.4%) were the most frequently preferred initial treatments. Factors that discouraged systemic therapy use included side effect profiles and suspected risks of long-term toxicities.

Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. Tan BB, Weald D, Strickland I, et al. *Lancet* 1996; 347: 15–8.

Measures to reduce house dust mites using a combination of Gore-Tex bedcovers, benzyl tannate spray, and a high-filtration vacuum cleaner were compared with cotton bedcovers, water spray, and a conventional vacuum cleaner in the households of 48 children and adults with AD. Both active and placebo treatments caused significant reductions in house dust mite antigen concentrations. The severity of eczema decreased in both groups, but the active group showed significantly greater improvement.

Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial. Taylor AL, Dunstan JA, Prescott SL. *J Allergy Clin Immunol* 2007; 119: 184–91.

The role of psoralen photochemotherapy (PUVA) in the treatment of severe atopic eczema in adolescents. Atherton DJ, Carabott F, Glover MT, et al. *Br J Dermatol* 1988; 118: 791–5.

Oral PUVA resulted in initial clearance of eczema in 14 of 15 children, 9 of whom achieved complete remission. This was associated with resumption of normal growth in children who were previously growing poorly.

Phototherapy for atopic eczema with narrow-band UVB. Grundmann-Kollmann M, Behrens S, Podda M, et al. *J Am Acad Dermatol* 1999; 40: 995–7.

Five patients with moderate-to-severe AD were treated with narrowband UVB (NB-UVB) for a cumulative dose of 9.2J/cm² over a mean of 19 treatments. NB-UVB was effective after 3 weeks in all patients.

When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. Simpson EL, Bruin-Weller M, Flohr C, et al. *J Am Acad Dermatol* 2017; 77: 623–33.

This article provides recommendations in making the decision to start systemic medications for AD based on the assessment of the severity of the disease, quality of life, the patient's general health status, psychological needs, and personal attitudes toward systemic agents.

Azathioprine in severe adult atopic dermatitis: a double-blind, placebo-controlled, crossover trial. Berth-Jones J, Takwale A, Tan E, et al. *Br J Dermatol* 2002; 147: 324–30.

In this double-blind crossover trial, adult patients with severe AD were treated with azathioprine 2.5 mg/kg daily and placebo for 3 months each. There was a significant difference in favor of azathioprine in the improvement of the six area, six sign atopic dermatitis (SASSAD) score, decreasing by 26% during treatment with azathioprine versus 3% on placebo. Pruritus, sleep disturbance, and disruption of work/daytime activity all improved significantly on active treatment, but the difference in mean improvement between azathioprine and placebo was statistically significant only for disruption of work/daytime activity. The authors suggested that a longer period of treatment might have further improved the eczema.

Efficacy and tolerability at 3 and 6 months following use of azathioprine for recalcitrant atopic dermatitis in children and young adults. Hon KL, Ching GK, Leung TF, et al. *J Dermatolog Treat* 2009; 20: 141–5.

The clinical efficacy of azathioprine, and its hematologic and biochemical effects (serum IgE level, liver, and renal function), were assessed at 3 months and 6 months in 17 patients with recalcitrant AD. Disease severity was evaluated with the scoring atopic dermatitis (SCORAD) score. Azathioprine reduced the severity of AD within 3 months in these children. Better efficacy was observed in females at 6 months. Mild transient elevation of glutamic-pyruvic transaminase was noted in one patient and mild elevation of serum bilirubin in two other patients.

Systemic treatment of pediatric atopic dermatitis with azathioprine and mycophenolate mofetil. Waxweiler WT, Agans R, Morrell DS. *Pediatr Dermatol* 2011; 28: 689–94.

Medical records of 28 pediatric patients with AD treated with either azathioprine (AZ) or mycophenolate mofetil (MM) were analyzed for laboratory values, TPMT levels, symptoms, infections, and other relevant data. Seventeen of 28 (61%) patients treated with AZ and 8 of 12 (66%) treated with MM reported

significant improvement. Lower rates of laboratory abnormalities and side effects were seen with MM compared with AZ; however, similar rates of cutaneous infections were noted.

Oral azathioprine for recalcitrant pediatric atopic dermatitis: clinical response and thiopurine monitoring. Caufield M, Tom WL. *J Am Acad Dermatol* 2012; 68: 29–35.

This prospective study of 12 children with severe, recalcitrant AD who were treated with oral azathioprine showed that azathioprine can be of benefit in the treatment of recalcitrant pediatric AD. In addition, repeat assessment of TPMT activity (not thiopurine metabolite levels) may be helpful for evaluation of non-response or change in response to treatment.

Cyclosporine in the treatment of patients with atopic eczema – a systematic review and meta-analysis. Schmitt J, Schmitt N, Meurer M. *J Eur Acad Dermatol Venereol* 2007; 21: 606–19.

The authors conducted a systematic review of the effectiveness of systemic ciclosporin in patients with severe atopic eczema and included 15 studies comprising a total of 602 patients. In all studies analyzed, ciclosporin consistently decreased the severity of atopic eczema. Data from 12 of the 15 studies were pooled and showed a dose-related response with a mean decrease in disease severity of 22% (95% CI: 8%–36%) under low-dose ciclosporin (3 mg/kg) and 40% (95% CI: 29%–51%) at dosages ≥ 4 mg/kg after 2 weeks of treatment. After 6–8 weeks the relative effectiveness was 55% (95% CI: 48%–62%). Effectiveness of ciclosporin was similar in adults and children, but tolerability may be better in children.

Double-blind, controlled, crossover study of cyclosporine in adults with severe refractory atopic dermatitis. Sowden JM, Berth-Jones J, Ross J, et al. *Lancet* 1991; 338: 137–40.

A multicenter, randomized, double-blind, controlled crossover clinical trial was conducted on 33 patients with severe refractory atopic dermatitis to determine the effects of ciclosporin (5 mg/kg/day) on their health-related quality of life. After treatment with ciclosporin, patients indicated significant improvement in quality of life; however, there was either no correlation or only a very poor correlation between the quality-of-life parameters and clinical measures of extent and activity of eczema. Relapse was noted when ciclosporin was stopped; however, the mean scores for disease activity and extent of disease in these patients were less than their baseline values.

Cyclosporine in atopic dermatitis: time to relapse and effect of intermittent therapy. Granlund H, Erkkö P, Sinisalo M, et al. *Br J Dermatol* 1994; 132: 106–12.

Forty-three patients with severe AD were treated with a 6-week course of ciclosporin 5 mg/kg daily and then re-treated after a follow-up of 6–26 weeks (depending on the time to relapse) with an identical course of ciclosporin. A significant reduction in disease activity was observed after 2 weeks of ciclosporin treatment. After both treatment periods, approximately half of the patients relapsed after 2 weeks; after 6 weeks' follow-up the relapse rates were 71% and 90%, respectively, for the two treatment periods. Notably, after the first treatment period, five patients did not relapse during the 26-week follow-up and, for the second treatment period, two did not relapse. All of these seven patients were still in remission at 1 year.

Cyclosporine in atopic dermatitis: review of the literature and outline of a Belgian consensus. Naeyaert JM, Lachapelle JM, Degreef H, et al. *Dermatology* 1999; 198: 145–52.

This excellent review summarizes all the major trials of ciclosporin for AD and gives practical recommendations for the clinician. These authors recommend that ciclosporin is reserved for adults with severe AD and only used in children with recalcitrant disease for short periods. A starting dosage of 2.5 mg/kg daily can be adjusted up after 2 weeks, depending on response, to a maximum dose of 5 mg/kg daily. Screening for gynecologic or prostate malignancy and skin biopsy to exclude cutaneous T-cell lymphoma, as well as close monitoring of renal function and blood pressure, are recommended.

An open-label, dose-ranging study of methotrexate for moderate-to-severe adult atopic eczema. Weatherhead SC, Wahie S, Reynolds NJ, et al. *Br J Dermatol* 2007; 156: 346–51.

This 24-week, open-label safety and efficacy study evaluated 12 adults with moderate-to-severe AD in a dose-ranging, prospective trial of methotrexate.

A randomized trial of methotrexate versus azathioprine for severe atopic eczema. Schram ME, Roekevisch E, Leeflang MM, et al. *J Allergy Clin Immunol* 2011; 128: 353–9.

Forty-two patients were randomly assigned to receive either methotrexate or azathioprine for 12 weeks. Both treatments were found to be safe in the short term and achieved clinically relevant improvement with a 42% reduction in AD severity seen with methotrexate and 39% with azathioprine.

Treatment of atopic eczema with oral mycophenolate mofetil. Neuber K, Schwartz I, Itschert G, et al. *Br J Dermatol* 2000; 143: 385–91.

Ten patients with severe AD were treated with oral MM at an initial dose of 1 g/day during the first week and then 2 g daily for a further 11 weeks. Median scores for disease severity improved by 68% (100% in one patient, >75% in three patients, and >50% in the remainder).

Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. Heller M, Shin HT, Orlow SJ, et al. *Br J Dermatol* 2007; 157: 127–32.

Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial. Haeck IM, Knol MJ, Ten Berge O, et al. *J Am Acad Dermatol* 2011; 64: 1074–84.

An observer-blinded, randomized controlled trial was conducted comparing enteric-coated mycophenolate sodium (EC-MPS) with cyclosporin A (CsA) as long-term treatment in adult patients with severe AD. This study showed that EC-MPS is as effective as CsA as maintenance therapy in patients with AD. However, clinical improvement with EC-MPS was delayed in comparison with CsA. Remission after stopping EC-MPS lasted longer compared with CsA.

Recombinant interferon gamma therapy for atopic dermatitis. Hanifin JM, Schneider LC, Leung DY, et al. *J Am Acad Dermatol* 1993; 28: 189–97.

In this randomized, double-blind study, patients with moderate-to-severe AD received recombinant human IFN- γ (rIFN- γ , 50 mcg/m²) or placebo by daily subcutaneous injection for 12 weeks. Significant reductions in erythema, pruritus, and excoriation occurred in rIFN- γ -treated patients. Edema, papulation, induration, scaling, dryness, and lichenification showed greater improvement in the rIFN- γ group, but differences were not statistically significant.

Do some patients with atopic dermatitis require long term oral steroid therapy? Sonenthal KR, Grammer LC, Patterson R. J Allergy Clin Immunol 1993; 91: 971–3.

Three patients with recalcitrant AD were successfully managed on oral corticosteroids.

Emerging therapies for atopic dermatitis: JAK inhibitors. Cotter DG, Schairer D, Eichenfield L. J Am Acad Dermatol 2018; 78(3 Suppl 1): S53–62.

The Janus kinase inhibitor class may be an effective alternative to conventional AD therapies; however, large safety and efficacy trials are needed.

Emerging treatment options in atopic dermatitis: topical therapies. Nygaard U, Deleuran M, Vestergaard C. Dermatology 2017; 233: 333–43.

Emerging treatment options in atopic dermatitis: systemic therapies. Nygaard U, Vestergaard C, Deleuran M. Dermatology 2017; 233: 344–57.

These review articles describe systemic and topical therapies in the pipeline that focus on targeting the skewed immune response in AD.

18

Atypical fibroxanthoma

Zoe Begun, Bilal Fawaz, Ashley Decker



Atypical fibroxanthoma (AFX) is an uncommon cutaneous neoplasm arising from mesenchymal or fibrohistiocytic cells. AFX is found predominantly in sun-damaged skin, especially of the head and neck of elderly males, and comprises approximately 0.2% of all skin tumors. Rare cases have also been reported in children with xeroderma pigmentosum. Risk factors include male sex, ultraviolet (UV) exposure, history of radiation therapy, immunosuppression, and trauma. Typically, these lesions appear as rapidly growing, ulcerated, exophytic, dome-shaped nodules, usually <2 cm in diameter. Despite its severe cytologic atypia, it tends to be less aggressive. Care should be taken to distinguish these tumors from pleomorphic dermal sarcoma (PDS) and undifferentiated pleomorphic sarcoma (UPS).

The classification of fibrohistiocytic tumors is ambiguous and controversial. This has been compounded by the evolving nomenclature as understanding of the genetic and molecular basis of these tumors improved. Previously, fibrohistiocytic tumors encompassed the superficial AFX and its deep dermal/subcutaneous version, the malignant fibrous histiocytoma (MFH). However, the term MFH is no longer favored due to the heterogeneity of these tumors, most of which are better aligned under other classifications. In the current nomenclature, AFX is primarily a dermally based tumor that remains a diagnosis of exclusion by use of immunohistochemical stains. If invasion into subcutaneous tissue is observed, it is superficial and focal. The presence of extensive or deep subcutaneous tissue invasion, perineural invasion, lymphovascular invasion, abundant atypical mitoses, or tumor necrosis in a tumor that otherwise resembles an AFX histologically is more appropriately classified as a PDS, which carries a worse prognosis. PDS is a term newly proposed in 2012 by Dr. C.D. Fletcher, and therefore its adoption in the literature is included only in newer publications.

Although AFX and PDS likely represent a disease spectrum, this has not been conclusively proven. PDS is clinically indistinguishable from AFX, although reports suggest these tumors are

typically larger on presentation (>2 cm). It similarly predominantly arises on sun-damaged skin of elderly men, especially on the scalp. Unlike AFX, PDS is associated with a recurrence rate of 29%, and estimates of metastasis are as high as 20%.

UPSs are a diagnosis of exclusion for sarcomas that do not fit into other categories, including AFX and PDS. Due to the controversial nomenclature of sarcomas, UPS is still used by some authors to describe what would now be considered PDS or AFX. Since the adoption of PDS in 2012, however, the World Health Organization recommends limiting the use of the term UPS to sarcomas arising from deeper tissues, often involving the extremities or retroperitoneum.

MANAGEMENT STRATEGY

Proper management relies on an adequate biopsy specimen that includes subcutaneous tissue to help distinguish between AFX and PDS. Because these are typically rapidly growing tumors, first-line management is aimed at complete eradication with surgery. Incomplete removal results in recurrences that usually manifest within a year postoperatively. In instances of incomplete removal of PDS, recurrence can present as satellite lesions that represent in-transit metastases.

Due to the rarity of these tumors, the lack of consensus for an excisional safety margin, and the overlap clinically with PDS, Mohs micrographic surgery (MMS) with complete margin evaluation is preferable over wide local excision (WLE) for primary tumors, especially for tumors with substantial subcutaneous invasion. Recurrent tumors should be treated with MMS.

Although radiation and chemotherapy are often used as adjunctive therapies, local tumor control remains the first-line therapy. Because AFX and PDS are induced by radiation exposure, the utility of radiation therapy is unclear. There is also literature suggesting that radiation-induced sarcomas are less responsive to radiation therapy. Additionally, early reports suggest immunotherapy may have the potential to revolutionize the treatment of recurrent or metastatic AFX/PDS.

Specific Investigation

- Biopsy with adequate subcutaneous tissue

Diagnosis requires an adequate biopsy specimen with appropriate immunohistochemical stains (high-molecular-weight cytokeratins, S100, SMA, MelanA/MART1, EMA, CD34, and CD31) to exclude other spindle cell tumors, particularly squamous cell carcinoma, melanoma, angiosarcoma, and leiomyosarcoma. Biopsy and excision specimens should also be evaluated for the extent of subcutaneous invasion, perineural invasion, lymphovascular invasion, atypical mitoses, and tumor necrosis to distinguish between AFX and PDS.

First-Line Therapy

- Mohs micrographic surgery

C

Atypical fibroxanthoma: systematic review and meta-analysis of treatment with Mohs micrographic surgery or excision. Tolkachjov SN, Kelley BE, Alahdab F, et al. *J Am Acad Dermatol* 2018; 79: 929–34.

This systematic review and meta-analysis included studies published from 1946 to 20 March 2017 with at least five patients treated surgically for AFX. Twenty-three studies were selected,

none of which were randomized controlled trials, two were comparative studies, and 21 were non-comparative studies. The review included 907 patients and 914 tumors with a mean patient age of 74.3 (range 25–99) years. Most tumors were located on the head and neck. The mean length of time to follow-up was 41.6 months.

Mohs micrographic surgery (MMS) was used to treat 175 cases and 732 were treated with WLE. In the MMS treatment group, there were five cases of local recurrence (2.0%, 95% confidence interval [CI] 0–4.1%) and five cases of metastasis (1.9%, 95% CI 0.1–3.8%). Of those treated with WLE, 68 had local recurrence (8.7%, 95% CI 5–12.3%) and 17 had metastases (1.0%, 95% CI 0.2–1.9%). The margins for WLE were inconsistently reported. Eleven patients in the MMS group were immunocompromised, and none of these patients experienced local recurrence or metastasis. Ten patients in the WLE group were immunocompromised; four of them (40%) had local recurrence and one (10%) experienced metastatic disease.

In patients with atypical fibroxanthomas, treatment with MMS is associated with a lower risk of local recurrence compared to those treated with WLE (2.0% vs. 8.7%). Of note, studies that used the terms MFH, UPS, or PDS were excluded from analysis.

Atypical fibroxanthoma: The Washington University Experience. Phelan PS, Rosman IS, Council ML. *Dermatol Surg* 2019; 45: 1450–8.

This is a retrospective cohort analysis of 75 cases of AFX tumors treated at Washington University Medical Center from January 2000 through July 2016. Treatment information was available for 63 of the cases. Median age at diagnosis was 73 years; 56 cases occurred in men, and 19 in women. All subjects with known race were white. Of those with known immune status, 11 (16.2%) were immunosuppressed (secondary to solid organ transplant, hematologic malignancy, or inflammatory bowel disease). Most cases (90.7%) occurred in the head and neck. Forty-two tumors were removed by MMS, 12 by local excision (LE), four by both MMS and LE, two by staged excision, one by multiple LE, one by LE with adjuvant radiation therapy, and one by shave biopsy.

Although preoperative size did not vary significantly between treatment groups, the size of tissue removed was much greater in LE (2.6 cm, 4.5 cm²) compared with MMS (0.6 cm, 1.2 cm²; $p=.002$ [linear], $p=.093$ [area]). Follow-up information was available for 50 cases, including 29 treated by MMS (median follow-up 26 months) and 12 treated by LE (median follow-up 50 months). Of these 50 cases, six experienced recurrence. The observed intention to treat recurrence rates were 3.4% for MMS and 25% for LE (RR 0.14 [95% CI 0.02, 1.2], $p=.068$). After exclusion of the three cases for which the final diagnosis was not AFX, the recurrence rate for true AFX was 8.5%. Recurrence rate did not vary significantly based on immune status.

Although median follow-up time for LE was double that for MMS, bias is unlikely given both groups' median follow-up was over 2 years, which is what previous studies have shown to be the time during which most recurrent cases of AFX will present. Despite a small sample size of recurrent cases, this retrospective cohort analysis suggests improved outcomes with MMS with the benefit of significantly less tissue removal.

More than 2 decades of treating atypical fibroxanthoma at Mayo Clinic: what have we learned from 91 patients? Ang GC, Roenigk RK, Otley CC, et al. *Dermatol Surg* 2009; 35: 765–72.

This is an updated retrospective chart review of 93 AFX tumors treated at the Mayo Clinic from 1980 to 2004. The average age at time of diagnosis was 71.7 years old. The majority of tumors (83.9%) were located on the face and scalp. The average clinical

size was 1.5 cm, with immunosuppressed patients having slightly larger tumors (1.6 vs. 1.3 cm, $p = 0.10$). Treatment information was available for 88 cases. Sixty-six of 88 tumors (67%) were treated with MMS, 23 (26.1%) with WLE, five cases with electrodesiccation and curettage (ED&C), and one with shave excision. The authors report that based on their MMS experience, a 2-cm margin would be needed to clear 96.6% of AFX tumors. Tumors treated with MMS were larger than those treated with WLE (1.5 vs. 1.0 cm, $p = 0.02$). Of the 86 tumors with follow-up data, two recurred and both had been treated with WLE.

The median follow-up time for patients treated with MMS was shorter than those treated with WLE (4.5 years vs. 8.7 years); however, because recurrences typically occur within the first 2 years postoperatively, this retrospective chart review suggests improved outcomes with MMS despite larger preoperative tumor size.

Second-Line Therapies

• Wide local excision	C
• Chemotherapy	B
• Immunotherapy	C
• Radiation therapy	D

Pleomorphic dermal sarcoma: adverse histologic features predict aggressive behavior and allow distinction from atypical fibroxanthoma. Miller K, Goodlad JR, Brenn T. *Am J Surg Pathol* 2012; 36: 1317–26.

This is an excellent retrospective chart review of histologically confirmed PDS cases treated with WLE. Tumors were large, with a median diameter of 2.5 cm and thickness of 1.15 cm. Local recurrence occurred in 28% of patients (three treated with ED&C and three with WLE) and metastasis in 10% of patients. The median time to recurrence was 10 months.

Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicenter, two-cohort, single-arm, open-label, phase 2 trial. Hussein AT, Burgess M, Bolejack V, et al. *Lancet Oncol* 2017; 18: 1493–501.

This prospective cohort study investigated the response of patients with soft-tissue and bone sarcomas to pembrolizumab (anti-PD-1) immunotherapy. Eligible patients had evidence of metastatic or surgically unresectable, locally advanced disease. Eighty-six patients were enrolled from 12 academic centers between 13 March 2015 and 18 February 2016; 84 received 200 mg of pembrolizumab via 30 min intravenous infusion every 3 weeks until disease progression or unacceptable toxicity.

The primary end point was investigator-assessed objective response. In the cohort of 40 patients with soft tissue sarcoma, 10 cases of undifferentiated pleomorphic sarcomas were included. Four patients (40%) with UPS achieved an objective response, including one patient with UPS achieving a complete response. Median progression-free survival was 30 weeks (95% CI 8–68) for the patients with UPS. Median 12-week progression-free survival for patients with UPS specifically was even higher than the rest of the cohort at 70% (42–98%). Seventy biopsies were analyzed pretreatment for PD-L1 expression, and it was found that PD-L1 was positive in only three (4%) samples, all of which were from patients with UPS. Two out of three of these patients were evaluated for response, one of which achieved complete response and the other a partial response. The most common adverse events in the soft-tissue sarcoma cohort were anemia, lymphopenia, and prolonged activated partial thromboplastin time. There were no fatal treatment-related adverse events.

Although the authors did not detail their definition of UPS, pembrolizumab therapy showed promising results in patients with metastatic or surgically unresectable UPS, with four out of 10 patients achieving an objective response to the therapy.

First report on two cases of pleomorphic dermal sarcoma successfully treated with immune checkpoint inhibitors. Klein S, Persa O, Mauch C, et al. *Oncoimmunology* 2019; 8: 12.

The authors present two patients with locally recurring PDS who were treated with the anti-PD-1 agent pembrolizumab. Patient A is a 77-year-old male who experienced local relapse and cutaneous metastasis of PDS 6 months after his initial excision with 1-cm margins. Both lesions were surgically excised and treated with radiotherapy. Five months later, the patient once again developed relapse of PDS at the initial site as well as multiple cutaneous metastases. The patient started pembrolizumab therapy (2 mg/kg every 3 weeks) and reached complete remission of the disease after eight cycles. Patient B is an 88-year-old male who, 2 years after surgical excision of PDS with 1-cm margins, developed an inoperable local relapse. He reached complete remission of disease 4 months after starting treatment with 200 mg of IV pembrolizumab every 3 weeks, along with adjuvant radiotherapy (2 Gy fractions and a total dose of 70 Gy).

Using next-generation gene sequencing and gene expression analysis, the authors were able to show that both PDS tumors demonstrated a proinflammatory microenvironment, with higher than normal levels of multiple checkpoint molecules, such as CD40LG, CTLA-4, HAVCR2/TIM-3, LAG-3, PDCD1, and TIGIT. The results were comparable to a previously published cohort, suggesting that immunotherapy is a promising therapeutic modality for recurrent or metastatic PDS.

Radiation-associated undifferentiated pleomorphic sarcoma is associated with worse clinical outcomes than sporadic lesions. Dineen SP, Roland CL, Feig R, et al. *Ann Surg Oncol* 2015; 22: 3913–20.

This is a retrospective chart review of 1068 patients with the diagnosis of UPS/MFH treated at a single institution from 1990 to 2012. Patients with sarcomas arising from bone were excluded. Of these cases, 55 (5.1%) were radiation-induced and the rest were sporadic. The median latency period between radiation and the development of radiation-associated sarcoma (RAS) was 9.33 years (range 1–40 years). The median dose of radiation these patients received was 50 ± 5.2 Gy. Twenty-four percent of patients with RAS underwent repeat radiation therapy without reduction in the rate of local recurrence.

Although radiation is often used as an adjunctive therapy to local control, this study suggests that radiation-induced sarcomas are not responsive to this treatment modality.

Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002. Maki RG, Wathen K, Patel SR, et al. *J Clin Oncol* 2007; 25: 2755–63.

In this multicenter, open-label, phase II clinical trial of 122 patients with recurrent or progressive soft-tissue sarcoma, patients were randomized to receive either gemcitabine alone or gemcitabine–docetaxel combination therapy. The combination therapy group achieved improved RECIST (Response Evaluation Criteria in Solid Tumors) partial response rate (16% vs. 8%). Within the subgroup of patients with MFH/UPS, four of 11 patients (31.6%) achieved partial response in the gemcitabine–docetaxel treatment arm compared with two of eight (25%) in the gemcitabine-only arm. The median overall survival was also improved in the combination therapy arm (17.9 months vs. 11.5 months).

The standard of care for the majority of soft-tissue sarcomas, including AFX and PDS, is local tumor control with surgery. Therefore, there is no literature for systemic chemotherapy treatment of localized tumors limited to the skin. However, metastatic soft-tissue sarcoma typically has a poor prognosis. In this phase II clinical trial, which included multiple types of metastatic soft-tissue sarcoma, the combination of gemcitabine with docetaxel showed improved outcomes in tumor size and overall survival.

Third-Line Therapies

• Electrochemotherapy	D
• Electrodesiccation and curettage	D

Electrochemotherapy as promising treatment option in rare recurrent cutaneous neoplasm of the scalp: case report of an elderly patient. Crimini E, Roberto M, Effetti VD, et al. *Case Reports in Oncological Medicine* 2019; Article ID 2507642. <https://doi.org/10.1155/2019/2507642>.

The authors report a case of a 78-year-old white male who presented with an AFX on the scalp. After failing WLE with unknown margins, electrochemotherapy utilizing bleomycin with 1-cm margins led to clinical remission. The authors report no disease relapse after 2 years.

Electrochemotherapy (ECT) is a treatment method in which electrical pulses are applied locally to a lesion to increase cell membrane permeability, thus augmenting intracellular chemotherapy levels in the skin and subcutaneous tissue. It has previously been indicated in the treatment melanoma, Kaposi sarcoma, and cutaneous metastases. This case report suggests ECT may be an effective treatment option for recurrent AFX, although larger studies are warranted to confirm its efficacy and safety.

Atypical fibroxanthoma: a case series and review of literature. Mahalingam S, Shah A, Stewart A. *Auris Nasus Larynx* 2015; 42: 469–71.

A case series of seven patients with AFX treated with ED&C (5) and LE (2). At 2 years' follow-up, two of the five patients (40%) treated with ED&C had developed local recurrence. These patients subsequently underwent complete excision without further recurrences.

This case series, along with multiple other case series previously discussed, have all demonstrated a high recurrence rate when the primary tumor is inadequately removed.

Atypical nevi

Ashfaq A. Marghoob, Emmanouil Chousakos



The dysplastic nevus, first described in 1978, continues to fuel much clinical, histopathologic, and molecular research. Despite four decades of study, clinicians and pathologists still debate the validity for the existence of this entity. While today the terms 'atypical nevus' and 'dysplastic nevus' are used interchangeably, dysplastic nevus continues to be the most favored term. Much of the controversy regarding dysplastic nevi (DN) stems from both diagnostic and biologic uncertainty.

DN are benign, acquired, melanocytic neoplasms. Once they are in a state of clinical senescence, they tend to be larger than 5 mm in greatest diameter and some may also display variable degrees of asymmetry, border irregularity, and color variegation. Some DN may be palpable but in all such lesions a macular component remains evident at their periphery. Before the advent of dermoscopy, clinicians often found it difficult to differentiate DN from melanoma and as such it was not uncommon to excise these nevi for fear of missing a melanoma. Fortunately, dermoscopy has greatly improved our ability to recognize DN and differentiate them from melanoma. This has contributed greatly to reducing the number of unnecessary biopsies being performed, noticeably reflected in improvements in clinicians' benign to malignant biopsy ratios.

Although agreement is lacking on what exactly defines an individual nevus as a DN or whether this entity even exists, there is good agreement that persons harboring many nevi including acquired nevi with diameter greater than 5 mm are at heightened risk for developing melanoma. Individuals manifesting this phenotype, known as atypical mole syndrome (AMS), will often display nevi of varying sizes, shapes, and colors, with varying hues of brown.

DN usually become clinically manifest during puberty or early adulthood. While some DN can evolve over time, most remain relatively unchanged. Individuals with AMS can continue to develop new nevi throughout life. It has been observed that the development of acquired nevi on the dorsum of feet, on the non-sun-exposed skin of the buttocks and suprapubic region, and

on the scalp of children is predictive for developing the AMS phenotype.

The risk of melanoma developing in association with DN remains an area of study. Publications to date show that, while melanoma may arise in association with DN, the vast majority of DN never progresses to melanoma. However, many studies have also shown that DN and AMS patients are at higher risk for developing melanoma. This apparent paradox is easily explained by the fact that DN, independent of the total nevus count, are stronger risk markers for developing melanoma than they are precursors to melanoma. In these patients, approximately 70% of melanomas arise *de novo* and only 30% arise in association with a nevus. It is important to underscore that the nevi found in association with melanoma are just as likely to be DN as they are to be non-DN. The annual risk of a single nevus transforming into melanoma has been calculated to be between 0.0005% (1 in 200,000) to 0.003% (1 in 33,000) in individuals <40 or >60, respectively, and the lifetime risk for a nevus to develop an associated melanoma was calculated to be between 0.03% (1 in 3164) to 0.009% (1 in 10,800). The clinical significance of DN and AMS primarily lies in their correlation with melanoma susceptibility. The presence of even one DN increases the risk for melanoma development 10-fold, and the higher the DN count, independent of total nevus count, the higher the risk for developing melanoma. It has been shown that individuals with sporadic AMS have a 10-year cumulative risk of developing melanoma of 10.7% compared with 0.62% risk for individuals without AMS. However, in patients with familial atypical multiple mole-melanoma, the lifetime risk approaches 100%.

MANAGEMENT STRATEGY

Differentiating DN from melanoma is the cornerstone of patient management and requires integrating information from multiple sources. The overarching goal in managing patients with DN and AMS is to find early melanoma while minimizing the unnecessary removal of nevi. The level of evidence-strength of recommendation of the various management options of DN is difficult to ascertain due to a paucity of prospective randomized studies.

Achieving the first objective of finding early melanoma requires patients' and physicians' vigilance for the presence of any new or changing lesions. Patients should be encouraged to perform *self-examination* on a periodic basis and if they notice any new, changing, or symptomatic lesions, to bring it to the attention of their physician. In addition, patients should visit their physician on a regular basis, at least annually.

Patient's profile is vitally important as patients with many nevi including multiple DN or personal or familial history of melanoma are at significantly higher risk for developing melanoma. Personal history of melanoma increases the risk for a subsequent melanoma by 100-fold; history of at least two family members with melanoma increases the risk 200-fold; and, for both personal and family history, the risk increases by 1200-fold.

The skin cancer surveillance examination should involve *examining the entire skin surface with dermoscopic evaluation of nevi and baseline photography*. Individuals with many nevi can get their entire skin surface imaged. These *total body photographs* serve as a baseline to which subsequent examinations of the patient are compared to detect new or changed lesions.

Once a lesion of interest has been identified, it can be examined further with dermoscopy to determine if a biopsy is warranted. Clinically distinguishing DN from melanoma using the clinical ABCD rule (Asymmetry, Border irregularity, Color variegation, Diameter >6mm) is of little use since DN and melanoma share

the same criteria. Dermoscopy of these lesions can help in distinguishing many DN from melanoma. In addition, the comparative approach, which relies on identifying the dermoscopic signature nevus pattern/s in a given individual and then isolating those lesions that deviate from the signature pattern/s (i.e., outlier lesion or ugly duckling lesion), is another means for finding lesions with a higher pre-test probability for being malignant. Baseline dermoscopy images of individual nevi can also be obtained for future comparison (digital dermoscopic monitoring). Over time these nevi can be examined and compared to their baseline dermoscopic images, with the aim of finding subtle changes that may herald the earliest signs of melanoma. Numerous studies have shown that total body photography and digital dermoscopy contribute to improvements in the clinician's diagnostic accuracy, both during in-person clinic visits and during teledermatology consultations.

Besides dermoscopy, other *in vivo* technologies such as *reflectance confocal microscopy* (RCM), optical coherence tomography, and electrical impedance spectroscopy may also help in differentiating nevi from melanoma. The most studied of these is RCM, which provides horizontal section images of the skin at cellular resolution. These quasi-histology RCM images can further enhance the clinician's diagnostic accuracy beyond that achieved with dermoscopy alone.

Specific Investigations

- Detailed history including personal and family history of melanoma and DN/AMS **B**
- History of any new, changing, symptomatic, or concerning lesions **B**
- Complete skin cancer surveillance examination using naked eye and dermoscopy **A**
- Juxtaposition and comparison of lesions to baseline images with total body photography **C**
- Juxtaposition and comparison of lesions to baseline images with digital dermoscopy **B**
- Suspicious lesions can be evaluated further via RCM or subjected to excisional biopsy **C**
- Genetic testing **C**

During the initial patient encounter, the dermatologist will need to evaluate all lesions and decide whether any are suspicious for skin cancer, based on patient history or findings noted on clinical-dermoscopic examination. Outlier lesions, lesions deviating from the normal dermoscopic nevus patterns, and lesions manifesting melanoma specific structures on dermoscopy require particularly close attention. Depending on the degree of concern, lesions can be subjected to further investigations with tools such as RCM or imaged for baseline for the purpose of close monitoring or subjected to excisional biopsy if concern for melanoma remains. For patients with AMS, total body photographs and digital dermoscopy imaging should be obtained and used for comparison during subsequent encounters. *Longitudinal monitoring* of lesions helps identify new and changing lesions with a higher pre-test probability for being melanoma. The monitoring intervals for individual lesions is separated into short-term (3–6-month interval) and long-term (>6-month interval) depending on the degree of concern. For lesions, where the index of suspicion for melanoma is high, a monitoring interval of between 3–6 months is recommended. Any dermoscopic changes noted comparing the baseline dermoscopy image and the follow-up dermoscopy image warrants strong consideration for biopsy. For lesions manifesting a benign clinical and dermoscopy morphology, follow-up

intervals of 6–12 months are recommended. Unlike short-term monitoring where the subtlest of changes warrants a biopsy, during long-term monitoring the changes that prompt a biopsy need to be more substantial.

The current recommendation by experts is that individuals at risk for developing melanoma should be screened at least annually. However, depending on the complexity of the examination, the number of nevi, the number of DN, and the history of melanoma, the examination frequency can be as short as 3 months.

First-Line Therapies

- Short-term (3–6 months) monitoring for single, non-palpable, somewhat concerning lesion/s **C**
- Long-term (>6 months) monitoring for patients with high-risk nevus phenotype with total body photography and digital dermoscopy **C**
- Excision of suspect lesions **C**
- Reexcision of equivocal, severe DN with positive margins **C**
- Patient education, self-examination **C**

Genetic testing should be considered after appropriate genetic counseling of AMS patients who have a strong family history of melanoma. Of all melanoma cases, 5–10% will be found to have one of the known germline mutations associated with familial AMS and melanoma. The most common of these mutations is in *CDKN2A*, with a frequency of 20–40% among those individuals. However, *CDKN2A* mutation carriers are not necessarily associated with an AMS phenotype. Individuals with germline *CDKN2A* mutations are at increased risk for developing mainly melanoma and pancreatic cancer. While there is strong evidence that skin cancer surveillance in these individuals leads to detection of thinner melanomas with improved survival, this cannot yet be said for pancreatic cancer surveillance. Other germline alterations that may be found in a subgroup of AMS patients are the BAP-1 mutations. These individuals are at increased risk for cutaneous melanoma, ocular melanoma, renal cell cancer, and mesothelioma, among other cancers.

The prophylactic excision of DN should be abandoned in favor of targeted excision of only those lesions that cannot be differentiated from melanoma. In such cases it will be necessary to perform a biopsy and the recommended technique, if feasible, is an *excisional biopsy* or deep shave/saucerization removal of the entire lesion with narrow margins. Incisional (partial) biopsy and shallow shave biopsies are discouraged and should only be considered in lesions located in certain anatomic sites such as the nose and eyelids, or in excessively large lesions. If the DN is completely excised with clear margins, no further action is required. However, if the margins of excision are positive, then the question of *re-excision* of DN to ensure clear margins needs to be addressed, and clinical–dermoscopic–pathologic correlation can prove helpful in shaping clinical management decisions. Clearly, the degree of cytologic atypia influences the management decisions, with DN manifesting severe atypia being reexcised much more commonly than DN manifesting lesser degree of atypia. In general, DN that clinically and dermoscopically display features consistent with melanoma or have severe atypia on histopathology should be re-excised. DN that manifest mild-to-moderate atypia can generally be followed up without the need to reexcise all such lesions.

Clinically recognized dysplastic nevi. A central risk factor for cutaneous melanoma. Tucker MA, Halpern A, Holly EA, et al. JAMA 1997; 277(18): 1439–44.

This case-control study of 716 newly diagnosed melanoma patients and 1014 controls found a twofold increased risk for melanoma associated with increased numbers of small nevi, a fourfold elevated risk associated with increased numbers of both small and large non-dysplastic nevi, a twofold increased risk associated with the presence of one clinically DN, and a 12-fold increased risk associated with 10 or more DN.

The genetic evolution of melanoma from precursor lesions. Shain AH, Yeh I, Kovalyshyn I, et al. *N Engl J Med* 2015; 373(20): 1926–36.

This study analyzed 293 cancer-related genes in 37 nevus-associated melanomas and compared the findings found in the melanoma with those found in its associated nevus. They found an accumulation of genetic alterations from banal nevi to an intermediate category of nevi (which presumably includes DN) to melanoma.

Their findings suggest that in nevus-associated melanomas there are successive genetic alterations that occur during melanoma progression from nevus to invasive melanoma.

Pathologists' diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study. Elmore JG, Barnhill RL, Elder DE, et al. *BMJ* 2017; 357: j2813.

In this study, 187 pathologists were asked to evaluate the same set of 36 or 48 histopathology slides of melanocytic neoplasms on two separate occasions at least 8 months apart. While the interobserver agreement for nevi with no to mild atypia and advanced invasive melanoma was good, the agreement for nevi with moderate-to-severe atypia, melanoma in situ, and early invasive melanoma was poor. The conclusion was that the diagnosis of moderate DN to early melanoma was neither reproducible nor accurate, highlighting the uncertainty present in pathologists' reports.

Total body skin examination for skin cancer screening in patients with focused symptoms. Argenziano G, Zalaudek I, Hofmann-Wellenhof R, et al. *J Am Acad Dermatol* 2012; 66(2): 212–9.

This prospective, cross-sectional, multicenter study included 14,381 patients presenting with a focused dermatology problem. The researchers found that for every 47 patients examined, one skin cancer was found, and for every 400 patients examined, one unsuspected melanoma was found at a location other than where their presenting focused problem was located. Furthermore, by not performing a total body skin examination in patients presenting with a focused dermatology problem, there is a 2.17% risk of missing a malignancy.

This study highlights the value of performing a skin cancer surveillance examination in patients presenting to the dermatology clinic.

Efficacy of skin self-examination for the early detection of melanoma. Hamidi R, Peng D, Cockburn M. *Int J Dermatol* 2010; 49(2): 126–34.

The results of this study were based on interviews conducted with melanoma patients. The study found that self-examination of at least some part of their skin was associated with finding thinner melanomas. The thoroughness of the self-skin examination was the best predictor of melanoma thickness (adjusted ratio, 0.58; 95% CI, 0.36–0.75) and highlights the importance of this practice in patients with DN/AMS.

Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies

performed in a clinical setting. Vestergaard ME, Macaskill P, Holt PE, et al. *Br J Dermatol* 2008; 159(3): 669–76.

This meta-analysis of nine eligible studies comparing the diagnostic accuracy of dermoscopic versus naked eye examination for melanoma detection found that dermoscopy had a superior sensitivity and specificity. Exclusion of two outlier studies resulted in sensitivity estimation of 0.69 and 0.87 for naked eye examination and dermoscopy, respectively, and specificity of 0.88 and 0.91, respectively.

Melanoma thickness: the role of patients' characteristics, risk indicators and patterns of diagnosis. Haenssle HA, Hoffmann S, Holzkamp R, et al. *J Eur Acad Dermatol Venereol* 2015; 29(1): 102–108.

The objective of this study was to identify factors that impacted thickness of melanomas in 347 melanoma patients. The screening of patients in specialized surveillance clinics resulted in thinner melanomas. On multivariate analysis the use of dermoscopy was independently associated with significantly thinner melanomas.

Benefits of total body photography and digital dermatoscopy ('two-step method of digital follow-up') in the early diagnosis of melanoma in patients at high risk for melanoma. Salerni G, Carrera C, Lovatto L, et al. *J Am Acad Dermatol* 2012; 67(1): e17–27.

This study investigated the impact of total body photography and digital dermoscopy in the monitoring of 618 high risk patients with a total of 11,396 lesions. During a median of 96 months of follow-up, only 1.86 lesions were excised per patient due to the development of concerning changes. Of the excised lesions, 8.5% proved to be melanoma. Approximately 53% of the melanomas were in situ and the remainder were invasive with a median thickness of 0.5 mm.

Both short-term and long-term dermoscopy monitoring is useful in detecting melanoma in patients with multiple atypical nevi. Moscarella E, Tion I, Zalaudek I, et al. *J Eur Acad Dermatol Venereol* 2017; 31(2): 247–51.

This study investigates the impact of short-term follow-up (evaluation of a single atypical lesion over a period of between 3 and 6 months in order to identify subtle morphological changes) versus long-term follow-up in patients with AMS. A total of 3823 lesions from 541 patients were monitored and 197 lesions were excised during follow-up with 60 of these lesions proving to be melanoma. It was determined that both short-term and long-term monitoring helped in melanoma detection, with 23 melanomas found on short-term monitoring and 37 found on long-term monitoring. There was no difference in the thickness of melanomas found via short- (mean thickness 0.42 mm) versus long-term (mean thickness 0.47 mm) monitoring. The number needed to excise during short-term monitoring was calculated to be 1.96, and for long-term monitoring it was determined to be 3.4.

This study highlights the synergy between short- and long-term monitoring.

Meta-analysis of digital dermoscopy follow-up of melanocytic skin lesions: a study on behalf of the International Dermoscopy Society. Salerni G, Terán T, Puig S, et al. *J Eur Acad Dermatol Venereol* 2013; 27(7): 805–14.

This meta-analysis evaluated 14 eligible studies with a total of 5787 patients with 52,739 lesions followed for a mean of 30 months. During follow-up, 4388 lesions were excised (<1 lesion per patient). The number needed to monitor to find a melanoma ranged from 31 to 1008 and, with every additional month

of monitoring, one additional melanoma was detected. The use of digital dermoscopy follow-up increased the proportion of in situ melanomas and thin melanomas found compared to the expected number in the general population. The authors also show that the chances to detect a melanoma during monitoring increased as the length of follow-up increased.

Systematic review of diagnostic accuracy of reflectance confocal microscopy for melanoma diagnosis in patients with clinically equivocal skin lesions. Stevenson AD, Mickan S, Mallett S, Ayya M. *Dermatol Pract Concept* 2013; 3(4): 19–27.

Based on five eligible studies with a total of 909 equivocal lesions, this study calculated the sensitivity and specificity for melanoma detection via RCM to be 93% and 76%, respectively.

The impact of partial biopsy on histopathologic diagnosis of cutaneous melanoma: experience of an Australian tertiary referral service. Ng JC, Swain S, Dowling JP, et al. *Arch Dermatol* 2010; 146(3): 234–9.

This study investigated the correlation between biopsy type and histopathologic misdiagnosis of melanoma. The authors found that misdiagnosis was least common when the lesion was completely excised (excisional biopsy). Misdiagnosis was more common in lesions sampled via punch biopsy (OR, 16.6 compared with excision) than sampled via shave biopsy (OR, 2.6 compared with excision).

A broad and deep shave biopsy likely provides the pathologist with more tissue, which is essential in rendering an accurate diagnosis, in

comparison to the amount of tissue obtained from a small punch biopsy. While an excisional biopsy remains the preferred means to sample a suspect melanocytic neoplasm, a broad shave biopsy remains an acceptable alternative if an excisional biopsy is not feasible.

Surgical re-excision vs. observation for histologically dysplastic naevi: a systematic review of associated clinical outcomes. Vuong KT, Walker J, Powell HB, et al. *Br J Dermatol* 2018; 179(3): 590–8.

A systematic review, including 12 eligible studies, investigating the outcomes of monitoring versus reexcision of biopsy-proven DN. The rates of biopsy-site primary melanoma were low for both the reexcision group (0.44%) and for the observation group (0.39%) among 2673 biopsied DN.

Addressing the knowledge gap in clinical recommendations for management and complete excision of clinically atypical nevi/dysplastic nevi: Pigmented Lesion Subcommittee consensus statement. Kim CC, Swetter SM, Curiel-Lewandrowski C, et al. *JAMA Dermatol* 2015; 151(2): 212–8.

Management consensus recommendations of the Melanoma Prevention Working Group concerning, among other issues, incompletely excised DN (DN with positive margins). The consensus opinion was that excised DN (no evidence of clinical residual pigment) revealing mild-to-moderate atypia with histopathologic positive margins can be safely observed rather than reexcised.

Autoimmune progesterone dermatitis

Adam R.A. Daunton, Ian H. Coulson



Autoimmune progesterone dermatitis (APD) is an uncommon, cyclical, pruritic dermatosis affecting women of childbearing age. The diagnosis is suggested by premenstrual flares and improvement during pregnancy. It can present in a variety of morphologies, including eczematous, vesicular, and papulovesicular, with urticarial and erythema multiforme-like lesions the commonest. Angioedema or anaphylaxis may accompany the skin eruptions. Hypersensitivity after exposure to exogenous progesterone, usually in the form of an oral contraceptive pill, has been implicated in some cases of APD. Endogenous progesterone may also serve as a trigger for APD in cases arising during menarche or pregnancy. The diagnosis is one of exclusion and is based upon the occurrence of cyclical premenstrual flares, the response to inhibition of ovulation, and the results of intradermal testing and hormone challenge.

MANAGEMENT STRATEGY

The mainstay of treatment is to *inhibit endogenous progesterone secretion* by suppressing ovulation. Classically, *conjugated estrogens* 0.625–1.25 mg daily in a 21-day cycle was a mainstay of therapy, but recently this treatment has been supplanted by gonadotropin-releasing hormone (GnRH) agonists. A transient worsening of the skin eruption is expected after initial treatment with GnRH agonists, with improvement thereafter. A major side effect of GnRH agonists is loss of bone density, which generally limits their use to 6 months of therapy. However, concomitant administration of osteoprotective agents may partly mitigate this risk and may allow longer treatment in carefully selected cases. Patients frequently require estrogen replacement while on GnRH agonist therapy.

The *antiestrogen tamoxifen*, 20 mg daily or 10 mg twice a day, exerts its effect by interfering with clinical estrogen sensitivity, possibly by competitive binding of the estrogen receptors.

Oral contraceptive pills have been implicated in triggering some cases of APD. However, in patients naive to exogenous

progesterone, inducing anovulation with oral contraceptive pills may be successful.

Mild cases of APD may be controlled with *short courses of systemic corticosteroids* before the luteal phase of the menstrual cycle. Very limited disease may respond to potent *topical corticosteroids* and *oral antihistamines*.

Danazol 200 mg twice daily for 1–2 days before menses and continued for 3 days thereafter may prevent the skin eruptions by inhibiting pituitary gonadotropins.

For severe, intractable cases, bilateral oophorectomy is curative.

Autoimmune estrogen dermatitis is a separate entity that can be difficult to distinguish clinically from APD. Intradermal testing that is positive to estrone and negative to progesterone clarifies the diagnosis. Autoimmune estrogen dermatitis responds to tamoxifen, progesterone, and oophorectomy.

The only alternative approach to the inhibition of endogenous progesterone production by suppressing ovulation is progesterone desensitization. This represents the only treatment option that preserves a patient's fertility, and it may be especially useful for patients undergoing in vitro fertilization (IVF) treatment, who are required to take high doses of exogenous progesterone.

There is wide variation between desensitization protocols. There is also a theoretical concern that desensitization treatment could aggravate latent autoimmunity in genetically predisposed women.

Specific Investigations

- Intradermal testing with progesterone
- Progesterone challenge (oral or intravaginal)
- Enzyme-linked immunosorbent assay (ELISA) and ELISpot testing

Different authors have advocated intradermal testing with progesterone in varying amounts and dilutions. One common method of intradermal testing is with 0.1 mL of aqueous progesterone suspension at 100 mg/mL diluted with normal saline to 0.1 mg/mL, 0.01 mg/mL, and 0.001 mg/mL, with normal saline serving as the control. There may be an immediate urticarial reaction within 30 minutes, or a delayed-type hypersensitivity reaction at 24–48 hours.

Progesterone challenge may also be attempted intramuscularly (medroxyprogesterone 10–20 mg) or orally (10 mg) in the first half of the menstrual cycle. Intramuscular skin testing with the depot form of medroxyprogesterone acetate is not advised because of the risk of severe systemic reactions.

ELISA and ELISpot testing can detect elevated levels of IFN- γ -producing peripheral blood mononuclear cells in response to progesterone.

If progesterone testing is negative, consider estrogen sensitivity. Intradermal testing with either estrone (0.1 mL at 1 mg/mL) or conjugated estrogen (0.1 mL of 1, 10, and 100 mcg/mL) can be attempted. A positive reaction may be immediate or delayed for several hours and should persist for more than 24 hours.

The use of a progesterone pessary has recently been proposed as an effective tool in the diagnosis of APD.

Autoimmune progesterone dermatitis: update and insights.

Nguyen T, Ahmed R. Autoimmun Rev 2016; 15: 191–7.

A systematic review of the 89 cases published in English, examining diagnostic tests and treatment methods.

Sixty four of 67 patients who underwent an intradermal progesterone challenge experienced a positive response within 24 hours. All six patients who underwent an intramuscular challenge

experienced a positive response. One patient was diagnosed after an intravaginal challenge. The remaining patients did not undergo a progesterone challenge.

Complete remission was attained in 4/86 (5%) patients without any intervention. Of the 86 patients, 14 (16%) eventually underwent bilateral oophorectomy after failure of other treatment modalities, and all subsequently attained complete remission. Of seven patients who underwent desensitization therapy, 4/7 (57%) attained complete remission, and 1/47 (14%) attained partial control; 4/12 (33%) attained complete remission on GnRH analogs, whereas 3/12 attained partial remission. All five of the patients treated with tamoxifen attained a partial remission. One of 19 patients treated with conjugated estrogen/ethinyl estradiol attained complete remission, and 8/19 attained partial remission. Seven of nine patients treated with the combined oral contraceptive pill attained partial remission.

The role of intradermal skin testing and patch testing in the diagnosis of autoimmune progesterone dermatitis. Stranahan D, Rausch D, Deng A, et al. *Dermatitis* 2006; 17: 39–42.

A case report and a detailed review of the various methods of performing intradermal progesterone testing, highlighting the need for standardization.

Progesterone sensitive interferon- γ -producing cells detected by ELISpot assay in autoimmune progesterone dermatitis. Cristaudo A, Bordignon V, Palamara F, et al. *Clin Exp Dermatol* 2007; 32: 439–41.

Describes the ELISpot technique of diagnosing APD.

Estrogen dermatitis. Kumar A, Georgouras KE. *Australas J Dermatol* 1999; 40: 96–8.

A case report comparing progesterone dermatitis and estrogen dermatitis, as well as useful information on the technique and interpretation of intradermal testing for both disorders.

Iatrogenic autoimmune progesterone dermatitis caused by 17 α -hydroxyprogesterone caproate for preterm labor prevention. Bandino JP, Thoppil J, Kennedy JS, et al. *Cutis* 2011; 88: 241–3.

A 30-year-old woman, gravida 2, para 1, developed APD 4 days after her third injection of 17- α -hydroxyprogesterone caproate (17P), presenting as an urticarial exanthema. Direct immunofluorescence was negative. The injections were discontinued and lesions resolved within 7 days.

The use of progestational agents, most recently 17P, to reduce preterm labor for patients at risk may result in more cases of APD being recognized.

First-Line Therapies

• Gonadotropin-releasing hormone agonists	A
• Tamoxifen	D
• Oral contraceptive pill	E
• Oral corticosteroids	E
• Potent topical corticosteroids	E
• Antihistamines	E

Recurrent anaphylaxis in menstruating women. Treatment with a luteinizing hormone-releasing hormone agonist – a preliminary report. Slater JE, Raphael G, Cutler GB, et al. *Obstet Gynecol* 1987; 70: 542–6.

A double-blind, placebo-controlled crossover study of four women with cyclic anaphylaxis associated with progesterone secretion. Two of the subjects experienced dramatic reduction in the severity and number of attacks while receiving an investigational luteinizing hormone-releasing agonist imbzl-D-his⁶-pro⁹-NEt-LHRH, 4 mcg/kg/day for 4 months. Liaison with a gynecologic endocrinologist may help in the selection of an appropriate GnRH agonist and estrogen combination of therapies.

Autoimmune progesterone dermatitis: a diagnosis easily missed. Toms-Whittle L, John L, Griffiths D, et al. *Clin Exp Dermatol* 2010; 36: 378–80.

Successful treatment with intranasal buserelin 150 mcg thrice daily. Symptoms recurred after cessation of buserelin after the maximum licensed period of 6 months, and consideration is being given to continuing it off-license with osteoprophylaxis.

Autoimmune progesterone dermatitis. Cocuroccia B, Gisondi P, Gubinelli E, et al. *Gynecol Endocrinol* 2006; 22: 54–6.

Treatment with tamoxifen 20 mg daily produced complete and durable clearing of the eruption after 3 months.

A case of autoimmune progesterone dermatitis in an adolescent female. Kakarla N, Zurawin RK. *J Pediatr Adolesc Gynecol* 2006; 19: 125–9.

A case report describing a patient with no prior exogenous hormone exposure who cleared on oral contraceptive therapy. For patients naive to exogenous progesterone, an oral contraceptive pill, is considered to be first-line therapy (the preparation used contained 30 mcg of ethinyl estradiol and 0.15 mg of levonorgestrel).

Autoimmune progesterone dermatitis. Anderson RH. *Cutis* 1984; 33: 490–1.

A case successfully treated with prednisolone 20 mg/day for 10 days during menstruation. The dosage of prednisolone was reduced slowly over several cycles, and the patient was eventually managed on topical corticosteroids only.

Autoimmune progesterone dermatitis associated with infertility treatment. Jenkins J, Geng A, Robinson-Bostom L. *J Am Acad Dermatol* 2008; 58: 353–5.

Oral contraceptives and GnRH agonists were contraindicated in this patient undergoing treatment for infertility. The limited disease was well controlled with halobetasol propionate 0.05% cream.

Autoimmune progesterone dermatitis. Case report with histologic overlap of erythema multiforme and urticaria. Walling HW, Scupham RK. *Int Soc Dermatol* 2008; 47: 380–2.

Durable improvement on cetirizine 10 mg every morning and hydroxyzine 10 mg at bedtime taken on the days of the menstrual cycle previously associated with skin eruptions.

Second-Line Therapies

• Conjugated estrogens	E
• Danazol	E
• Azathioprine	E
• Progesterone desensitization	D
• Omalizumab	E

Autoimmune progesterone anaphylaxis. Bermanian MH, Gharagozlu M, Farashahi MH, et al. *Iran J Allergy Asthma Immunol* 2007; 6: 97–9.

A case report of a patient with perimenstrual urticaria associated with angioedema and respiratory symptoms, all of which improved on conjugated estrogen 0.625 mg once daily.

Autoimmune progesterone dermatitis: effective prophylactic treatment with danazol. Shahar E, Bergman R, Pollack S. *Int J Dermatol* 1997; 36: 708–11.

Successful prophylactic treatment with danazol in two patients at a dose of 200 mg twice daily, starting 1–2 days before menstruation and continuing for 3 days thereafter.

Case 2. Diagnosis: erythema multiforme as a presentation of autoimmune progesterone dermatitis. Warin AP. *Clin Exp Dermatol* 2001; 26: 107–8.

Successful treatment with azathioprine 100 mg daily.

Autoimmune progesterone dermatitis: clinical presentation and management with progesterone desensitization for successful in vitro fertilization. Prieto-Garcia A, Sloane DE, Gargiulo AR, et al. *Fertil Steril* 2011; 95: 1121. e9–13.

Six patients with documented APD were desensitized by a rapid 8- or 10-step protocol, receiving escalating intravaginal progesterone suppositories. The initial dose of intravaginal progesterone was either 0.05 mg or 0.1 mg. The same dose was repeated for a total of 2–3 doses, before being increased by a factor of 10. This pattern was completed for a total of 8–10 doses. Intravaginal suppositories were administered every 20 minutes. One of the patients received an oral protocol. Four patients achieved desensitization. Three patients received successful IVF subsequently.

Iatrogenic autoimmune progesterone dermatitis treated with a novel intramuscular progesterone desensitization protocol. Hill JL, Carr TE. *J Allergy Clin Immunol Pract* 2013; 1: 537–8.

A single case of a patient desensitized with an intramuscular progesterone protocol.

Autoimmune progesterone dermatitis. Soloman M, Itsekson A, Lev-Sagie A. *Curr Derm Rep* 2013; 2: 258–63.

Authors' description of their own protocol for both diagnosis and desensitization. For desensitization, they suggest monthly intradermal progesterone injections, commencing with 0.04 mL of 50 mg/mL progesterone, doubled each month for a total of 3 months.

Progesterone hypersensitivity in 24 cases: diagnosis, management, and proposed renaming and classification. Foer D, Buchheit K, Gargiulo A, et al. *J Allergy Clin Immunol Pract* 2016; 4: 723–9.

Nine patients with symptomatic APD underwent oral desensitization therapy aimed at symptom control, while three underwent rapid intramuscular (IM) desensitization aimed at permitting IVF therapy. Of those who underwent oral desensitization, 8/9 attained symptomatic improvement, while 3/3 who underwent IM desensitization tolerated IVF, and 2/3 attained pregnancy.

Anaphylaxis due to progesterone hypersensitivity successfully treated with omalizumab. Heffler E, Fichera S, Nicolosi G, et al. *J Allergy Clin Immunol Pract* 2017; 5: 852–4.

An adolescent female treated with omalizumab 300 mg s/c monthly experienced complete resolution of her symptoms. Omalizumab was stopped after 6 months, and no recurrence of symptoms at time of last follow-up 5 months after last injection. Progesterone prick and intracutaneous tests were negative immediately following her final injection (positive pretreatment).

Third-Line Therapy

- Bilateral oophorectomy

E

Autoimmune progesterone dermatitis: treatment with oophorectomy. Medeiros S, Rodrigues-Alves R, Costa M, et al. *Clin Exp Dermatol* 2010; 35: e12–3.

Bilateral oophorectomy was curative in this case of APD that was unresponsive to oral corticosteroids and GnRH agonist.

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Bacillary angiomatosis

Floriane Kouby, Olivier Chosidow



First described in 1983, bacillary angiomatosis (BA) is a vasculoproliferative disorder caused by the *intraerythrocytic* bacteria *Bartonella henselae* and *Bartonella quintana* (previously *Rochalimaea* spp.). It typically presents in profoundly immunocompromised patients (e.g., advanced HIV infection, posttransplant, or during cytotoxic chemotherapy), although the incidence in patients receiving newer biologic therapies is unknown. Cutaneous lesions can be superficial, cherry-red, round papules with an eroded surface, similar to pyogenic granulomas; violaceous, lichenoid plaques; or deep subcutaneous nodules. Single lesions have been reported in immunocompetent patients at inoculation sites, whereas in the immunocompromised the entire body surface may be affected. Lesions can be mistaken for Kaposi sarcoma or in-transit metastatic amelanotic melanoma because of the highly vascular and erosive nature of the lesions. In advanced HIV, deep fungal infection (e.g., cryptococcosis and histoplasmosis) should also be considered. Patients with extracutaneous disease may or may not have skin signs and can present with vomiting, abdominal pain, and deranged liver function (peliosis hepatis) or pancytopenia and splenomegaly (peliosis splenis). Fever, lymphadenopathy, night sweats, endocarditis, blindness, and anemia can also be present.

B. henselae is transmitted through a cat scratch or bite and can also result in a localized skin papule and regional lymphadenitis known as *cat scratch disease*. *B. quintana* is transmitted by the human body louse and also causes trench fever (fever, headache, dizziness, and shin pain). (*B. quintana* has also been found on head lice in poor-resource children.) A few cases of BA were described in immunocompetent individuals. More frequently, localized cutaneous lesions virtually identical to BA and typically in immunocompetent individuals are seen in *verruca peruana*, which occurs in Peru, Ecuador, and Colombia due to *B. bacilliformis*, which is transmitted by sandflies. Preceding acute infection known as *Oroya fever/Carrion disease* results in massive hemolytic anemia with >85% mortality if untreated.

MANAGEMENT STRATEGY

Prompt diagnosis is essential to prevent dissemination, which can be fatal. Clinical suspicion should be aroused in the context of a low CD4 lymphocyte count (<100) or other immunosuppression, especially with a history of exposure to cats (>35% harbor *B. henselae*) or body lice (*B. quintana*). Treatment is determined by species, clinical course, and immunologic status.

The response of BA to antibiotic treatment is usually dramatic, in contrast to cat scratch disease. Due to antiinflammatory and antiangiogenic effects, *erythromycin* is the first-line therapy at a dose of 500 mg four times daily, but *doxycycline* 100 mg twice daily is also consistently successful. In patients who are not able to tolerate erythromycin or doxycycline, *azithromycin* or *clarithromycin* may be used. In severe or complicated disease either of these drugs combined with rifampicin 300 mg twice daily has been advocated and intravenous treatment may be required. Treatment should be continued for 3 months where there is only skin disease and 4 months where there is bone/visceral involvement. Should relapse occur on these regimens, long-term prophylaxis with erythromycin or doxycycline may be indicated. However, in practice highly active antiretroviral therapy should reverse the immunocompromised state, making long-term antibiotic therapy less necessary. The patient should be evaluated for parenchymal and osseous disease before treatment and warned that a Jarisch–Herxheimer reaction may occur after the first few doses of antibiotic.

In the case of *verruca peruana* oral rifampicin at a dose of 10 mg/kg/day for 2–3 weeks achieved a cure in over 93% of patients. *Streptomycin* (15–20 mg/kg/day for 2–3 weeks) has a reported cure rate of 56% and is therefore considered second line.

In the absence of randomized clinical trials, treatment is guided by anecdotal experience, retrospective cohort studies/case series, and microbiologic susceptibility data. A wide variety of therapeutic agents are mentioned in the literature, but there is a lack of correlation between the *in vitro* and *in vivo* drug susceptibility of *Bartonella* spp., which reduces the usefulness of laboratory data. The picture is clouded further by the different response of *Bartonella* spp. to drugs in each of the diseases it causes.

Specific Investigations

- Full blood count, liver function tests, HIV serology, and CD4 lymphocyte count
- Biopsy, hematoxylin and eosin stain, and Warthin–Starry stains/electron microscopy
- Prolonged culture of blood and biopsy tissue
- Polymerase chain reaction (PCR) of biopsy material
- Serology – indirect fluorescence assay

Multiple investigations are frequently required to confirm infection. Culture of the fastidious Gram-negative rods of *Bartonella* spp. is extremely difficult, requiring special media and prolonged incubation of up to 45 days; it is invariably negative if antibiotics have been given. Skin biopsy is the essential diagnostic tool and shows a characteristic lobular proliferation of capillaries and venules with swollen endothelial cells containing clumps of bacteria. Hematoxylin and eosin stain demonstrate endothelial-lined peliosis spaces. *Bartonella* spp. can also be visualized using the Warthin–Starry silver stains or electron microscopy and PCR can confirm the species. Reliance on serology in the immunosuppressed is hazardous, but the Centers for Disease Control (CDC) definition of a positive test is an indirect fluorescence assay titer >1:64.

Exams to exclude peliosis of the liver and spleen should be conducted: liver enzyme assay, complete blood count, eventually radiologic evaluation, and liver biopsy. Further evaluation can be done based on the associated symptoms and physical exam (e.g., bone radiography, echocardiography, lumbar puncture).

Bacillary angiomatosis and bacillary peliosis in patients infected with human immunodeficiency virus: clinical characteristics in a case-control study. Mohle-Boetani JC, Koehler JE, Berger TG, et al. Clin Infect Dis 1996; 22: 794–800.

Forty-two cases were compared with 84 matched controls and the distinguishing clinical characteristics were evaluated. Significant differences included the presence of anemia (hematocrit <0.36), raised alkaline phosphatase and aspartate aminotransferase levels, and a low CD4 lymphocyte count (median being 21/mm³ compared with 186/mm³ in controls). Clinical signs included fever, abdominal pain, and lymphadenopathy.

Cutaneous manifestations of bartonellosis. Lins KA, Drummond MR, Velho PENE. An Bras Dermatol 2019; 94(5): 594–602.

There are three main histological features: (1) angioproliferation in lobules, with vessels formed by prominent endothelial cells, with atypia and mitoses being seen in areas with dense cellularity; (2) predominance of neutrophils in the inflammatory infiltrate and occasional leukocytoclasia; and (3) presence of interstitial or intracellular bacterial clumps found with Warthin–Starry staining, immunohistochemistry, transmission electron microscopy, or confocal microscopy.

Laboratory diagnosis of Bartonella infections. Agan BK, Dolan MJ. Clin Lab Med 2002; 22: 937–62.

Culture methods have improved but are still prolonged. Serologic testing for *B. henselae* has become the cornerstone for diagnosis in the immunocompetent patient. Ideal antigens for enzyme immunoassays have yet to be clearly identified. PCR currently offers the ability to establish the diagnosis when other tests fail.

Development of a specific and sensitive enzyme-linked immunosorbent assay as an in vitro diagnostic tool for detection of Bartonella henselae antibodies in human serum. Jost M, Latz A, Ballhorn W, et al. J Clin Microbiol 2018; 56(12): e01329–18.

The authors report the development of an enzyme-linked immunosorbent assay (ELISA) that can detect human anti-*B. henselae* antibodies from serum samples. By use of well-characterized human sera from the strictly quality-controlled serum library of the German National Consiliary Laboratory for *Bartonella* infections, the sensitivity of this ELISA was 100% for PCR-proven infections and 76% for clinically suspected infections at a specificity of 93%.

Development of a real-time PCR for Bartonella spp. detection, a current emerging microorganism. Parra E, Segura E, Tijero J, et al. Mol Cell Probes 2017; 32: 55–9.

The single-step assay described provided a simple and rapid means of identifying *Bartonella* spp.

Utility of molecular identification and quantitation of Bartonella species with species-specific real-time PCR for monitoring treatment response: a case series. Mazzitelli M, Lamberti AG, Quirino A, et al. Open Microbiol J 2018; 12: 148–53.

This case series indicated the utility of molecular identification and quantification of *Bartonellae* spp. infections with species-specific RT PCR both for **diagnosis and monitoring** of treatment response. Indeed, RT PCR was consistent with the clinical course of patients, permitting to stop therapy after *Bartonella* DNA was found to be persistently negative.

First-Line Therapies

• Erythromycin	C
• Doxycycline	C
• Rifampicin	D

Bacillary angiomatosis. Akram SM, Rawla P. StatPearls. Treasure Island (FL): StatPearls; 2020.

The drug of choice in this article is erythromycin or doxycycline. Mild cutaneous BA can be treated for 12 weeks. The response is seen by 3–4 weeks. If the response is not satisfactory, the duration of therapy can be extended. In patients who are immunosuppressed or in HIV patients, therapy should be continued until the CD4 T-helper cell count normalizes.

Cryotherapy, electrodesiccation with curettage, and surgical excision of solitary cutaneous lesions can be useful as adjunctive therapy after treatment with antibiotics to prevent occult bacteremia during the procedure.

Pathogenicity and treatment of Bartonella infections. Angelakis E, Raoult D. Int J Antimicrob Agents 2014; 44: 16–25.

An excellent review of existing data and treatment recommendations for all *Bartonella* infections based on pathogenicity. A table clearly summarizes the various organisms, disease manifestations, and current treatment regimens (including doses and durations).

Treatment outcomes of human bartonellosis: a systematic review and meta-analysis. Prutsky G, Domecq JP, Mori L, et al. Int J Infect Dis 2013; 17: e811–9.

This systematic review of treatment regimens for *B. henselae*, *B. quintana*, and *B. bacilliformis* identified only two randomized controlled trials analyzing the treatment of cat scratch disease and chronic bacteremia along with seven observational studies. With respect to BA they concluded that erythromycin might be better than other antibiotics, but there was no statistically significant difference compared with doxycycline.

Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Kaplan JE, Benson C, Holmes KK, et al. Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009; 58(RR-4): 1–207.

These guidelines recommend a combination therapy with the addition of rifampin to either erythromycin or doxycycline for immunocompromised patients with acute, life-threatening *Bartonella* infections.

AIDS commentary: bacillary angiomatosis and bacillary peliosis in patients infected with human immunodeficiency virus. Koehler JE, Tappero JW. Clin Infect Dis 1993; 17: 612–4.

This review article refers to 50 patients whose lesions and symptoms responded to erythromycin, 500 mg four times daily, or doxycycline, 100 mg twice daily.

Molecular epidemiology of *Bartonella* infections in patients with bacillary angiomatosis-peliosis. Koehler JE, Sanchez MA, Garrido CS, et al. *N Engl J Med* 1997; 337: 1876–83.

A case-control study of 49 patients (92% HIV positive) in whom macrolides, doxycycline, tetracycline, and rifampin were found to be effective. This was in contrast to patients treated with trimethoprim-sulfamethoxazole, ciprofloxacin, penicillins, and cephalosporins in whom *Bartonella* spp. could be isolated on PCR or culture.

Bacillary angiomatosis: presentation of six patients, some with unusual features. Schwartz RA, Nychay SG, Janniger CK, et al. *Br J Dermatol* 1997; 136: 60–5.

This article describes a variety of successful treatment regimens, including tetracycline 2 g daily and ciprofloxacin 750 mg twice daily.

Second-Line Therapies	
• Azithromycin	C
• Clarithromycin	C
• Streptomycin	D

MICs of 28 antibiotic compounds for 14 *Bartonella* (formerly *Rochalimaea*) isolates. Maurin M, Gasquet S, Ducco C, et al. *Antimicrob Agents Chemother* 1995; 39: 2387–91.

The newer macrolides were highly effective in preventing bacterial growth with minimal inhibitory concentration (MIC) 90s, defined as the minimum concentration at which 90% of the isolates are inhibited, of 0.03 mcg/mL for azithromycin and

clarithromycin. Erythromycin, doxycycline, and rifampin all had MIC 90s of 0.25 mcg/mL.

Recommendations for the treatment of human infections caused by *Bartonella* species. Rolain JM, Brouqui P, Koehler JE, et al. *Antimicrob Agents Chemother* 2004; 48: 1921–33.

A good review article. Although erythromycin and clarithromycin are the authors' first-line treatments for BA, their use has been based on case series and case reports rather than on controlled clinical trials.

Third-Line Therapies	
• Gentamicin	E
• Third- and fourth-generation cephalosporins	E

Identification of FDA-approved drugs with activity against stationary phase *Bartonella henselae*. Li T, Feng J, Xiao S, et al. *Antibiotics (Basel)* 2019; 8(2): E50.

In this study, authors performed a high-throughput screen of an FDA-approved drug library against stationary phase *B. henselae*. While the currently used drugs for treating bartonellosis, including rifampin, erythromycin, azithromycin, and doxycycline had very low MIC against growing *B. henselae*, they had relatively poor activity against stationary phase *B. henselae*, except aminoglycosides, which had the capacity to completely eradicate stationary phase *B. henselae* after 3-day drug exposure in subculture.

Bacillary angiomatosis in a pregnant patient with acquired immunodeficiency syndrome. Riley LE, Tuomala RE. *Obstet Gynecol* 1992; 79: 818–9.

A pregnant patient was treated with a third-generation cephalosporin, ceftizoxime. However, there are inadequate data to recommend use at present.

Balanitis

R. Matthew McLarney, Warren R. Heymann



Balanitis is a general term for inflammation of the glans penis, which may also extend to the foreskin (prepuce), in which case it is called balanoposthitis. It may be seen in all age groups and occurs more frequently in the uncircumcised. Etiologies include inflammatory, infectious, and neoplastic disorders. All types of balanitis may be aggravated by poor hygiene, warmth, and friction. This chapter will focus on Zoon balanitis and balanitis xerotica obliterans (BXO, lichen sclerosus).

Balanitis plasmacellularis (Zoon balanitis) represents a non-venereal, non-specific, chronic inflammation of the glans penis occasionally extending to the foreskin. It normally occurs in uncircumcised men past the second decade of life, but has been reported in children. The shiny, red, sharply demarcated patch is often asymptomatic, though symptoms of pruritus, dysuria, and pain may be reported. The evaluation for Zoon balanitis should include a thorough history and clinical workup to exclude genital herpes, secondary syphilis, and other etiologies of penile lesions. Zoon balanitis can also be associated with dermatoses of the genital area such as erosive lichen planus, lichen sclerosus, and penile psoriasis as a type of reaction pattern.

Other differential diagnoses (allergic contact dermatitis, erythroplasia of Queyrat or Bowen disease of the glans penis, and pemphigus vulgaris) should be ruled out. Biopsy demonstrates an atrophic epidermis with diamond-shaped keratinocytes overlying a predominately plasma cell-rich, bandlike infiltrate in the papillary dermis. Complications may include fissuring and pain, phimosis (inability to retract the foreskin due to agglutination/scarring), and stenosis of the urethral meatus; surgical correction of sequelae may be necessary.

Lichen sclerosus (BXO) is treated similarly to Zoon (plasma cell) balanitis. Lichen sclerosus is also of unclear etiology, although an autoimmune pathogenesis associated with other autoimmune conditions may be involved. This condition may be underrecognized in boys. It is important to identify the disorder and have continued follow-up because of the approximately 5% lifetime risk of developing a squamous cell carcinoma.

MANAGEMENT STRATEGY

Evaluation of a patient with balanitis should include a chief complaint, history of present illness, past medical and surgical history, medications, allergies, and review of systems. Specific information should be sought regarding sexual habits and alleviating or exacerbating factors. To identify potential allergens and/or irritants, the patient's genital hygiene practices and the use of oral and topical agents (condoms, spermicides, sexual-enhancing products, lubricants, etc.) should be sought. A complete mucocutaneous examination, including extragenital sites, should be performed. The genital examination includes skin and soft tissue structures extending from the lower abdomen to the perianal skin/gluteal cleft. Examination findings should direct the acquisition of microbiologic studies (KOH preparation; bacterial, fungal, and viral cultures), biopsy (hematoxylin and eosin, direct immunofluorescence), and serologic studies. All males with balanoposthitis should be screened for diabetes.

Patients with balanitis should be instructed about appropriate local hygiene, including retraction of the foreskin before cleansing. The glans and shaft should be cleaned with plain water or normal saline twice daily and after sexual activity. Soap and topical products may be irritants or allergens and should be avoided. A bland emollient applied twice daily will minimize friction and improve barrier function.

Medical therapy for balanitis is directed by etiology. Circumcision is indicated in refractory cases. Surgical procedures may be required for patients with significant anatomic distortion or compromised urinary function. Collaboration with urologic specialists is essential.

Specific Investigations

- KOH microscopy for fungi
- Tzanck smear or direct fluorescent antigen testing for herpes viruses
- Swab culture for bacteria, viruses, and fungi
- Biopsy for routine histopathology and direct immunofluorescence, if indicated
- Hemoglobin A1c
- Urinalysis and urine glucose
- Serologic tests for syphilis, herpes virus, and human immunodeficiency virus
- Serologic tests for vesiculobullous diseases (systemic lupus erythematosus, pemphigus vulgaris, bullous pemphigoid, etc.)
- Patch testing

2013 European guideline for the management of balanoposthitis. Edwards S, Bunker C, Ziller F, et al. *Int J STD AIDS* 2014; 25: 615–26.

Comprehensive review of the many causes of balanitis with specific recommendations for evaluation and management.

Zoon balanitis: a comprehensive review. Dayal S, Sahu P. Indian J Sex Transm Dis 2016; 37: 129–38.

A complete review of Zoon balanitis with history, differential diagnosis, and treatment.

Balanitis xerotica obliterans: an update for clinicians. Nguyen ATM, Holland AJA. Eur J Pediatr 2020; 179(1): 9–16

A summary of studies on topical and intralesional corticosteroids, topical immunomodulators, ozonated olive oil with vitamin E acetate, preputioplasty, and circumcision.

Diagnostic criteria, severity classification and guidelines of lichen sclerosus et atrophicus. Hasegawa M, Ishikawa O, Asano Y, et al. Journal of Dermatology 2018; 45: 891–7.

Comprehensive reference for diagnosis and guidelines for management of lichen sclerosus.

Zoon's plasma cell balanitis: clinical and dermoscopic features in pediatric patients. Chessa MA, Sechi A, Baraldi C, et al. Int J Dermatol 2018; 57: 142–4.

A case series of three pediatric patients aged 7, 8, and 13 months with Zoon balanitis demonstrated serpentine, linear-irregular, and spermatozoa-like vessels; orange-brown structureless areas; and dotted vessels on dermoscopy. The patients were treated with 4 weeks of fusidic acid cream and betamethasone twice daily. Two patients experienced resolution, while one required a shift to 1% pimecrolimus cream twice daily, which led to resolution.

First-Line Therapies

• Hygiene	B
• Emollients	B

Clinical features and management of recurrent balanitis: association with atopy and genital washing. Birley HD, Walker MM, Luzzi GA, et al. Genitourin Med 1993; 69: 400–3.

Forty-three patients with recurrent balanitis were evaluated. Thirty-one patients diagnosed with irritant contact dermatitis had a greater lifetime incidence of atopy and more frequent genital hygiene habit; 90% responded to conservative treatment, use of emollient creams, and restriction of soap use.

Second-Line Therapies

• Topical corticosteroids	A
• Circumcision	B
• Mupirocin	E

Systematic review and meta-analysis of randomized controlled trials on topical interventions for genital lichen sclerosus. Chi C, Kirtschig G, Baldo M, et al. J Am Acad Dermatol 2012; 67: 305–12.

Topical clobetasol propionate 0.05% applied for 3 months and mometasone furoate 0.05% applied for 5 weeks were both superior to placebo. Pimecrolimus 1% cream and clobetasol propionate 0.05% cream after 12 weeks of application were both effective at relieving pruritus and burning; there were no significant differences between clobetasol propionate and pimecrolimus. No evidence was found supporting the topical use of androgens and progesterone.

Randomized open-label trial comparing topical prescription triamcinolone to over-the-counter hydrocortisone for the treatment of phimosis. Chamberlin JD, Dorgalli C, Abdelhalim A, et al. J Pediatr Urol 2019; 15 (4): 388.e1–5.

Fifty-two boys with grades 4–5 phimosis (phimosis grade scale 0–5) were randomized to over-the-counter hydrocortisone or triamcinolone 0.1% cream with manual retraction of the foreskin twice daily for 12 weeks. Hydrocortisone and triamcinolone yielded 61.5% and 68.4% success rates at 12 weeks, which were not statistically different.

Plasma cell balanitis of Zoon: response to Trimovate cream. Tang A, David N, Horton LW. Int J STD AIDS 2001; 12: 75–8.

Ten patients with plasma cell balanitis treated with a topical mixture of oxytetracycline 3%, nystatin 100,000 U/g, and clobetasone butyrate 0.05% (Trimovate) for 3–12 weeks had complete resolution. Four required retreatment(s).

Does application of topical steroids for lichen sclerosus (balanitis xerotica obliterans) affect the rate of circumcision? A systematic review. Folaranmi SE, Corbett HJ, Losty PD. J Pediatr Surg 2018; 53: 2225–7.

This is a systematic review comprising 89 boys with lichen sclerosus, who were treated with topical corticosteroids. Circumcision was avoided in 31/89 (35%) with median follow-up of 4 months.

The diagnosis and management of male genital lichen sclerosus: a retrospective review of 301 patients. Kravvas G, Shim TN, Dorion PR, et al. J Eur Acad Dermatol Venereol 2018; 32: 91–5.

A retrospective review of 301 males with lichen sclerosus (41 with concomitant penile intraepithelial neoplasia) who were treated with circumcision or ultrapotent topical steroids. Over 90% of patients were cured. None progressed to squamous cell carcinoma.

Surgical management of genitourinary lichen sclerosus et atrophicus in boys in England: a 10-year review of practices and outcomes. Green PA, Bethell GS, Wilkinson DJ, et al. J Pediatr Urol 2019; 15(1): 45.

In total, 7893 boys had circumcision, primary preputioplasty, or preputioplasty plus concomitant steroid injection for lichen sclerosus; 22% of boys receiving primary preputioplasty required subsequent circumcision – this risk was reduced if concomitant steroid injection was given.

Plasma cell balanitis: clinical and histopathological features – response to circumcision. Kumar B, Sharma R, Rajagopalan M, et al. Genitourin Med 1995; 71: 32–4.

Twenty-seven patients with plasma cell balanitis were cured with circumcision. There were no recurrences at 3-year follow-up.

Plasma cell balanitis: clinicopathologic study of 112 cases and treatment modalities. Kumar B, Narang T, Dass Radotra B, et al. J Cutan Med Surg 2006; 10: 11–5.

A study of 112 males with plasma cell balanitis demonstrated complete resolution and no recurrence in the 85 who underwent circumcision. Twenty-two of 27 showed healing at 2–3 months with topical therapy (corticosteroids, corticosteroids–antifungal, or tacrolimus).

Successful management of Zoon's balanitis with topical mupirocin ointment: a case report and literature review of

mupirocin-responsive balanitis circumscripta plasmacellularis. Bari O, Cohen PR. *Dermatology and Therapy* 2017; 7: 203–10.

Two patients with Zoon balanitis that had failed to improve with topical clotrimazole experienced complete resolution within 90 days using mupirocin 2% ointment applied three times a day. The authors propose that mupirocin 2% ointment may be used as a diagnostic and monotherapeutic agent as similar-appearing dermatoses lack response to this agent.

Third-Line Therapies

• Topical tacrolimus	B, C (for Zoon's)
• Topical pimecrolimus	A/D (for Zoon's)
• Imiquimod	E
• CO ₂ laser	C
• Erbium:YAG laser	B
• Photodynamic therapy	E
• Acitretin	A
• Thalidomide	E
• Water of the three sulfates	A
• Intraurethral steroids	C

Treatment of male genital lichen sclerosis with clobetasol propionate and maintenance with either methylprednisolone aceponate or tacrolimus: a retrospective study. Kyriakou A, Patsialas C, Parsatsi A, et al. *J Dermatolog Treat* 2013; 24: 431–4.

Forty-one males with genital lichen sclerosis were treated with clobetasol propionate cream 0.05% twice a day for 8 weeks; 37 patients were responsive to treatment. These patients were further treated with either methylprednisolone aceponate 0.1% cream twice weekly or tacrolimus 0.1% ointment once daily as maintenance. At week 20, there were no significant differences noted in global assessment, pruritus, or quality of life scores between the patients treated with methylprednisolone aceponate and tacrolimus.

Multicentre, phase II trial on the safety and efficacy of topical tacrolimus ointment for the treatment of lichen sclerosis. Hengge UR, Krause W, Hofmann H, et al. *Br J Dermatol* 2006; 155: 1021–8.

Prospective, multicenter phase II study of tacrolimus 0.1% ointment in 84 patients (49 women, 32 men, 3 girls) with lichen sclerosis twice daily for 16 weeks demonstrated clearance of clinical disease in 43% and partial resolution in 34% at 24 weeks. Maximal response occurred at 10–24 weeks. No gender difference in response to therapy was noted.

Safety and tolerability of adjuvant topical tacrolimus treatment in boys with lichen sclerosis: a prospective phase 2 study. Ebert AK, Rosch WH, Vogt T. *Eur Urol* 2008; 54: 932–7.

Twenty boys with biopsy-confirmed lichen sclerosis underwent circumcision followed by topical tacrolimus 0.1% ointment twice daily for 3 weeks. All completed treatment without adverse side effects and no evidence of clinical disease at follow-up.

Therapeutic efficacy of topical calcineurin inhibitors in plasma cell balanitis: case series and review of the literature. Kyriakou A, Patsatsi A, Patsialas C, et al. *Dermatology* 2014; 228: 18–23.

Nine cases of Zoon balanitis, seven of which were previously treated with topical steroids or antifungals, were treated with tacrolimus 0.1% ointment twice daily for 4 weeks. Eight out of

nine cases had a complete response. One patient remained refractory and underwent circumcision. Two patients experienced a burning sensation with application that resolved within 2–3 days.

Although the use of calcineurin inhibitors appears to be effective for both BXO and Zoon balanitis, with continued use, surveillance for the development of squamous cell carcinoma (notably in BXO) is essential because of the theoretical possibility that these agents increase the risk of malignancy.

Zoon's balanitis treated with imiquimod 5% cream. Marconi B, Campanati A, Simonetti O, et al. *Eur J Dermatol* 2010; 20: 134–5.

A case series of Zoon balanitis successfully treated with imiquimod 5% cream three times weekly for 12 weeks.

Ablative erbium:YAG laser treatment of idiopathic chronic inflammatory non-cicatricial balanoposthitis (Zoon's disease). A series of 20 patients with long-term outcome. Wollina U. *J Cosmet Laser Ther* 2010; 12: 120–3.

Ablative erbium:YAG laser treatment was used in 20 patients with Zoon balanitis with complete reepithelialization within 2–3 weeks in all patients.

Genital lichen sclerosis treated by carbon dioxide laser. Aynaud O, Plantier F. *Eur J Dermatol* 2010; 20: 387–8.

A report of four cases of penile lichen sclerosis successfully treated with CO₂ laser and a review of the literature on CO₂ laser treatment for genital lichen sclerosis.

Zoon's balanitis: presentation of 15 patients, five treated with a carbon dioxide laser. Retamar RA, Kien MC, Chouela EN. *Int J Dermatol* 2003; 42: 305–7.

Discussion of CO₂ laser treatment in five patients with Zoon balanitis with variable efficacy.

Zoon's balanitis successfully treated with photodynamic therapy: case report and literature review. Borgia F, Vaccaro M, Foti A, et al. *Photodiagnosis Photodyn Ther* 2016; 13: 347–9.

A patient with recalcitrant Zoon balanitis who refused circumcision was treated with 10% aminolevulinic acid in polyethylene glycol ointment under occlusion for 3 hours followed by diode red light at 630 nm at a distance of 50 mm from the skin surface for a total time of 8 minutes with a resulting light dose of 75 J/cm². Almost complete clearance was seen at 3 months' follow-up after a total of three treatments at 2-week intervals.

Feasibility of 5-aminolevulinic acid mediated photodynamic therapy for male genital lichen sclerosis. Hao J, Liu J. *Photodiagnosis Photodyn Ther* 2020; 29: 101666.

Three male patients with genital lichen sclerosis and a history of circumcision were treated with ALA-PDT (patient 1: 12 treatments at 4-week intervals; patients 2 and 3: four treatments at 2-week intervals), and demonstrated a 30–70% reduction of lesion size after treatments. Adverse effects included pain and swelling, which disappeared soon after irradiation and without medication.

Acitretin for severe lichen sclerosis of male genitalia: a randomized, placebo-controlled study. Ioannides D, Lazaridou E, Apalla Z, et al. *J Urol* 2010; 183: 1395–9.

A randomized, double-blind, placebo-controlled study to evaluate the efficacy of a 35-mg daily dose of acitretin for 20 weeks compared with placebo in men with severe, recalcitrant lichen sclerosis. Of 49 patients completing the study, 24 of the 33 in the

acitretin group had complete or partial resolution, whereas only 3 out of 16 in the control group responded. This study found acitretin to be safe and effective.

Thalidomide in plasma cell balanitis refractory to conventional topical treatment. Serrao LM, Sarmenghi KDA, Pinto BCBP, et al. *An Bras Dermatol* 2018; 93: 881–3.

A 32-year-old male with HIV and Zoon balanitis was refractory to topical tacrolimus and systemic antibiotics. He refused circumcision. Thalidomide 100 mg/day for 6 weeks resulted in remission of disease and no relapse through 8 months of follow-up.

Clinical study of the effectiveness of the ‘water of 3 sulfates’ on balanitis and balanoposthitis. Gonzalvo V, Polo A, Serralach F, et al. *Actas Urol Esp* 2015; 39: 118–21.

Fifty patients with acute balanitis or balanoposthitis were randomized to ‘water of the three sulfates’ (copper sulfate, zinc

sulfate, and alum) or saline solution. Exudate, erythema, edema, burning, and itching were assessed. The outcomes obtained for water of the three sulfates for all clinical parameters were higher than control, although significant differences were only found for amount of exudate.

Intraurethral steroids are a safe and effective treatment for stricture disease in patients with biopsy-proven lichen sclerosis. Potts BA, Belsante MJ, Peterson AC. *J Urol* 2016; 195: 1790–6.

A retrospective review of 28 males with lichen sclerosis complicated by urethral stricture, who underwent topical intraurethral steroid application. The protocol was clobetasol 0.05% cream used to lubricate a urinary catheter or meatal dilator, applied twice daily for 2–3 months, at which point the patient was able to titrate medication use as needed. The success rate was 89% and no patient went on to require urethroplasty.

Basal cell carcinoma

Kalee Shah, Maxim Polansky, Kishwer Nehal



Basal cell carcinoma (BCC) is a slow-growing, locally destructive keratinocyte carcinoma (KC) that rarely metastasizes. It is the most common type of skin cancer, with nearly 4.3 million new cases diagnosed annually in the United States alone. BCCs most commonly arise in areas that are chronically exposed to ultraviolet light, especially the head and neck. Although the risk of metastasis is low, BCCs can be challenging to treat given their frequent location in functionally and cosmetically sensitive areas on the face.

MANAGEMENT STRATEGY

Therapeutic intervention for BCC is geared toward complete tumor eradication with maximal preservation of function and the optimal cosmetic result. Based on the best available evidence and consensus from leading experts, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN) divide BCC into low- and high-risk based on the likelihood of local recurrence.

BCC is considered low-risk if it is less than 1 cm in diameter and located on the cheeks, forehead, scalp, neck, and pretibial lower extremities (area M) or if it is less than 2 cm and located on the trunk or extremities (excluding the hands, nail units, pretibial skin, ankles, and feet) (area L). Other tumor-related factors that are considered low-risk are primary nature, well-circumscribed clinical borders, non-aggressive growth pattern (nodular, superficial, keratotic, infundibulocystic, and fibroepithelioma of Pinkus), and absence of perineural involvement. Patient-related factors that are considered low-risk by the NCCN include immunocompetent patients and those without a prior history of radiotherapy (RT) at the site of the primary BCC.

BCCs that are high-risk for local recurrence include any tumor that occurs in the 'mask' areas of the face including the central face, eyelids, eyebrows, periorbital nose, lips, chin, mandible, preauricular skin, postauricular skin, temple, and ear, as well as the genitalia, hands, and feet (area H). Tumors that are greater than 1 cm in area M or 2 cm in area L are also considered high-risk. The presence of an aggressive growth pattern (infiltrative, micronodular, morphea, basosquamous, or sclerosing), perineural invasion, ill-defined clinical borders, and recurrent nature is considered a high-risk feature. BCCs occurring in patients that are immunosuppressed or with a history of RT at the tumor site are also high-risk.

Individual patient characteristics, such as medical comorbidities/life expectancy, functional status, and patient preference, may also inform shared decision-making. It is important to note that in the very elderly population, age alone is inadequate for making treatment decisions.

Comorbidity scores associated with limited life expectancy in the very elderly with nonmelanoma skin cancer. Rogers EM, Connolly KL, Nehal KS, et al. *J Am Acad Dermatol* 2018; 78: 1119–24.

In a single-center, retrospective study of 488 patients, age 85 or older, who presented to dermatologic surgeons for management of non-melanoma skin cancer, the Adult Comorbidity Evaluation-27 (ACE-27) and Age-Adjusted Charlson Comorbidity Index (ACCI) predicted limited life expectancy at scores of 3 and 7 or more, respectively. Use of validated comorbidity indices such as the ACE-27 or ACCI may help inform the shared decision-making approach in the treatment of BCC in the very elderly.

Mohs micrographic surgery (MMS) is considered the gold standard for treatment of high-risk BCCs, providing the highest cure rate. Given its unique ability to have precise margin control and tissue sparing qualities, it is the favored approach for tumors in the high-risk H zone. Recurrence rates from a well-designed, prospective study over a 10-year follow-up period are 4.4%, compared with 12.2% for surgical excision. In 2012, the American Academy of Dermatology (AAD), American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery created appropriate use criteria (AUC) for MMS. A Mohs surgery AUC mobile application is available to assist practitioners and can be downloaded from the AAD website.

Surgical excision can be considered for both low- and high-risk tumors. Long-term (greater than 5 years) recurrence rates are higher with surgical excision compared with MMS for high-risk facial BCCs. The NCCN guidelines recommend at least a 4-mm margin for BCCs with low-risk features that are less than 2 cm in diameter. Tumors with larger size, aggressive growth pattern, and history of recurrence require larger margins, staged excision with delayed repair, or intraoperative histologic control, such as with MMS.

Curettage and electrodesiccation (C&E) is a simple, rapid, and inexpensive method to treat low-risk BCC. Prospective studies directly comparing C&E with other therapeutic modalities are lacking, and retrospective studies not controlled for size, histology, location, and history makes comparisons with other treatment modalities impossible. The NCCN guidelines acknowledge the utility of C&E for properly selected, low-risk BCC but highlight that C&E should not be used in areas of terminal hair growth due to risk of follicular extension. Furthermore, if the subcutaneous layer is reached during C&E, surgical excision should be performed instead.

RT can be considered as a first-line therapy for tumors that are unresectable either due to location, size, patient comorbidities, or patient preference. Contraindications to RT include genetic syndromes that predispose to skin cancer such as xeroderma pigmentosum and nevoid BCC syndrome, and connective tissue diseases. The NCCN guidelines suggest avoiding RT in patients less than 60 years old due to long-term toxicity and risk of secondary malignancy. Postradiation adverse events include skin toxicity, increased risk of subsequent skin cancers, and increased difficulty in management of tumor recurrences within the radiation field. Adjuvant RT should be considered for deeply invasive BCCs with positive margins following resection or those with clinically significant perineural invasion.

Imiquimod is a toll-like receptor 7 agonist that exerts an anti-tumor effect by modulating the immune system and stimulating apoptosis of BCC tumor cells. It is FDA-approved for non-surgical management of superficial BCC; tumor-free survival is 80% at 5 years.

Topical 5-fluorouracil (5-FU) is a chemotherapy agent that, when applied topically, induces cancer cell death in the top layers of the skin. It is FDA-approved for the treatment of small superficial BCCs. In a recent randomized, controlled trial (RCT), tumor-free survival at 5 years was 70%.

Photodynamic therapy (PDT) performed with photosensitizers, methyl-aminolevulinate (MAL), or aminolevulinic acid (ALA) yields a lower cure rate but may offer a better cosmetic outcome than surgical excision. PDT is approved for the treatment of BCCs in Europe, but remains off-label in the United States. It should only be used to treat small, superficial BCCs in patients that decline surgical treatment or when surgery is impractical.

Cryosurgery is a simple and cost-effective modality for treating low-risk superficial BCCs, but recurrence rates are high. Studies have found a large variability in recurrence rates of BCCs treated with cryosurgery, likely due to differences in interoperator techniques. This treatment modality should be considered in very specific cases only when other treatment options are impractical or prohibitive. Recommended regimens include two freeze-thaw cycles and the use of a cryoprobe to assess tissue temperature achieved: -50°C is generally regarded as sufficiently cytotoxic.

Systemic therapies are reserved for metastatic tumors or for tumors not amenable to surgery. Mutations in the sonic hedgehog pathway occur in up to 90% of BCCs. Essential to this pathway is the protein smoothened, and two inhibitors of this protein are now FDA-approved for treatment of advanced BCC, *vismodegib* and *sonidegib*. Trials have shown an objective response rate (ORR) between 30% and 60% and a complete response rate (CR) between 4% and 5%. Given the low rates of CR, hedgehog pathway inhibitors are often

seen as a neoadjuvant therapy to bridge to definitive treatment with surgery or radiation. Long-term tolerability is low; side effects include muscle spasms, weight loss, abnormal taste, and alopecia. Alternative dosing regimens have been proposed to reduce the side effect profile. Other systemic therapies used for advanced BCC include immunotherapy and cytotoxic chemotherapy.

Secondary prevention should focus on sun protection and regular skin cancer screening. The risk of developing a subsequent KC after first lifetime KC is 40.7% at 5 years and 59.6% at 10 years. There is limited evidence to support chemoprevention for BCC in high-risk, non-transplant patients; however, early data are promising for oral nicotinamide supplementation. Oral retinoids and topical 5-FU do not alter the incidence of subsequent BCC in those with a history of KC.

National Comprehensive Cancer Network. Basal Cell Skin Cancer (Version 1.2021). The NCCN guidelines are created based on the best available evidence as well as expert opinion from a multidisciplinary group of specialists including dermatologists, surgical oncologists, medical oncologists, radiation oncologists, and dermatopathologists. They are available for free on the NCCN website. For low-risk BCC, the NCCN recommends C&E, standard excision with 4 mm margins and postoperative margin assessment, or RT for non-surgical candidates. High-risk BCC should be treated with MMS, resection with complete circumferential peripheral and deep margin assessment, or standard excision with wider margins and delayed repair. RT and systemic therapy should be employed for non-operable, high-risk BCC.

Specific Investigation

- Dermoscopy to improve diagnostic accuracy prior to tissue analysis
- Biopsy with adequate dermal component
- Radiologic examination (CT, MRI) if high-risk tumor

An adequate biopsy is critical in assessing BCC histologic subtype. Deep shave, punch, incisional, or excisional biopsy can all give sufficient dermis for such an evaluation. Curettage biopsy is often insufficient to establish the diagnosis and the tumor subtype. Use of dermoscopy may improve diagnostic accuracy (sensitivity 91.2%, specificity 95%).

A number of non-invasive imaging technologies are being investigated to improve diagnostic accuracy including reflectance confocal microscopy (RCM), optical coherence tomography, infrared spectroscopy, and ultrasound. RCM demonstrates 91.7% sensitivity and 91.3% specificity for diagnosis of BCCs.

Rarely, a BCC may reach a size such that direct bony invasion or large nerve involvement has occurred. If this is strongly suspected, a preoperative computed tomography (CT) scan with contrast to assess for bony invasion or magnetic resonance imaging (MRI) to assess for perineural spread can be considered. When faced with a locally advanced or metastatic BCC, a multidisciplinary care team of dermatologists, medical oncologists, surgical oncologists, radiation oncologists, and palliative care physicians should be convened.

First-Line Therapies

• Mohs micrographic surgery	B
• Excisional surgery	B
• Radiation therapy	B
• Curettage and electrodesiccation	B

Surgical excision versus Mohs micrographic surgery for basal cell carcinoma of the face: a randomized clinical trial with 10 year follow up. van Loo E, Mosterd K, Krekels GA, et al. *Eur J Cancer* 2014; 50: 3011–20.

In a randomized, prospective study, 408 high-risk facial BCCs and 204 recurrent facial BCCs were randomized to conventional surgery or MMS. There was no significant difference between recurrence rate of primary BCC between MMS and conventional surgery at 5-year follow-up. At the 10-year follow-up, the recurrence rate for primary BCC treated with MMS was 4.4%, whereas for conventional surgery it was 12.2%. For recurrent facial BCC, MMS had a 3.9% recurrence rate versus 13.55% for conventional surgery at 10-year follow-up. A substantial number of recurrences occurred more than 5 years following treatment: 56% for primary BCC and 14% for recurrent BCC.

Adverse events associated with Mohs micrographic surgery: multicenter prospective cohort study of 20,821 cases at 23 centers. Alam M, Ibrahim O, Nodzenski M, et al. *JAMA Dermatol* 2013; 149: 1378–85.

A multicenter prospective cohort study of 20,821 MMS procedures recorded 149 adverse events (0.72%) including four serious events (0.02%). There were no deaths reported. The most common adverse events were infections (61.1%), dehiscence and partial or full necrosis (20.1%), and bleeding (15.4%). Most bleeding and wound healing complications occurred in patients on anticoagulation.

FACE-Q Skin Cancer Module for measuring patient-reported outcomes following facial skin cancer surgery. Lee EH, Klasen AF, Cano SJ, et al. *Br J Dermatol* 2018; 179: 88–94.

The FACE-Q Skin Cancer Module is a new, validated, patient-reported outcomes measurement for patients undergoing surgery for facial skin cancers. Dermatologic and reconstructive surgeons may use this tool to evaluate patient satisfaction with regard to facial/scar appearance, psychosocial stress, cancer worry, and patient experience.

Suggested excisional margins for cutaneous malignant lesions based on Mohs micrographic surgery. Schell AE, Russell MA, Park SS. *JAMA Facial Plast Surg* 2013; 15: 337–43.

A retrospective review of 495 lesions treated with MMS recorded margins necessary for clearance of both low- and high-risk BCC. The margin required to completely excise 95% of low-risk BCCs was 4.75 mm and high-risk BCCs was 8 mm. Established high-risk zones, such as the H zone, were not associated with larger margins in this study.

Surgical margins for basal cell carcinoma. Wolf DJ, Zitelli JA. *Arch Dermatol* 1987; 123: 340–4.

One hundred seventeen low-risk BCCs were prospectively studied to determine the extent of subclinical tumor invasion. Normal skin surrounding the tumor was marked in 2 mm intervals and the tumor was subsequently excised using the MMS method. A surgical margin of 4 mm histologically cleared 98% of the tumors less than 2 cm.

Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomized study. Avril MF, Auperin A, Margulis A, et al. *Br J Cancer* 1997; 76: 100–6.

A randomized trial in which 347 primary BCCs less than 4 cm in size were assigned to surgical excision or RT. The 4-year recurrence rate was 0.7% for surgical excision and 7.5% for RT. Cosmesis, as judged by the patient and blinded judges, was significantly better in the surgery group than in the RT group.

Therapeutic ionizing radiation and the incidence of basal cell carcinoma and squamous cell carcinoma. The New Hampshire Skin Cancer Study Group. Lichter MD, Karagas MR, Mott LA, et al. *Arch Dermatol* 2000; 136: 1007–11.

This study demonstrated a statistically significant increased risk (relative risk 3.30) of the development of BCC in the exposure window after therapeutic RT. The development of subsequent tumors is a significant possible side effect of radiation therapy.

Recurrence rates of treated basal cell carcinomas. Part 2: curettage–electrodesiccation. Silverman MK, Kopf AW, Grin CM, et al. *J Dermatol Surg Oncol* 1991; 17: 720–76.

This retrospective study of 2314 primary BCCs treated by C&D at a university dermatology clinic reported a 13.2% 5-year recurrence rate after C&D. Further analysis showed that size and location were important variables, with 5-year recurrence rates varying from 9.5% in low-risk locations to over 16.3% in high-risk sites. Similarly, 5-year recurrence rates ranged from 8.5% for tumors less than 5 mm to 19.8% for tumors 20 mm or more.

Recurrence rates of aggressive histologic types of basal cell carcinoma after treatment with electrodesiccation and curettage alone. Blixt E, Nelsen D, Stratman E. *Dermatol Surg* 2013; 39: 719–25.

Of 37 primary, aggressive BCCs (infiltrative, desmoplastic, morpheaform, or micronodular subtype), 10 recurred within 3.3 years (27%). The median follow-up was 6.5 years.

Second-Line Therapy

• Topical imiquimod	A
• Topical 5-fluorouracil	A
• Photodynamic therapy	A
• Cryosurgery	B
• Topical ingenol mebutate	B

Comparing treatments for basal cell carcinoma in terms of long-term treatment-failure: a network meta-analysis. Fukumoto T, Fukumoto R, Oka M, et al. *J Eur Acad Dermatol Venereol* 2019; 33: 2050–7.

In patient-level meta-analysis of 1738 tumors, surgery had the lowest odds of treatment failure, followed by radiotherapy [odds ratio (OR) 3.38], imiquimod (OR 12.29), cryotherapy (OR 19.91), 5-FU (OR 22.37), and PDT (OR 30.49). In tumor-level meta-analysis, MMS had the lowest odds of treatment failure (OR 0.50), followed by surgery (OR 1.00), cryotherapy (OR 4.06), and PDT (10.30). This rank order was maintained with subgroup analysis based on histologic subtype.

Surgery versus 5% imiquimod for nodular and superficial basal cell carcinoma: 5-year results of the SINS randomized controlled trial. Williams HC, Bath-Hextall F, Ozolins M, et al.; Surgery Versus Imiquimod for Nodular and Superficial Basal Cell Carcinoma (SINS) Study Group. *J Invest Dermatol* 2017; 137: 614–9.

Participants of this controlled trial were randomized to imiquimod 5% cream once daily (total course 6 weeks for superficial BCC and 12 weeks for nodular BCC) or excisional surgery with 4-mm margins. Five-year success rates for imiquimod were 83.8% for superficial BCC and 81.1% for nodular BCC. The 5-year success rates for surgery were 96.8% for superficial BCC and 98.8% for nodular BCC. Most imiquimod failures occurred in the first year after treatment.

Five-year results of a randomized controlled trial comparing effectiveness of photodynamic therapy, topical imiquimod, and topical 5-fluorouracil in patients with superficial basal cell carcinoma. Jansen MHE, Mosterd K, Arits AHMM, et al. *J Invest Dermatol* 2018; 138: 527–33.

A prospective, non-inferiority, randomized, controlled, multicenter trial with 601 patients showed that 5% imiquimod cream was superior to 5-FU and MAL-PDT at 1 and 3 years after treatment of superficial BCC. Five years after treatment, the probability of tumor-free survival was 80.5% for imiquimod compared with 70.0% for 5-FU and 62.7% for MAL-PDT.

Comparison of long-term cosmetic outcomes for different treatments of superficial basal cell carcinoma. Jansen MHE, Koekelkoren FHJ, Nelemans P, et al. *J Am Acad Dermatol* 2018; 79: 961–4.

MAL-PDT had a statistically significant better cosmetic outcome than imiquimod or 5-FU therapy for the treatment of superficial BCC at 5 years' posttreatment in recurrence-free patients. However, treatment failure occurred more frequently after treatment with MAL-PDT necessitating retreatment with surgery, which was associated with a lower chance of favorable cosmetic outcome.

Photodynamic therapy of basal cell carcinoma: clinical and pathological determinants of response. Fantini F, Greco A, Del Giovane C, et al. *J Eur Acad Dermatol Venereol* 2011; 25: 896–901.

Clinical and pathological characteristics of 194 BCCs that were treated with MAL-PDT were analyzed. Complete response was 82% for superficial BCC and 33% for nodular BCC. Factors associated with complete response were superficial histotype, location on the trunk, absence of ulceration, and thickness less than 5 mm. Patient age, gender, and tumor size were not significant predictors of treatment response.

Five year follow-up of a randomized prospective trial of topical methyl aminolevulinate photodynamic therapy vs. surgery for nodular basal cell carcinoma. Rhodes LE, de Rie MA, Leifsdottir R, et al. *Arch Dermatol* 2007; 143: 1131–6.

Fifty-three nodular BCCs were treated with 2–4 sessions of MAL-PDT and 52 nodular BCCs were treated by surgical excision. At 5-year follow-up there was a 14% recurrence rate in the PDT group versus 4% in the surgical excision group. The cosmetic outcome was rated to be better in the PDT group than in the excision group.

Photodynamic therapy in the treatment of basal cell carcinoma: a systematic review and meta-analysis. Wang H, Xu Y, Shi J, et al. *Photodermatol Photoimmunol Photomed* 2015; 31: 44–53.

A systematic review and meta-analysis of eight RCTs (1583 patients) comparing PDT versus non-PDT treatments for BCC found that PDT was associated with a lower complete clearance rate and higher 1-year and 5-year recurrence rates when compared with surgical excision. There was no statistically significant difference between PDT and cryotherapy or topical therapy (imiquimod and 5-FU). PDT had a significantly better cosmetic outcome than all other modalities.

A systematic review on the use of cryotherapy versus other treatments for basal cell carcinoma. Tchanque-Fossuo CN, Eisen DB. *Dermatol Online J* 2018; 24.

A systematic review of six RCTs demonstrated similar efficacy between PDT and cryosurgery for the treatment of primary superficial and nodular BCC. Recurrence rates for cryotherapy range

from 6.3% to 39% at 2 years' follow-up. One study with 5-year follow-up data reported a recurrence rate of 20%.

Locally Advanced and Metastatic BCC

• Adjuvant radiation therapy	D
• Hedgehog pathway inhibitors	A
• Immunotherapy	C
• Cytotoxic chemotherapy	D

Outcomes of radiation therapy for advanced T3/T4 non-melanoma cutaneous squamous cell and basal cell carcinoma. Kim SK, Barker CA. *Br J Dermatol* 2018; 178: e30–2.

Outcomes of curative-intent RT and adjuvant RT for 25 T3/T4 BCCs were reviewed in a retrospective study from a single institution. Three-year disease specific survival was 87.8% for patients treated with curative-intent RT and 85.7% for adjuvant RT. Survival was not associated with tumor stage or treatment intent.

Hedgehog pathway inhibitor therapy for locally advanced and metastatic basal cell carcinoma: a systematic review and pooled analysis of interventional studies. Jacobsen AA, Aldahan AS, Hughes OB, et al. *JAMA Dermatol* 2016; 152: 816–24.

A review of eight pooled articles included 744 total patients with 704 patients clinically evaluable. Sonidegib did not yield enough publications for a formal analysis. ORR to vismodegib for locally advanced BCC had a weighted average of 64.7%; CR averaged 31.1%. ORR for metastatic BCC was 33.6%; CR averaged 3.9%. Median duration of therapy was 35.8 weeks.

Long-term efficacy and safety of sonidegib in patients with advanced basal cell carcinoma: 42-month analysis of the phase II randomized, double-blind BOLT study. Dummer R, Guminski A, Gutzmer R, et al. *Br J Dermatol* 2020; 182(6): 1369–78.

At 42 months, the ORR for locally advanced BCC treated with sonidegib 200 mg daily was 56% compared to 46.1% in the 800 mg daily group. CR for locally advanced BCC were 5% and 1.6% in the 200 mg daily and 800 mg daily groups, respectively. ORR for metastatic BCC was 8% in the 200 mg daily group versus 17% in the 800 mg daily group. No patients with metastatic BCC demonstrated complete response regardless of dose.

Pembrolizumab for advanced basal cell carcinoma: an investigator-initiated, proof-of-concept study. Chang ALS, Tran DC, Cannon JGD, et al. *J Am Acad Dermatol* 2019; 80: 564–6.

Nine patients received pembrolizumab monotherapy at a dose of 200 mg intravenously every 3 weeks and seven patients received pembrolizumab with vismodegib in this open-label, non-randomized study. The ORR for pembrolizumab monotherapy group was 44% and for dual therapy was 29%. The median time to response for all responders was 10.4 weeks and the median duration of response was 67.3 weeks.

Chemoprevention

• Oral nicotinamide	A
• Oral retinoids	A
• Topical 5-fluorouracil	A
• (not effective)	

A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. Chen AC, Martin AJ, Choy B, et al. *N Engl J Med* 2015; 373: 1618–26.

In this randomized, double-blind, placebo-controlled trial of oral nicotinamide 500 mg twice daily for the prevention of actinic keratosis and KCs, 386 patients with a history of KC were randomized to nicotinamide or placebo arm for 12 months. The mean number of BCCs per person through the 12-month intervention period was reduced by 20%; however, the difference was not statistically significant.

Randomized controlled trial of acitretin versus placebo in patients at high-risk for basal cell or squamous cell carcinoma of the skin. Kadakia KC, Barton DL, Loprinzi CL, et al. *Cancer* 2012; 118: 2128–37.

Prospective, randomized, double-blind, placebo-controlled trial of oral acitretin in 70 non-transplant patients with a history of KC. After 2 years of treatment, the patients treated with acitretin 25 mg five times weekly did not have a statistically significant reduction in BCC.

Chemoprevention of basal and squamous cell carcinoma with a single course of fluorouracil, 5%, cream: a randomized clinical trial. Weinstock MA, Thwin SS, Siegel JA, et al. *JAMA Dermatol* 2018; 154: 167–74.

A randomized, double-blind, placebo-controlled trial in which 932 participants were assigned to placebo or topical 5% FU application to the face and ears twice daily for 2–4 weeks. There was no statistically significant reduction in subsequent BCCs between the treatment and placebo groups at 12 months.

Becker nevus

Aiteh S. Jibbe, Bahar F. Firoz, Leonard H. Goldberg



Becker nevus, also called pigmentary hairy epidermal nevus, is a cutaneous hamartoma that may have increased epidermal pigmentation (melanocyte), appendageal (hair follicle), and dermal (smooth muscle) components. Becker nevus is first noticed around puberty on the shoulders and chest but may also be congenital and involve any area of the body with a sixfold greater prevalence in men. This direct relationship to puberty is thought to be due to the increased density of androgen receptors within the Becker nevus.

MANAGEMENT STRATEGY

Becker nevus is asymptomatic and may come to the attention of a physician for cosmetic or diagnostic purposes. Management of asymptomatic benign lesion should comprise confirmation of diagnosis and an evaluation for any associated pathology such as developmental abnormalities that can accompany Becker nevus or within the spectrum of Becker nevus syndrome. Reported cutaneous associations include an acneiform eruption, eczematous dermatitis, hypohidrosis, lichen planus, localized lipoatrophy, localized scleroderma, polythelia, psoriasisiform dermatitis, unilateral breast hypoplasia, osteoma cutis, capillary malformations, dermal melanocytosis, and neurofibromatosis type-1. Musculoskeletal associations include limb asymmetry, pectus excavatum/carinatum, scoliosis, and other vertebral defects.

Association of Becker nevus with cutaneous malignancies, including basal and squamous cell carcinoma, was described separately in three young individuals without significant risk factors. Although melanoma has been described in patients with Becker nevus, the risk of malignant transformation of the nevus itself is very low, thus enhanced screening is unnecessary.

The treatment of a Becker nevus depends on multiple factors including skin type, desired treatment end point, pigmentary involvement, hypertrichosis, and extent of musculoskeletal

involvement. Becker nevus is primarily treated for pigment or hair removal with lasers. *Surgical excision, oral and topical antian-drogens, topical depigmenting agents, and topical glycolic acid* and a variety of *light and laser sources* have also been used to treat both the pigmentary and musculoskeletal manifestations of Becker nevus.

Postzygotic mutations in beta-actin are associated with Becker's nevus and Becker's nevus syndrome. Cai ED, Sun BK, Chiang A, et al. *J Invest Dermatol* 2017; 137: 1795–8.

A postzygotic lethal mutation in ACTB, a gene encoding beta-actin, underlies the development of Becker nevi in both isolated Becker nevi and Becker nevus syndrome. These mutations potentiate the Hedgehog signaling pathway, thereby disrupting hair follicle and pilar muscle development causing this clinical phenotype.

Specific Investigations

- Skin biopsy – although skin biopsy is diagnostic, it is often unnecessary
- Inquire about family history and evaluate for associated pathology
- Dermoscopy – reticulated pigment network, focal hypopigmentation, furrow hypopigmentation, hair follicles, perifollicular hypopigmentation, and vessels are the main dermoscopic features

First-Line Therapies

Treatment can be divided into two components:

- Reduction of hyperpigmentation
- Removal of hair

Reduction of Hyperpigmentation

• Intense pulsed light	B
• Erbium:YAG laser	C
• Long-pulsed alexandrite laser	D
• Long-pulsed Nd:YAG	D
• Erbium-doped fiber laser (Fraxel)	D

Intense pulsed light for treatment of Becker's nevus. Wu PR, Lan-Ju L, Zhang Y-X, et al. *J Dermatolog Treat* 2019; 2: 1–6.

A prospective study of 24 patients with Becker nevus treated with intense pulsed light at a filter of 590nm. Treatments were repeated a mean of five times with 3-month duration between treatments. The majority of patients experienced at least 50% improvement in their lesion in both hyperpigmentation and hypertrichosis without signs of repigmentation at 6-month follow-up.

Efficacy and safety of short-pulse erbium:yttrium aluminum garnet laser treatment of Becker's nevus in Saudi patients: a pilot study. Al-Saif F, Al-Mekhadab E, Al-Saif H. *Int J Health Sci (Qassim)* 2017; 11: 14–7.

This study evaluated the use of 2940nm Er:YAG to treat pigmentation of Becker nevus in a series of seven patients. The study showed improvement in pigmentation in all seven patients with no infections, hypertrophic, or keloids posttreatment and no recurrence at 1 year.

Lasers for Becker's nevus. Zhong Y, Yang B, Huang L, et al. *Lasers Med Sci* 2019; 34: 1071–79.

This paper reviewed the efficacy of lasers from the range of 504–10,600 nm to treat Becker nevi. If a single laser is desired to treat both the pigmentary changes and hypertrichosis changes seen in Becker's nevus, a diode laser (808/810 nm) may be optimal over Nd:YAG laser (1064 nm) in order to minimize damage to uninvolved tissue. The greatest clinical efficacy for pigmentary changes was seen with Er:YAG 2940 nm laser after only one treatment with 1–5 passes.

Becker's naevus: a comparative study between Erbium:YAG and Q-switched Neodymium:YAG; clinical and histopathological findings. Trelles MA, Allones I, Moreno-Arias GA, et al. *Br J Dermatol* 2005; 152: 308–13.

Twenty-two patients with Becker nevi were studied, 11 with each laser. Both Erbium:YAG and Nd:YAG safely treated the lesions. For pigment removal, one pass with Erbium:YAG was superior to three treatment sessions with Nd:YAG.

Treatment of Becker's nevi with a long-pulse alexandrite laser. Choi JE, Kim JW, Seo SH, et al. *Dermatol Surg* 2009; 35: 1105–8.

Eleven Korean patients with Becker nevi were treated with a 755-nm long-pulse alexandrite laser (20–25 J/cm² fluence, 3 ms pulse duration, 15–18 mm spot size). Two patients had an excellent response, five good, and four a fair response. There was one case of partial hypertrophic scarring, and some patients had mild hypopigmentation; all outcomes were noted to be cosmetically acceptable.

Successful treatment of Becker's nevus with long-pulsed 1064-nm Nd:YAG and 755-nm alexandrite laser and review of the literature. Wulkan AJ, McGraw T, Taylor M. *J Cosmet Laser Ther* 2018; 20: 211–4.

Significant reduction in both pigment and hair seen in a Becker nevus on a 20-year-old male with Fitzpatrick skin type IV treated with a combination of six sessions of long-pulsed 1064-nm Nd:YAG (26–27 J/cm² fluence, 10-ms pulse duration, 15-mm spot size) 6 weeks apart followed by five sessions of long-pulsed 75-nm alexandrite laser (60–70 J/cm², 1.5 ms, 6 mm) at 3-month interval.

Hypertrichotic Becker's nevi treated with combination 1,550nm non-ablative fractional photothermolysis and laser hair removal. Balaraman B, Friedman PM. *Lasers Surg Med* 2016; 48: 350–3.

Retrospective analysis of three patients with Becker nevi treated with long-pulsed 1064 nm Nd:YAG in combination with non-ablative fractional erbium-doped (1550 nm). This combination resulted in greater than 75% clinical improvement in pigmentation and hypertrichosis.

Reduction of Hypertrichosis

- Diode laser **C**
- Normal mode ruby laser **D**
- Long-pulsed Nd:YAG **D**

Treatment of a Becker's nevus using a 694-nm long-pulsed ruby laser. Nanni CA, Alster TS. *Dermatol Surg* 1998; 24: 1032–4.

Single case report that showed reduction in pigmentation and a 90% reduction in hair growth after three treatments with the long-pulsed ruby laser with improvement for 10 months.

Hypertrichosis in Becker's nevus: effective low-fluence hair removal. Lapidoth M, Adatto M, Cohen S, et al. *Lasers Med Sci* 2014; 29: 191–3.

Fifteen patients treated with low-fluence, 808–810-nm diode laser had decreased hair growth at 6 and 12 months, without adverse effects.

800 nm diode laser does not display long-term benefit for hair removal in Becker's nevus: a retrospective analysis of 24 cases. Zhong Y, Huang L, Chen Y, et al. *Photodermatol Photoimmunol Photomed*. 2020; 36: 387–9.

Retrospective study of 24 patients with Becker nevi and Fitzpatrick type III skin treated with 800-nm diode laser. The study noted all patients showed at least a 25% reduction in hair within the nevus and 50% showed greater than 75% reduction in hair. However, hair regrowth of unknown extent was noted in all patients within 6-months of follow-up.

Second-Line Therapy

Reduction of hyperpigmentation

- Frequency-doubled Q-switched (QS) Nd:YAG **D**
- QS ruby laser **D**
- Picosecond alexandrite laser **E**

Laser treatment of epidermal nevi: a multicenter retrospective study with long-term follow-up. Alkhalifah A, Fransen F, Le Duff F, et al. *JAAD* 2019 Jun 13 [Epub ahead of print].

A study of 26 patients with Becker nevi treated with Q-switched laser ranging from 1064 nm, 755 nm, 694 nm, to 532 nm. Only three patients experienced any degree of improvement with only one patient maintaining the results after four sessions of Q-switched laser at 755 nm after a 12-month follow-up. Thus, this study concludes that Q-switched lasers are not an optimal treatment for Becker nevus regardless of their wavelengths.

Treatment of flat and elevated pigmented disorders with a 755-nm alexandrite picosecond laser: clinical and histological evaluation. Alegre-Sanchez A, Jiménez-Gómez N, Moreno-Arrones ÓM, et al. *Lasers Med Sci* 2018; 33: 1827–31.

Significant improvement in a Becker nevus of a 22-year-old female with type II Fitzpatrick skin treated with a 755-nm picosecond alexandrite laser after two sessions of 3.5 mm–2.08 J/cm².

Reduction of Excess Hair

- Electrolysis **E**

Electrolysis is a well-established method of epilation, but its use in removing hair from Becker nevus has not been published.

Third-Line Therapies	
• Spironolactone	E
• Topical flutamide	E
• Topical glycolic acid	E
• Topical azelaic acid	E
• Corrective camouflage	E

Becker’s nevus with ipsilateral breast hypoplasia: improvement with spironolactone. Jung JH, Kim YC, Park HJ, et al. *Journal of Dermatology* 2003; 30: 154–6.

A 17-year-old female with improvement of ipsilateral breast hypoplasia associated with Becker nevus on spironolactone on 50 mg a day.

Two similar cases have been reported in the literature at the same dose with similar outcomes.

Treatment of Becker nevus with topical flutamide. Taheri A, Mansoori P, Sandoval F, et al. *JAAD* 2013; 6: e147–8.

A 22-year-old Caucasian woman with a 10-year history of Becker’s nevus treated with topical 4% solution of flutamide applied twice daily. After 8 weeks of therapy there was significant improvement; no follow-up.

Lightening Becker nevus with topical glycolic acid. Zhong Y, Chen Y, Huang L, et al. *JAAD* 2019; 80: e3.

Application of topical 70% glycolic acid solution immediately followed by 10% sodium bicarbonate showed marked improvement in the pigmentation of a Becker nevus after five treatments with each treatment, with no recurrence at 3-month follow-up.

A case of Becker’s nevus with pityriasis versicolor. Sharma M, Kansal NK, Gautam RK. *J Eur Acad Dermatol Venereol* 2014; 28: 1827–8.

A 22-year-old male patient with Becker nevus developed pityriasis versicolor within the lesion. Hypopigmentation of pityriasis versicolor is hypothesized to be due to competitive inhibition of the enzyme tyrosinase by certain dicarboxylic acids (like azelaic acid) produced by the fungus, so the authors suggest topical azelaic acid as an option for treatment.

Corrective camouflage in pediatric dermatology. Tedeschi A, Dall’Oglio F, Micali G, et al. *Cutis* 2007; 79: 110–2.

Corrective camouflage using a variety of water-resistant and light to very opaque products was used in two patients with Becker nevi with great cosmetic results.

Bed bugs

Whitney A. High, Glen R. Needham



Human bed bugs (*Cimex lectularius*) are insects that require a blood meal to complete their life cycle, and this meal is typically acquired by biting sleeping humans. The bite can elicit an allergic reaction, creating pruritic, erythematous papules that are often excoriated and may become secondarily infected.

MANAGEMENT STRATEGY

Bed bug infestations are more common due to resistance and/or subsequent banning of the pesticide, dichlorodiphenyltrichloroethane (DDT).

Bed bugs usually bite just before dawn and lie in close proximity to humans' sleeping quarters. Although the bite of a bed bug is painless, an allergic reaction may ensue in some individuals, resulting in a skin lesion. Bed bugs typically bite exposed surfaces, such as the extremities or head/neck. The insect will not usually venture beneath bedding or bed clothes. A linear arrangement to bites is common.

The insect does not reside or lay eggs upon humans. Treatment focuses upon *detection and eradication of the household infestation*. *Insecticides, growth-regulating agents, and destructive modalities* may be employed to kill adults, progeny, and eggs. Many authorities believe that safe and successful eradication requires professional assistance.

Use of insecticides in the United States is regulated by the Environmental Protection Agency. The extended residual effect of DDT resulted in environmental damage; its use was banned. Resistance, first to DDT and later to malathion, may be an issue with its reemergence of bed bugs. More recently, pyrethroids (e.g., deltamethrin) have been utilized in controlling bed bug infestations, but, again, resistance has emerged.

There is interest in use of temperature extremes to eradicate infestations. *Steam* may be utilized to sterilize a mattress or similar materials for which insecticides are inappropriate, but a target temperature of 160–180°F must be reached over the entirety of the surface.

Commercial *whole room/whole home heating*, using propane heaters and fans, is available. Most of these systems achieve

a target temperature of around 113°F, held for 15–60 min. Although this temperature is less than the thermal death point of bed bugs (118°F), such treatments are often successful, presumably due to powerful convection currents that desiccate the insects. Other comparatively simplistic measures, such as impermeable mattress covers, are also widely employed.

The manipulation of insect pheromones is gaining interest, as bed bugs use pheromones to aggregate for mating and to increase local humidity and avoid desiccation. Ergo, blocking of this pheromone signaling may have disastrous effects upon a bed bug colony.

Treatment of bed bug bites among humans is directed at symptoms. Skin lesions are due to an allergic reaction to the saliva leaked during feeding. Sensitization is not universal, and some individuals will not react to bites.

Symptomatic bed bug bites produce an erythematous wheal, followed by a firm, reddish papule, sometimes with a central hemorrhagic punctum. Papulonecrotic and bullous forms have been described. Bites are often pruritic and are usually present on surfaces that are exposed during sleep, such as the head, neck, and extremities. Bite symptoms are treated with *potent topical steroids and antihistamines*.

The position of the US Centers for Disease Control and Prevention (CDC), and the bulk opinion of other experts, is that, as of yet, there is no clear evidence of successful transmission of a bloodborne pathogen via bed bug bites. Additional laboratory testing beyond bacterial culture of superinfected bites is not recommended.

Travel is a widely recognized contributing factor to the 'epidemic' of bed bug infestations. Hotels and other lodging facilities, regardless of cleanliness or cost, may be infested, and it is possible to bring an infestation home after a stay in infested lodgings.

It is important to inspect lodging facilities upon check-in. Luggage should be kept closed, or even sealed in plastic bags, to be left at the destination upon departing. Use of dressers and bureaus in a hotel room is discouraged. Metal luggage stands are preferable to wooden stands.

The re-emergence of the bed bug as a nuisance pest: implications of resistance to the pyrethroid insecticides. Davies TG, Field LM, Williamson MS. *Med Vet Entomol* 2012; 26: 241–54.

Resistance of bed bugs to insecticides is contributing to its resurgence as a pest. Reports of increasing resistance to pyrethroids exist throughout the world. The authors of this review report deltamethrin resistance in colonies obtained from more than 20 cities in the United States.

Insecticide resistance among bed bugs may be mediated by genetic mutations on target proteins, by overexpression of detoxifying enzymes, or by thickening of the insect cuticle with reduced insecticide penetration. The existence of multiple pathways of resistance bodes ominously for ever-increasing problems with eradication of infestations.

Acute illnesses associated with insecticides used to control bed bugs – seven states, 2003–2010. Centers for Disease Control and Prevention (CDC). *MMWR* 2011; 60: 1269–74.

Although subject to concerns of over/underreporting, the CDC recently detailed 111 illnesses spanning 2003–2010, including one fatality, attributed to excessive and/or inappropriate use of insecticides for bed bugs. The authors encourage persons with bed bug infestations to seek the services of a certified exterminator; strict adherence is necessary with regard to product instructions and warnings.

Use of consumer-grade indoor 'foggers' or 'bombs' for bed bugs is discouraged by experts because such products typically only scatter bed bugs over a larger area. Silica gel or diatomaceous earth may be used as a less toxic (but also less effective) alternative that kills via dehydration. There is no effective 'repellent' for bed bugs.

Bed bug aggregation pheromone finally identified. Gries R, Britton R, Holmes M, et al. *Angew Chem Int Ed Engl* 2015; 54: 1135–8.

Adult males, virgin adult females, and juvenile bed bugs respond to an airborne aggregation pheromone. In this article, the authors identified five volatile components (dimethyl disulfide, dimethyl trisulfide, (*E*)-2-hexenal, (*E*)-2-octenal, 2-hexanone) that attract bed bugs to safe shelters, and one less-volatile component (histamine), which causes arrestment upon contact.

Bed bugs reproduce via traumatic insemination, and females have structural adaptations to deal with this insult, whereas males have no such adaptations. Young males secrete pheromones to discourage other adult males from destructive same-sex copulation, and this represents another avenue of potential susceptibility.

Bedbugs as vectors for drug-resistant bacteria. Lowe CF, Romney MG. *Emerg Infect Dis* 2011; 17: 1132–4.

A report from Canada demonstrated that bed bugs may be capable of transmitting methicillin-resistant *Staphylococcus aureus* within an impoverished community.

Bedbugs. Kolb A, Needham GR, Neyman KM, et al. *Dermatol Ther* 2009; 22: 347–52.

In this review article the authors instruct that, upon returning home, immediate inspection of luggage and other belongings aids in the discovery of bed bugs or eggs in the midst of transport. Unpacking in the garage and/or vacuuming the exterior and interior of bags, with immediate disposal of the vacuum bag in a sealed plastic bag, may be of benefit in preventing undesired translocation.

Specific Investigations

- Visualization of the bed bugs by inspection, traps, or trained dogs
- Skin biopsy

The eggs, adults, and nymphal stages of the organism may be seen with the human eye. Therefore, when bed bug bites are suspected clinically, an appropriate starting point in investigation is careful inspection of sleeping quarters. Other techniques to detect infestation include simple taping of bed legs with sticky tape, placing bed posts in isolating devices or traps (homemade or purchased), or using trained dogs to localize areas of infestation.

Visual Inspection

Visual inspections should begin around the bed area. Adult bed bugs are 5–7 mm in length and vary in color from light brown to dark brown or even violaceous if they recently have fed. Nymphs are smaller and are often clearer in appearance, again unless having fed. Eggs are about 1 mm long, are ovoid with an operculum, and are sticky, adhering to surfaces in small aggregates.

In addition to detecting the organism, there should be a search for fecal smears or flecks of blood upon the bed linens and upon the edges of the mattress and box springs. Bed bugs, even adults, may fit within extraordinarily narrow cracks and crevices in furniture and walls, behind peeling wallpaper, and even behind switch plates. If a credit card can be inserted into a crevice, then it may also host bed bugs!

Lastly, when populations of bed bugs are particularly dense, a pungent but sweet odor, likened to coriander or cut cilantro, may permeate an infested room or an entire house.

Canine Inspection

Dogs have been successfully trained to detect the odor of bed bugs. The training protocol of the commercial kennels is proprietary, and the exact odor the dogs are detecting is unknown.

Bed Bug Traps

Bed bugs are attracted to humans via a combination of heat, carbon dioxide exhalation, and perhaps other detectable scents, such as human body volatiles, such as aldehydes and sulcatone.

Using this information, two commercial bed bug trapping devices have been marketed, and plans to build a homemade trap (using a cat feeding bowl, dry ice, and a Thermos vessel) have been widely published.

The principle in all these devices is to attract bugs coupled with a 'pitfall area' into which the bed bugs fall and cannot escape, or where sticky material entraps the bugs.

Other Monitoring Devices

A marketed device (Climbup Interceptor) consists of two nested plastic bowls, one inside the other, into which the feet of the bed are placed. Bugs migrating into or away from the bed are entrapped between the bowls. Along these same lines, inverted duct tape may be placed, 'sticky-side out,' upon the legs of the bed to entrap bed bugs as they traverse.

Effectiveness of a sugar–yeast monitor and a chemical lure for detecting bed bugs. Singh N, Wang C, Cooper R. *J Econ Entomol* 2015; 108: 1298–1303.

Many active bed bug monitoring devices are expensive or ineffective. Homemade dry ice traps require significant preparation and inconvenience. The authors designed a simple and affordable active bed bug monitor that used a sugar–yeast fermentation reaction to generate CO₂, instead of dry ice or bottled gas, as well as an experimental chemical lure to detect bed bugs. The authors concluded the tool was useful for monitoring bed bug infestations.

Ability of bed bug-detecting canines to locate live bed bugs and viable bed bug eggs. Pfister M, Koehler PG, Pereira RM. *J Econ Entomol* 2008; 101: 1389–96.

The authors examined dogs trained to locate bed bugs by smell. Under test conditions they were able to discriminate bed bugs from other insects with a 97.5% positive indication rate (correct indication of bed bugs when present) and with zero false positives (incorrect indication of bed bugs when not present). They were able to discriminate live bed bugs and viable bed bug eggs from dead bed bugs, cast skins, and feces, with a 95% positive indication rate and a 3% false-positive rate on bed bug feces. In experimentally contrived 'hotel rooms', canines were 98% accurate in locating live bed bugs.

Dermoscopy

Dermoscopy is useful for bed bug (*Cimex lectularius*) bites. Shirato T, Iwata H, Yoshimoto N, et al. J European Acad Dermatol 2016; 30: 539–40.

In this article, the authors report hemorrhagic spots observed by dermoscopy at bite sites, confirmed by biopsy and histologic exam. While not reporting pathognomonic dermoscopic findings, the authors feel dermoscopy is a convenient tool to identify potential bites.

Skin Biopsy

The histology of bed bug bites is non-specific, and similar to other insect and arthropod assault reactions. It includes a perivascular infiltrate of lymphocytes, histiocytes, eosinophils, and mast cells in the upper dermis, perhaps with dermal edema and/or extravasated erythrocytes.

Bullous reactions to bedbug bites reflect cutaneous vasculitis. De Shazo RD, Feldlaufer ME, Mihm MC, et al. Am J Med 2012; 125: 688–94.

The authors examined 'severe' cutaneous reactions, termed *bullous* or *complex reactions*, to bed bug bites and concluded the phenomenon is not rare. Of 357 photographs of bed bug bites posted on the Internet, 6% were bullous. Histopathologic evaluation of

bullous reactions showed a polymorphous picture with histologic evidence of an urticarial-like reaction early on that rapidly developed into a hybrid leukocytoclastic vasculitis, similar to the dermal vasculitis in patients with Churg–Strauss disease.

First-Line Therapies

• Identify and eradicate the infestation	A
• Control symptoms associated with the bites using antihistamines, topical steroids, and, in rare cases, oral steroids	E

Toxicity and potential utility of ivermectin and moxidectin as xenointoxicants against the common bed bug, *Cimex lectularius*. Sheele JM, Ridge GE. Parasitol Res 2016; 115: 3071–81.

In a controlled laboratory experiment, laboratory-reared bed bugs were exposed to varying concentrations of ivermectin and moxidectin using a feeding apparatus. Exposure to ivermectin, more than moxidectin, resulted in long-term sequelae among the insects to include reduced fecundity, feeding difficulty, and incomplete molting, but this was not a clinical trial.

Although interest in a xenotoxicant approach persists, the authors speculated that if ivermectin were used in such a schema, it might require a daily dose of 0.2 mg/kg for a 20-day period, and the safety of such a regimen in humans is not yet well established.

Behçet disease

Erkan Alpsoy



Behçet disease (BD) is a chronic, relapsing, inflammatory, multi-system disease of unknown etiology characterized by oral ulcers (OU), genital ulcers (GU), cutaneous lesions (e.g., erythema nodosum [EN]-like lesions, papulopustular lesions [PPL], superficial thrombophlebitis, extragenital ulcers, pathergy test positivity), ocular, vascular, articular, gastrointestinal, urogenital, neurologic, and cardiac involvement. Diagnosis in most patients can be made clinically only based on mucocutaneous symptoms, which figure prominently in the presentation and diagnosis and are considered the hallmarks of the disease. Therefore, their recognition may permit earlier diagnosis and treatment with beneficial results for prognosis. Due to the lack of a universally recognized pathognomonic laboratory test, the diagnosis is based on clinical criteria. Worldwide, the International Study Group criteria are the most widely used and well-accepted criteria among the experts of this field, which depends on the presence of recurrent OU, relapsing at least three times in 12 months, plus any two of recurrent GU, typical eye lesions, typical cutaneous lesions, or a positive pathergy test.

MANAGEMENT STRATEGY

BD generally runs a chronic course with unpredictable exacerbations and remissions. Male sex and a younger age of onset are associated with more severe disease. Each or any combination of mucocutaneous, articular, and ocular symptoms of the disease may produce significant pain or loss in function, or both. Besides considerable morbidity, the disease confers increased mortality, mainly because of pulmonary as well as large vessel involvement, neurologic, gastrointestinal, and cardiac involvement. BD usually starts with relatively milder manifestations, and severe involvement, in general, appears later. The main aim of the treatment should be the suppression of new inflammatory attacks to prevent irreversible organ damage, especially during the early, active phase of the disease.

In the absence of severe organ involvement, BD treatment is primarily based on the severity and extent of the mucocutaneous symptoms. *Colchicine* 0.5 mg two to four times daily should be the first choice in the treatment of OU, GU, EN-like lesions, and PPL. In resistant patients, *benzathine penicillin* (1.2 MU per month) can be used in addition to colchicine. Short-term corticosteroids (prednisolone, initial dose 40–60 mg daily for 2–4 weeks, tapered over the ensuing 4–6 weeks) in combination with other drugs such as colchicine should be considered as an effective treatment for acute attacks of OU, GU, EN-like lesions, and superficial thrombophlebitis. *Dapsone* 100–150 mg daily can also be used in the treatment of mucocutaneous symptoms as an effective alternative to colchicine but requires more frequent laboratory follow-up. Apremilast (30 mg twice daily) can be evaluated as an important alternative in the first-line treatment in patients who do not respond to previous treatments.

In patients inadequately controlled with the treatments above, azathioprine (2–2.5 mg/kg daily), anti-TNF- α agents (etanercept 25 mg, twice weekly, and infliximab and adalimumab in their usual dosages in psoriasis) and IFN- α (3–12 MU, thrice weekly) can represent effective second-line treatments of mucocutaneous lesions in BD. Cyclosporin (5 mg/kg daily), thalidomide (100–300 mg daily), zinc sulfate (300 mg daily), rebamipide (300 mg daily), isotretinoin (20 mg daily) are other alternatives to control the disease.

Secukinumab (150–300 mg at weeks 0, 1, 2, 3, and 4 and monthly after that), ustekinumab (90 mg at inclusion, at week 4, and then once every 12 weeks), IL-1 receptor antagonist anakinra (100 mg daily) and the full human anti-IL-1 β antibody canakinumab (150 mg every 6–8 weeks), methotrexate (7.5–20 mg weekly), pentoxifylline (400 mg thrice daily) can be used as third-line therapies.

The topical therapeutic agents used in the treatment of BD in randomized, controlled studies are still limited. It is imperative to ensure for the clinician that topical treatment of the disease has an only local effect and should almost always be associated with systemic treatment. *Topical corticosteroids* alone (triamcinolone acetonide in oral paste or dexamethasone ointment, thrice daily) for OU and in conjunction with *antiseptics* (e.g., fusidic acid/beta-methasone) for GU are useful, especially when they are used in the early stage of these lesions. Although the efficacy of anecdotal use of *intralesional triamcinolone acetonide* 5–10 mg/mL has been noted, it should be reserved for large and deep OU or GU since it is a very painful intervention. Topical corticosteroid eye drops are also used in mild attacks of anterior and intermediate uveitis together with mydriatics or cycloplegic agents. *Sucralfate* (5 mL solution, four times daily) can also accelerate healing and diminish the pain in both OU and GU. *Pimecrolimus* cream, twice daily, seems to be safe and efficient in the treatment of GU. *Wet dressings such as aluminum acetate* 3–5% (Burow's solution) can be applied in the early stage of EN-like lesions and superficial thrombophlebitis. This treatment should be combined with rest in bed.

Most experience in the treatment of OU in patients with BD comes from the studies performed in patients with recurrent aphthous stomatitis (RAS). OU of BD are identical to RAS in appearance. Therefore, therapeutic remedies related to RAS, to some extent, can be applied to OU of BD. Topical antibiotics, such as *tetracyclines* (four times daily) and their derivatives (doxycycline once at the initial visit and minocycline four times daily) in gel or mouthwash, *antimicrobial agents* (Listerine mouth rinse and chlorhexidine gel, 2–4 times daily), *amlexanox* (5% in the oral paste, four times daily), and *triclosan mouthwash* twice daily are beneficial by accelerating healing and can be used as first-line treatments of OU of BD. *Hydroxypropyl cellulose*, *diclofenac*, *lidocaine*, *silver nitrate*, *CO₂ laser*, and *Nd:YAG laser* are useful in decreasing pain and can be used in the topical treatment of OU as second-line options (see Ch. 16).

In the presence of severe organ involvement such as ocular, neurologic, gastrointestinal, or large vessel involvement, working in collaboration with other specialties to improve patient outcomes is mandatory. Depending on the organ involved, the drugs listed below can be used alone or in combination: *prednisolone, azathioprine, ciclosporin-A, cyclophosphamide, anti-TNF- α agents, IFN- α , interleukin-1 receptor antagonists, alemtuzumab, tocilizumab, rituximab, and stem cell transplantation.*

Specific Investigations

- Skin pathergy test
- Culture/PCR from oral or GU to exclude herpes simplex virus (HSV) infection
- Serum iron, folate, zinc, and vitamin B₁₂
- Complete blood count
- Urinalysis
- Comprehensive blood biochemistry
- HLA-B51
- A thorough review of systems, and referral for ophthalmologic, rheumatologic, neurologic, gastroenterologic, etc. assessment as appropriate
- Advanced laboratory and/or imaging methods based on organ involvement
- Tissue biopsy, in selected cases (skin primarily, but also tissue from the involved organs such as intestines)

Behçet's disease: a comprehensive review with a focus on epidemiology, etiology and clinical features, and management of mucocutaneous lesions.

Alpsoy E. J Dermatol 2016; 43: 620–32. This review reflects a dermatologist's view of BD. Besides the current state of knowledge regarding the epidemiology, etiopathogenesis, clinical features, and diagnosis, therapeutic approaches, including local and systemic agents for the treatment of mucocutaneous BD, are reviewed.

2018 update of the EULAR recommendations for the management of Behçet's syndrome.

Hatemi G, Christensen R, Bang D, et al. Ann Rheum Dis 2018; 77: 808–18. In this updated systematic literature review, management of BD was analyzed for treating different aspects of the disease.

First-Line Therapies

• Colchicine	A
• Colchicine + benzathine penicillin	B
• Corticosteroids	A
• Dapsone	A
• Apremilast	A
• Topical corticosteroids	A
• Sucralfate	A
• Pimecrolimus	A
• Topical antibiotics (tetracycline, doxycycline, minocycline)	A
• Topical amlexanox	A
• Topical antimicrobials (chlorhexidine, Listerine)	A
• Triclosan	A

A double-blind trial of colchicine in Behçet's syndrome.

Yurdakul S, Mat C, Tuzun Y, et al. Arthritis Rheum 2001; 44: 2686–92. In a prospective, randomized and placebo-controlled study, colchicine 1–2 mg daily reduced the occurrence of GU, EN-like lesions, and arthritis among women, and the occurrence of arthritis among men.

Colchicine and benzathine penicillin in the treatment of Behçet disease: a case comparative study.

MM Al-Waiz, KE Sharquie, MH A-Qaissi, et al. Dermatol Online J 2005; 11: 3. This study found the combined use of colchicine (1 g daily) and benzathine penicillin (1.2 MU monthly) treatment more effective in decreasing clinical manifestation index, the numerical sum of the clinical features, than either drug alone.

A double-blind trial of depot corticosteroids in Behçet's syndrome.

Mat C, Yurdakul S, Uysal S, et al. Rheumatology (Oxford) 2006; 45: 348–52. Low-dose depot steroid (40 mg methylprednisolone acetate every 3 weeks) in 86 patients who had active mucocutaneous lesions without eye and major organ involvement was found to be helpful in controlling EN-like lesions, especially among females.

Several retrospective studies and case series reported the efficacy of corticosteroids in daily and/or higher doses, especially in mucocutaneous lesions, acute uveitis, and neurologic disease. Corticosteroids can be used as monotherapy or in combination with other drugs such as colchicine, interferon (IFN)- α , ciclosporin, or azathioprine.

Dapsone in Behçet's disease: a double-blind, placebo-controlled, cross-over study.

Sharquie KE, Najim RA, Abu-Raghib AR. J Dermatol 2002; 29: 267–79. Study of 20 patients treated with either dapsone 100 mg daily or placebo reported significant reductions in the number, duration, and frequency of OU and number of GU in dapsone-treated patients. Dapsone treatment also decreased the frequency of EN-like lesions and PPL, and suppressed arthritis and epididymitis.

Comparing the effect of phenytoin syrup and triamcinolone acetonide ointment on aphthous ulcers in patients with Behçet's syndrome.

Fani MM, H Ebrahimi, S Pourshahidi, et al. Iran Red Crescent Med J 2012; 14: 75–8. In this randomized, controlled study, 30 patients were treated with 0.1% triamcinolone acetonide ointment thrice daily and other 30 patients with phenytoin syrup thrice daily. The healing response to triamcinolone acetonide (86.7%) was more than phenytoin (53.3%) 1 week later.

The use of sucralfate suspension in the treatment of oral and genital ulceration of Behçet disease: a randomized, placebo-controlled, double-blind study.

Alpsoy E, Er H, Durusoy C, et al. Arch Dermatol 1999; 135: 529–32. Sucralfate (1 g/5 mL), four times daily, for 3 months' duration used as an oral rinse for 1–2 minutes after routine oral care and before bed, decreased significantly the frequency, healing time, and pain of OU and healing time and pain of GU compared with the pretreatment period.

Pimecrolimus versus placebo in genital aphthous ulcers of Behçet's disease: a randomized double-blind controlled trial. Chams-Davatchi C, Barikbin B, Shahram F, et al. *Int J Rheum Dis* 2010; 13: 253–8.

Pimecrolimus, a topical immunomodulator, twice a day seems to be safe and efficient in the treatment of GU, by accelerating healing.

Second-Line Therapies

• Azathioprine	A
• Anti-TNF- α agents	A/B
• IFN- α	A
• Ciclosporin-A	A
• Thalidomide	A
• Zinc sulfate	A
• Rebamipide	A
• Isotretinoin	A
• Diclofenac	A
• Lidocaine	A
• Hydroxypropyl cellulose	C
• Silver nitrate	A
• CO ₂ laser	A
• Nd:YAG laser	A
• Intralesional corticosteroids	E

A controlled trial of azathioprine in Behçet's syndrome. Yazici H, Pazarli H, Barnes CG, et al. *N Engl J Med* 1990; 322: 281–5.

In a randomized, double-blind, placebo-controlled study of 73 patients, azathioprine 2.5 mg/kg daily was sufficient in OU and GU besides ocular inflammation and arthritis. Azathioprine was significantly better than placebo in preventing the development of new eye disease.

Thalidomide in the treatment of the mucocutaneous lesions of Behçet syndrome: a randomized, double-blind, placebo-controlled trial. Hamuryudan V, Mat C, Saip S, et al. *Ann Intern Med* 1998; 128: 443–50.

A remission of OU, GU, and PPL treated with thalidomide 100 mg or 300 mg daily was detected in 22% of 63 patients over 8 weeks. During the 6-month treatment, 30% of the patients remained free of lesions. However, the efficacy was temporary, and discontinuation of the treatment resulted in recurrence of the OU and GU.

Thalidomide therapy was associated with exacerbation of nodular lesions.

Apremilast for Behçet's syndrome – a phase 2, placebo-controlled study. Hatemi G, Melikoglu M, Tunc R, et al. *N Engl J Med* 2015; 372: 1510–8.

One hundred eleven patients have received 30 mg apremilast twice daily or placebo for 12 weeks followed by a 12-week extension phase in which the placebo group was switched to apremilast with a 28-day posttreatment observation phase. Apremilast was useful, particularly in decreasing OU count and pain. It also decreased the number of GU significantly.

The Food and Drug Administration has approved apremilast for the treatment of mucocutaneous manifestations in BD.

Third-Line Therapies

• Secukinumab	D
• Ustekinumab	C
• Anti-interleukin-1	C
• Methotrexate	E
• Pentoxifylline	E
• Mycophenolate sodium	C
• Sulfasalazine	B
• Minocycline	C
• Indomethacin	B
• Cyclophosphamide	E
• Chlorambucil	D
• Tacrolimus	B
• Rituximab	B
• Alemtuzumab	C
• Allicin	B
• Azithromycin	D
• Irsogladine	D
• Tocilizumab	E
• Stem cell transplantation	E
• Intravenous immunoglobulin	E

Short-term trial of etanercept in Behçet's disease: a double blind, placebo controlled study. Melikoglu M, Fresko I, Mat C, et al. *J Rheumatol* 2005; 32: 98–105.

In a study of 40 male patients, etanercept (25 mg twice weekly for 4 weeks) was effective in suppressing most of the mucocutaneous lesions. The drug had an apparent effect on OU and nodular lesions, and the response was as early as the first week. There was a significant decrease in the mean numbers of OU and nodular lesions as well as PPL.

Efficacy of anti-TNF alpha in severe and/or refractory Behçet's disease: multicenter study of 124 patients. Vallet H, Riviere S, Sanna A, et al. *J Autoimmun* 2015; 62: 67–74.

Anti-TNF- α treatments (mainly infliximab [62%] and adalimumab [30%]) in 124 BD patients showed an overall clinical response rate of 90.4%. Clinical responses were found to be 96.3%, 88%, 70%, 77.8%, 92.3%, and 66.7% of patients with severe and/or refractory ocular, mucocutaneous, articular, gastrointestinal, neurologic, and cardiovascular manifestations, respectively.

Anti-TNF- α treatment seems to be efficient in all severe and refractory BD manifestations, and effectiveness is almost similar regardless of the anti-TNF agent used (infliximab or adalimumab).

Interferon alfa-2a in the treatment of Behçet disease: a randomized placebo-controlled and double-blind study. Alpsoy E, Durusoy C, Yilmaz E, et al. *Arch Dermatol* 2002; 138: 467–71.

Interferon (IFN)- α_{2a} treatment, 6 MU thrice weekly, was found to be an effective alternative, particularly for the management of mucocutaneous lesions, and its effect decreased gradually after the cessation of treatment. IFN- α_{2a} treatment decreased the duration and pain of OU and the frequency of GU and PPL significantly at the end of the 3-month treatment.

Many open studies evaluated IFN- α treatment in cases of sight-threatening refractory uveitis with promising results. IFN- α seems to be able to control and achieve remission of uveitis in most patients.

Double-masked trial of cyclosporine versus colchicine and long-term open study of cyclosporine in Behçet's disease. Masuda K, Nakajima A, Urayama A, et al. *Lancet* 1989; 1: 1093–6.

Ciclosporin-A is capable of markedly ameliorating uveitis as well as mucocutaneous lesions. In a controlled study of 96 patients with recurrent uveitis, ciclosporin-A (10 mg/kg) was superior to colchicine (1 mg/day) in reducing the number and frequency of OU and cutaneous lesions (EN-like lesions, thrombophlebitis, and PPL).

Lower doses were also found to be as effective as higher doses. For this reason, 5 mg/kg doses are preferred today.

Oral zinc sulfate in the treatment of Behçet's disease: a double blind cross-over study. Sharquie KE, Najim RA, Al-Dori WS, et al. *J Dermatol* 2006; 33: 541–6.

In a controlled study of 32 patients with mucocutaneous and/or joint disease treated with zinc sulfate 100 mg thrice daily, Sharquie et al. reported an improvement in the clinical manifestations index of mucocutaneous lesions without any side effect.

Efficacy of rebamipide as adjunctive therapy in the treatment of recurrent oral aphthous ulcers in patients with Behçet's disease. Matsuda T, Ohno S, Hirohata S, et al. *Drugs R&D* 2003; 4: 19–28.

In a randomized, double-blind, placebo-controlled study, 35 BD patients, having as the main symptom OU, were treated with rebamipide 300 mg daily plus usual therapy for 3–6 months. Moderate to marked improvement in OU count and pain was 36% in the placebo group and 65% in the drug group.

Rebamipide, an amino acid derivative of 2-quinolinone, is used for mucosal protection, healing of gastroduodenal ulcers, and treatment of gastritis that enhances mucosal defense, scavenging free radicals, and temporarily activating genes encoding cyclooxygenase.

Pulse cyclophosphamide (PCP) for ocular lesions of Behçet's disease: double blind crossover study. Davatchi F, Shahram F, Chams H et al. *Arthritis Rheum* 1999; 42: S320.

Combination of cyclophosphamide (1 g/m² monthly) and corticosteroid therapy was found superior to corticosteroid therapy alone in eye involvement.

Many open studies reported this compound as a beneficial treatment for systemic vasculitides, such as neurologic involvement and arterial aneurysms. However, due to the severe toxicity (e.g., myelosuppression, pulmonary fibrosis, renal toxicity, hemorrhagic cystitis, infertility, malignancy, alopecia),

cyclophosphamide should be selected in cases with the clinically significant disease who are refractory to other agents.

The therapeutic role of isotretinoin in the management of Behçet's disease: a single-blinded, controlled therapeutic study. Sharquie KE, Helmi RM, Noiami AA, et al. *J Drugs Dermatol* 2013; 12: e68–73.

Thirty patients received isotretinoin 20 mg daily. At week 12, isotretinoin was stopped, and patients were given placebo therapy for another 3 months. Authors reported significant reductions in OU parameters and other cutaneous manifestations with isotretinoin treatment.

Efficacy and safety profile of anti-interleukin-1 treatment in Behçet's disease: a multicenter retrospective study. Emmi G, Talarico R, Lopalco G, et al. *Clin Rheumatol* 2016; 35: 1281–6.

Thirty patients receiving anti-IL-1 agents (anakinra 100 mg daily and canakinumab 150 mg every 6–8 weeks) were evaluated. Anti-IL-1 β drugs are efficacious and safe with overall acceptable retention on treatment.

Efficacy of the anti-IL 17 secukinumab in refractory Behçet's syndrome: a preliminary study. Di Scala G, Bettiol A, Cojan RD, et al. *J Autoimmun* 2018; 97: 108–13.

Secukinumab, either 150 mg or 300 mg monthly, improved active mucocutaneous and articular manifestations refractory to colchicine, conventional disease-modifying anti-rheumatic drugs (DMARDs), and at least one anti-TNF- α agent in five patients.

Long term outcome of ustekinumab therapy for Behçet's disease. Mirouse A, Barete S, Desbois A, et al. *Arthritis Rheumatol* 2019; 71: 1727–32.

In a multicenter, prospective study with 30 patients with active oral ulcers resistant to colchicine, ustekinumab (90 mg at inclusion, at week 4, and then once every 12 weeks) decreased the median number of OU significantly at week 12 compared to baseline. Complete response was achieved in 60.0% and 88.9% of patients at weeks 12 and 24, respectively.

Mycophenolate sodium in the treatment of mucocutaneous Behçet's diseases. Köse O, Sizmek I, Pay S. *Int J Dermatol* 2011; 50: 895–6.

Eight of 10 patients with recalcitrant mucocutaneous BD experienced a remarkable improvement of the mucocutaneous lesions after 6 months of treatment with mycophenolate sodium 720 mg twice daily.

Bites and stings

Dirk M. Elston



MANAGEMENT STRATEGY

Bite Reactions

DEET is effective against a broad range of arthropods, but despite many years of use there are still concerns about systemic absorption and safety. Picaridin is effective against mosquitoes and many other arthropods. Permethrin can be used on fabric and has a persistent effect against ticks and chiggers. It paradoxically attracts Southwest Asian *Hyalomma* ticks that carry Congo-Crimean hemorrhagic fever and should be avoided where these ticks are endemic. If prevention fails, second-line treatments aim to improve pruritus. *Topical antipruritics*, such as 1/4% camphor and menthol, *topical anesthetics* such as pramoxine and lidocaine can be helpful. For persistent bite reactions, topical or intralesional corticosteroids may be helpful. Bites are an occasional cause of eosinophilic cellulitis. A veterinarian should be consulted about flea infestation in pets. Antivenin is available for many arachnid toxins, but most respond to rest, ice, and elevation.

Individuals who experience anaphylaxis in response to stings should be referred to an allergist for *desensitization*. Rush desensitization is possible for those with life-threatening allergy. Patients with a history of anaphylaxis should also carry an *epinephrine autoinjector* (EpiPen).

Proteins, formic acid, histamine, and kinins are involved in the pathogenesis of various bite and sting reactions. Both exaggerated local and systemic responses may be IgE-mediated. *Amblyomma testudinarium* tick bites are associated with increased galactose- α -1,3-galactose carbohydrate IgE levels and red meat allergy. Implicated ticks include *Amblyomma species* in the US, *Ixodes* in Australia and Europe, and *Haemaphysalis* in Japan. Basophils serve as antigen-presenting cells and allergic symptoms may be noted with beef, pork, and lamb.

Most arthropod reactions are self-limiting and treatment is largely symptomatic. Most tickborne illnesses other than babesiosis respond to tetracyclines and the prognosis relates to how quickly definitive antibiotic therapy is instituted.

Vectorborne Disease

Most tickborne illness responds to *doxycycline*. For early Lyme disease, evidence suggests that a 10-day course is as effective as longer courses of antibiotic. Babesiosis responds to *clindamycin* and *quinine*, but *azithromycin* and *atovaquone* may be as effective with a lower incidence of side effects. *Atovaquone-proguanil* has been effective in refractory cases in immunocompromised patients.

Specific Investigations

- CBC and fibrin split products after brown recluse spider bite
- Rickettsial immunofluorescence and immunoperoxidase
- Lyme serology
- Enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR), and immunofluorescence for virus such as West Nile, dengue, and chikungunya

PCR assays can also be used to identify biting insects that are too small for conventional identification. IgE typing, skin testing, and basophil activation testing can be used to confirm the cause of anaphylaxis. Tryptase levels can be used to predict severe reactions and in forensic investigations to confirm death from anaphylaxis. Expression of Th1 and Th2 trafficking can be used to follow the course of immunotherapy.

Insect bites as a trigger factor of eosinophilic cellulitis. Kucharzyk M, Slowik-Rylska M, Krecisz B. Ann Agric Environ Med 2019; 17: 256–9.

Several biopsies may be required to establish diagnosis. Prior administration of corticosteroids may alter biopsy findings.

If clinical manifestations are suggestive, multiple biopsies may be required. Treated lesions may be misleading.

First-Line Therapies

Prevention

• DEET	A
• Permethrin and other pyrethroids	A
• Picaridin	B
• Combinations of DEET and permethrin	A

Flea treatments for pets

• Lufenuron	A
• Fipronil	A
• Imidacloprid	A

Anaphylaxis

• Epinephrine	A
• Immunotherapy	A

Spider bites

• Rest, ice, and elevation	B
• Tetracycline or triamcinolone for brown recluse bites	C
• Antivenin for brown recluse bites	C
• Antivenin for black widow and redback spider bites	A

Scorpion stings

• Antivenin for some toxic scorpions	B
• Prazosin for Indian red scorpion stings	A

First-Line Therapies—cont'd

Arthropod-borne infections

• Lyme borreliosis	A
• Tetracycline	A
• Amoxicillin in children	A
• Ceftriaxone	A
• Rocky Mountain spotted fever	
• Doxycycline	A
• Human monocytic ehrlichiosis	
• Doxycycline	A
• Human anaplasmosis	
• Doxycycline	A
• Babesiosis	
• Azithromycin and atovaquone	A
• Quinine and clindamycin	A

Insect repellents: an updated review for the clinician. Nguyen QD, Vu MN, Hebert AA. *J Am Acad Dermatol* 2018 Nov 2 [Epub ahead of print].

The use of insect repellents (IR) to prevent systemic infections constitutes a fundamental tenet of public health efforts to eradicate disease. DEET has an excellent safety profile and remarkable protection against mosquitoes and various other arthropods. Other EPA-registered ingredients include permethrin, picaridin, IR3535, oil of lemon eucalyptus, oil of citronella, catnip oil, and 2-undecanone.

Arthropod-borne disease remains a major cause of morbidity and mortality around the globe. Zika virus, malaria, West Nile virus, dengue fever, and Lyme disease are among the best-known of these diseases. This excellent review summarizes currently available EPA-registered repellents.

Effects of sublethal exposure to metofluthrin on the fitness of *Aedes aegypti* in a domestic setting in Cairns, Queensland. Buhagiar TS, Devine GJ, Ritchie SA. *Parasit Vectors* 2017; 10: 274.

Metofluthrin has been shown to be highly effective at reducing bites from *Aedes aegypti*. Its efficacy relates to rapid onset of confusion, knockdown, and subsequent kill of the mosquito. Sublethal exposure does not affect the ability of the mosquito to reproduce, creating opportunities for development of pyrethroid resistance.

Resistance to pyrethroids is common among headlice and is emerging as an issue with pyrethroids used to prevent insect bites.

Canadian recommendations on the prevention and treatment of Zika virus: update. Zika Working Group; Committee to Advise on Tropical Medicine; Travel (CATMAT). *Can Commun Dis Rep* 2016; 42: 101–11.

All travelers to endemic areas should use personal protective measures including IR and barriers against mosquito entry to living areas. Pregnant women should avoid travel to endemic areas. Sexual transmission from male partners has been documented and couples should practice abstinence or use condoms until viral shedding has likely ceased.

Zika virus is a cause of microcephaly and other congenital abnormalities as well as Guillain-Barré syndrome, and these guidelines serve as an important reference.

Reduced effectiveness of repellents in a pyrethroid-resistant strain of *Aedes aegypti* (Diptera: Culicidae) and its correlation with olfactory sensitivity. Yang L, Norris EJ, Jiang S, et al. *Pest Manag Sci* 2019 July 24 [Epub ahead of print].

Behavioral performance in 15-, 30-, and 60-min exposures was assessed for N,N-diethyl-3-methylbenzamide (DEET), ethyl 3-[acetyl(butyl)amino] propanoate (IR3535), and 2-undecanone, as well as pyrethrum extract, transfluthrin, and metofluthrin in susceptible and pyrethroid-resistant *Aedes aegypti*. Reduced sensitivity to these repellents correlated with the *kdr* mutation present in resistant mosquitoes.

Aedes aegypti (Diptera: Culicidae) is a vector of dengue fever, Zika, chikungunya, and yellow fever viruses, and in many areas possesses significant levels of resistance to pyrethroids. Pyrethroid resistance correlates with resistance to other repellents.

Environmentally responsive and anti-bugs textile finishes - Recent trends, challenges, and future perspectives. Saleem F, Iqbal HMN. *Sci Total Environ* 2019 Nov 10; 690: 667–82.

Repellent textile finishes have numerous applications such as in-home textiles, bed nets, and tenting, camping gear, as well as in military uniforms. A large number of insect repellent textile finishes (i.e., N-N-diethyl-m-toluamide, permethrin, cypermethrin, pyrethrum, picaridin, bioallethrin, Citriodiol, and essential oils), as well as commonly used antimicrobial agents (i.e., chitosan, zwitterionic compounds, silver and silver-based compounds, titanium dioxide nanoparticles, imidazolium salts, triclosan, and quaternary ammonium salts), have been evaluated.

Textile finishes have the potential to offer protection against bites and arthropod-borne disease with less impact on the environment.

Susceptibility of *Dermacentor reticulatus* tick to repellents containing different active ingredients. Gliniewicz A, Borecka A, Przygodzka M, et al. *Przegl Epidemiol* 2019; 73: 117–25.

The authors evaluated four different formulations containing DEET, icaridin, IR3535, and mixes of three compounds: DEET, IR3535, and geraniol, against *Dermacentor reticulatus* ticks.

At 90 minutes after application the repellent A (DEET 30%), repellent D (DEET 30%, IR3535 20%, geraniol 0.1%), and repellent G (IR3535 12%) exhibited a 100% effectiveness in protection against ticks, but icaridin 20% dropped to 95%.

DEET remains the 'gold' standard for IR. At 7 hours after application, DEET retained up to 90% efficacy while the other formulation containing DEET 30%, IR3535 20%, and geraniol 0.1% dropped to 60%. Icaridin 20% and IR3535 12% were only effective up to 4 hours after application (85% and 40%, respectively).

Is DEET a dangerous neurotoxicant? Swale DR, Bloomquist JR. *Pest Manag Sci* 2019; 75: 2068–70.

This study reviews data regarding DEET toxicity. There have been few lethal cases of DEET poisoning, usually due to deliberate overdoses. Deleterious effects typically involve skin reactions and encephalopathies, such as seizures; they often abate without sequelae. There is little direct effect on acetylcholinesterase, but G protein-coupled receptors deserve further investigation. Studies with pregnant women found no effect on the developing fetus from proper use and its continued deployment as a repellent is endorsed by both the Centers for Disease

Control and Prevention and the Environmental Protection Agency.

With the rise of Zika virus, there is renewed interest in the safety of DEET products during pregnancy. Overall, the results are reassuring, and the risk–benefit ratio favors use of repellents in areas with a high risk of disease transmission.

Bug off! Severe toxicity following inhalational exposure to N,N-diethyl-meta-toluamide (DEET). Tavares EM, Judge BS, Jones JS. *Am J Emerg Med* 2019; 37(7): e3–e1395. e4.

DEET has been used by millions of people since its introduction in 1956. Overall it has an excellent safety profile. Severe toxicity in this case following inhalational exposure to a ‘bug bomb’ containing 98% DEET.

Stimulation of eryptosis by broad-spectrum insect repellent N,N-Diethyl-3-methylbenzamide (DEET). Alfhili MA, Nkany MB, Weidner DA, et al. *Toxicol Appl Pharmacol* 2019; 370: 36–43.

DEET has been shown to possess cytotoxic and apoptotic properties in nucleated cells. Red blood cells lack intracellular organelles but can undergo programmed cell death, termed eryptosis.

Although generally safe, DEET should be used with caution in patients with severe anemia.

Insecticide resistance modifies mosquito response to DEET and natural repellents. Deletre E, Martin T, Duménil C, et al. *Parasit Vectors* 2019; 12: 89.

Pyrethroid and organophosphate resistance in the malaria vector *Anopheles gambiae* is a growing problem and resistance genes can modify the behavior of *An. gambiae*, increasing or decreasing the effectiveness of DEET and natural compounds.

There is a complex interaction between insecticide resistance genes and resistance to repellents.

Bioabsorption and effectiveness of long-lasting permethrin-treated uniforms over three months among North Carolina outdoor workers. Beard CB, White A, Balanay JA, et al. *Parasit Vectors* 2019; 12(1): 52.

State and county park employees from North Carolina wore treated uniforms for 3 months. The authors collected spot urine samples for biomonitoring of permethrin metabolites at 1 week, 1 month, and 3 months after first use of the uniform. Bioactive amounts of permethrin remained in all clothing swatches tested, although there was great variability. Tick mortality was high overall, with 78% of pant and 88% of sock swatches having mean knockdown percentages ≥85%. In contrast, mosquito mortality was low. The absorbed dosage of permethrin was low.

Pyrethroid resistance associated with a decreased DEET repellency in the common bed bug (Hemiptera: Cimicidae). Vassena CV, Cáceres M, Santo-Orihuela PL. *J Econ Entomol* 2019; 112(2): 997–1000.

This study examined the repellence of DEET against two bed bug colonies from Argentina (one colony susceptible and the other field-collected pyrethroid-resistant) under two starving periods. DEET had a lower effect on the permethrin-resistant colony.

The global resurgence of the bed bug (Cimex lectularius L.) and widespread resistance to pyrethroid insecticides have created the need to find alternatives to chemical control. Unfortunately, this study suggests that permethrin resistance also translates to DEET resistance.

Second-Line Therapies

Repellents

- Botanicals C
- Novel pyrethroids C

Relief of pruritus

- Camphor and menthol E
- Pramoxine E
- Lidocaine E
- Benzocaine E
- Lidocaine/prilocaine E

Treatment of bite and sting reactions

- Superpotent and potent topical corticosteroids E
- For young children: mild-to-moderate strength topical corticosteroids E
- Local ice
- Topical camphor and menthol C
- Topical anesthetics C
- New immunotherapy agents B
- Omalizumab for patients with adverse reactions to immunotherapy C

Indian red scorpion stings

- Captopril C
- Antivenin D

Arthropod-borne infections

- Babesiosis
- Atovaquone-proguanil in immunosuppressed patients C

Cooling the itch via TRPM8. Liu B, Jordt SE. *J Invest Dermatol* 2018; 138: 1254–6.

Menthol causes a cooling sensation and is commonly used in a eutectic mixture with camphor. TRPM8, a menthol- and cold-activated ion channel, is essential for cooling to relieve itch.

Camphor and menthol have long been used in combination for their antipruritic effects. This study suggests that pharmacologic TRPM8 activation holds promise for development of other agents that target itch.

Chemical composition and repellency of *Origanum vulgare* essential oil against *Cimex lectularius* under laboratory conditions. Sharififard M, Alizadeh I, Jahanifard E, et al. *J Arthropod Borne Dis* 2018; 25: 12: 387–97.

The authors examined the repellency effect of oregano essential oil prepared from dried leaves using a hydrodistillation method. The 40% oregano essential oil exhibited 100% repellency against bed bugs at 3, 5, 9, and 24 hours after application while the repellency index of DEET 33% was 100% at 3 and 5 hours, and it decreased to 80% and 27% at 9 and 24 hours.

The common bed bug (Cimex lectularius) has reemerged as a modern plague. In this study, 40% oregano oil exhibited greater repellency compared with commercial insect repellent sticks containing 33% DEET.

Eave ribbons treated with the spatial repellent, transfluthrin, can effectively protect against indoor-biting and outdoor-biting malaria mosquitoes. Mmbando AS, Ngowo H, Limwagu A, et al. *Malaria J* 2018; 17: 368.

The authors studied ribbons treated with 0.02%, 0.2%, 1.5%, or 5% transfluthrin emulsion spatial repellents and wrapped around eaves of houses to prevent outdoor-biting and indoor-biting mosquitoes. Indoor- and outdoor-biting decreased >99% in huts fitted with eave ribbons having $\geq 0.2\%$ transfluthrin.

This technique offers a simple, low-cost means of mosquito control.

Bicomponent fibres for controlled release of volatile mosquito repellents. Sibanda M, Focke W, Braack L, et al., Mater Sci Eng C Mater Biol Appl 2018; 91: 754–61.

Core-sheath, high-density polyethylene with a concentrate containing volatile N,N-diethyl-m-toluamide (DEET) in poly(ethylene-co-vinyl acetate) (EVA) as core showed high residual repellence activity even after 20 cold washes or after 8 months aging under laboratory conditions.

New technology offers an alternative to spray repellents to prevent outdoor mosquito bites.

Repellent and mosquitocidal effects of leaf extracts of *Clausena anisata* against the *Aedes aegypti* mosquito (Diptera: Culicidae). Mukandiwa L, Eloff JN, Naidoo V. Environ Sci Pollut Res Int 2016; 23: 11257–66.

Clausena anisata is used traditionally as an insect repellent by various communities in Africa and Asia. In this study, the repellency and insecticidal activities of leaf extracts and compounds isolated from this plant were evaluated against *Aedes aegypti*, the yellow fever vector. Acetone crude extract (15%) demonstrated 93% repellence and the hexane fraction (7.5%) 67% repellence after 3 hours. Mosquitoes are rapidly developing resistance to insecticides and repellents, suggesting the urgent need for new agents. *C. anisata* leaf extracts have potential to be included in personal protection products against mosquitoes.

Plants traditionally used as mosquito repellents and the implication for their use in vector control. Tisgratog R, Sanguanpong U, Grieco JP, et al. Acta Trop 2016; 157: 136–44.

The authors identified 37 plant species that showed mosquito-repellent properties, and five essential oils extracted from plants demonstrated promising insect repellent activity.

These active ingredients show promise as alternatives to DEET and permethrin.

Larvicidal compounds extracted from *Helicteres velutina* K Schum (Sterculiaceae) evaluated against *Aedes aegypti* L. Fernandes DA, Barros RPC, Teles YCF, et al. Molecules 2019; 22: 24.

Helicteres velutina K. Schum (Sterculiaceae) is a Brazilian plant used by indigenous tribes as an insect repellent. Five molecules were isolated with potential larvicidal activity and three showed an ability to bind with sterol carrier protein-2 (1PZ4), a protein found in the larval intestine.

Tiliroside and 7,4'-di-O-methyl-8-O-sulfate flavone derived from this Brazilian plant showed in vitro larvicidal activity, with LC50 values of 0.275 mg/mL after 72 h and 0.182 mg/mL after 24 h of exposure, respectively, supporting H. velutina as an alternative source of

insecticide for the control of A. aegypti, which is a vector for severe arboviruses, including yellow fever, dengue, and chikungunya.

Andean flora as a source of new repellents against insect pests: behavioral, morphological and electrophysiological studies on *Sitophilus zeamais* (Coleoptera: Curculionidae). Romani R, Bedini S, Salerno G, et al. Insects 2019; 14: 10.

Plant-derived essential oils from *Clinopodium tomentosum* and *C. nubigenum* are promising tools for pest control.

The repellency and toxicity effects of essential oils from the Libyan plants *Salvadora persica* and *Rosmarinus officinalis* against nymphs of *Ixodes ricinus*. Elmhalli F, Garbouei SS, Borg-Karlson AK, et al. Exp Appl Acarol 2019; 77: 585–99.

The results suggest that essential oils have potential as alternative repellents and insecticides for tick control.

Chemical composition and biting deterrent activity of essential oil of *Tagetes patula* (Marigold) against *Aedes aegypti*. Ali A, Tabanca N, Amin E, et al. Nat Prod Commun 2016; 11: 1535–38.

Essential oil distilled from marigolds exhibited good activity against *Aedes aegypti* L. Sesquiterpenes have potential as IR, but also significant potential as contact sensitizers.

Third-Line Therapies

Treatment of bites

- Intralesional corticosteroids **E**
- Enhanced penetration topical antihistamines **B**

Repellents

- Newer agents and botanicals **C**
- New vaccines in development for vectorborne illness **E**

Evaluation of commercial agrochemicals as new tools for malaria vector control. Hoppé M, Hueter OF, Bywater A, et al. Chimia (Aarau) 2016; 70: 721–9.

Four new insecticides and three fungicides with promising activity against adult malaria-carrying mosquitoes were identified, namely acetamiprid, thiamethoxam, thiocyclam, and metaflumizone and the fungicides diflufenetorim, picoxystrobin, and fluazinam.

Commercial agricultural chemicals show promise as potential insecticides for control of malaria.

A preventive immunization approach against insect bite hypersensitivity: intralymphatic injection with recombinant allergens in Alum or Alum and monophosphoryl lipid A. Jonsdottir S, Svansson V, Stefansson SB, et al. Vet Immunol Immunopathol 2016; 172: 14–20.

IgE-mediated insect bite hypersensitivity was examined in a horse model. Immunotherapy demonstrated that induced antibodies could block binding of allergen specific IgE.

This is an important proof of concept study for desensitization against insect bites.

Blastomycosis

Wanda Sonia Robles, Mahreen Ameen



Mason, A.R., Cortes, G.Y., Cook, J., Maize, J.C. and Thiers, B.H. (2008), Cutaneous blastomycosis: a diagnostic challenge. *International Journal of Dermatology*, 47: 824-830. <https://doi.org/10.1111/j.1365-4632.2008.03732.x>; with permission.

Blastomycosis is a systemic, suppurative granulomatous fungal infection caused by thermally dimorphic fungi belonging to the genus *Blastomyces*. These pathogens show great genetic and geographic diversity. The most common pathogen is *Blastomyces dermatitidis*. However, there are other less common species including *Blastomyces gilchristii*, *Blastomyces parvus*, and atypical forms of the condition caused by *Blastomyces helicus*. Their natural habitat is considered to be woods and soil close to rivers. The disease has a primary pulmonary stage as it is acquired by the inhalation of conidia. This is transformed into the yeast form once in the lungs followed by dissemination to other body sites. It is an endemic mycosis more prevalent in the North American continent mainly in areas of the United States and Canada surrounding the Ohio and Mississippi river valleys and the Great Lakes. However, more recently, different species have been described in South Africa as responsible for human blastomycosis. These include *Blastomyces percursoris* and *Blastomyces emzantsi*. Cases have also been reported in other parts of Africa, Latin America, the Middle East, India, and Poland.

Blastomycosis is associated with a spectrum of disease from asymptomatic subclinical infection to acute or chronic pneumonia. Most cases are restricted to the respiratory system, and many are asymptomatic. Clinically there are three different forms of the disease: primary cutaneous, pulmonary, and disseminated. Most cases are restricted to the respiratory system, many of which are asymptomatic. Some individuals may have flu-like symptoms and others may have severe pneumonia. Extrapulmonary infection occurs in 25%–40% of cases and most commonly affects the skin. Cutaneous manifestations of the disease range from papules, pustules, and subcutaneous nodules to ulcers and crusty sores. Over a period of months and years lesions grow larger and may become raised, wart-like scars or verrucous lesions, causing disfigurement. The bones, genitourinary system, and central nervous system (CNS) may be involved. Dissemination occurs more frequently in the immunocompromised and those with human immunodeficiency virus (HIV) infection. The immunocompromised are at higher risk of CNS involvement and fast, progressive, severe acute

respiratory distress syndrome (ARDS). Their prognosis is poor and therefore they require more aggressive management.

MANAGEMENT STRATEGY

In the immunocompetent individual with mild disease, the condition may be self-limiting, requiring no treatment with spontaneous clearance. However, all diagnosed cases are treated in order to prevent extrapulmonary dissemination. When infection spreads and skin involvement is evident, spontaneous resolution does not occur and treatment is necessary. *Itraconazole* is the drug of choice for mild-to-moderate infection that is not life-threatening including pulmonary infection, disseminated infection and infection in children. For moderately severe to severe disease the drug of choice is a lipid formulation of *amphotericin B (AmB)* or *AmB deoxycholate*, including pulmonary, disseminated, immunosuppressed patients and in children until improvement becomes evident (1–2 weeks), followed by oral *itraconazole* for a total of 6–12 months. In pregnant women the treatment of choice is lipid AmB. This is also the drug of choice for those who fail on treatment with azoles. Patients with osteoarticular blastomycosis should be treated for at least 12 months. Patients with CNS blastomycosis should be treated with *AmB* for 4–6 weeks followed by oral azole, either *fluconazole* or *itraconazole*, for at least 12 months and until resolution of cerebrospinal fluid (CSF) abnormalities. This step-down therapy to an azole is common practice. Immunosuppressed patients including those with acquired immune deficiency syndrome (AIDS) should be treated with lipid AmB or deoxycholate AmB for 1–2 weeks followed by step-down therapy with *itraconazole*. In this population *fluconazole* is not as effective as *itraconazole*. Serum levels of *itraconazole* should be monitored during the first 2–4 weeks of treatment and lifelong suppressive therapy is recommended. In pregnancy azoles should be avoided due to possible teratogenicity. In infection of the newborn the recommended drug of choice is *AmB deoxycholate*.

Specific Investigations

- Direct microscopy
- Culture. Specimens for diagnosis:
 - Pneumonia: sputum, bronchial washing, bronchial lavage
 - Cutaneous or subcutaneous: skin or deep tissue biopsy, scrapings, exudate
 - Osteoarticular: joint fluid, synovial tissue biopsy, bone biopsy
 - Genitourinary: prostate biopsy specimen, urine
 - Meningitis: CSF
 - Disseminated disease: bone marrow
- Histopathology:
 - Antibody tests
 - Antigen detection
- Chest X-ray
- Bone scanning (radionuclide bone scan/computed tomography [CTI]/magnetic resonance imaging [MRI])
- Serology for HIV infection (where relevant)

Direct examination should be performed in addition to culture. The presence of yeast cells allows a rapid diagnosis. Definitive diagnosis is based on the identification of characteristic thick-walled, broad-based budding yeasts by direct examination of tissue or the isolation of *Blastomyces* in culture. Specimens for direct microscopy in 10% potassium hydroxide (KOH) solution can be skin scrapings, pus from skin lesions, sputum, and biopsy tissue

from any lesion suspicious of infection. This can be used with or without the addition of calcofluor white. Culture is the most sensitive method of diagnosis. Successful culture in a variety of media from sputum, tissue biopsy specimens, CSF, or urine produces a white mold at 25°C on Sabouraud agar and a brown wrinkled colony at 37°C in blood agar. Histopathology of infected tissues shows a granulomatous response without caseation and pseudo-epitheliomatous hyperplasia and the finding of the classic yeast form in tissues. Classic antibody testing has poor sensitivity and specificity. A newer antibody enzyme immunoassay (EIA) that uses *Blastomyces dermatitidis* surface protein BAD-1 has better sensitivity and specificity. Analysis of fungal microbiome (mycobiome) of the lungs during fungal infection by sequencing has lately been used as an adjunct to traditional microbiology testing.

First-Line Therapies

- Itraconazole **B**
- Lipid and deoxycholate amphotericin B **C**

Itraconazole therapy for blastomycosis and histoplasmosis. NIAID Mycosis Study Group; Dismukes WE, Badcher RW, Cloud JC, et al. *Am J Med* 1992; 93: 489–97.

A prospective non-randomized, multicenter trial involving 48 patients with pulmonary or disseminated blastomycosis without CNS involvement. Patients were treated with itraconazole 200–400 mg/day for a median period of 6.2 months with a 90% cure rate (43/48). Treatment was very well tolerated and there was no therapeutic advantage for patients treated with the higher dose.

Blastomycosis. Castillo CG, Kauffman CA, Miceli MH. *Infect Dis Clin North Am* 2016; 30: 247–64.

This very good review advocates the use of itraconazole for either mild-to-moderate pulmonary or extrapulmonary infection and lipid formulation AmB for severe or life-threatening infection followed by step-down therapy with itraconazole.

Clinical manifestations and treatment of blastomycosis. McBride JA, Gauthier GM, Klein BS. *Clin Chest Med* 2017; 38(3): 435–49.

A very good review focusing on the often diagnostic and therapeutic challenge of the condition. It also stresses the need for awareness from clinicians that Blastomyces spp. can infect and disseminate on both the immunocompetent and the immunocompromised, as well as the common issues associated with the use of polyene and azole antifungal drugs to minimize risks associated with treatment.

Blastomycosis of the central nervous system: a multicentre review of diagnosis and treatment in the modern era. Bariola JR, Perry P, Pappas PG, et al. *Clin Infect Dis* 2010; 50: 797–804.

A retrospective study of 22 patients with CNS infection treated with either AmB deoxycholate or lipid formulation AmB followed by a prolonged course of oral azole therapy (voriconazole, fluconazole, or itraconazole).

The most favorable outcomes were achieved with initial treatment with a lipid formulation of AmB followed by a prolonged course of oral voriconazole.

Blastomycosis. Schwartz IS, Kauffman CA. *Semin Respir Crit Care Med* 2020; 41: 31–41.

The latest formal review, which highlights the clinical spectrum of the disease from asymptomatic to fatal disease. It also contains good scientific evidence on treatment of severe complications of blastomycosis.

These include the need for early and effective treatment of blastomycosis-associated ARDS if the patients are to survive as well as reports on the increasing number of institutions using extracorporeal membrane oxygenation for these patients with good outcomes.

Second-Line Therapies

- Fluconazole **B**
- Voriconazole **C**
- Posaconazole **D**

Treatment of blastomycosis with higher doses of fluconazole. The National Institute of Allergy and Infectious Disease Mycoses Study Group; Pappas PG, Bradsher RW, Kauffman CA, et al. *Clin Infect Dis* 1997; 25: 200–5.

This multicenter, randomized, open-label study investigated the efficacy of high-dose fluconazole (400–800 mg/day) for the treatment of non-life-threatening blastomycosis. There was an 87% cure rate (34/39) after a mean period of treatment of 8.9 months.

This study demonstrates a much higher efficacy for fluconazole at dose of 400–800 mg daily.

The role of voriconazole in the treatment of central nervous system blastomycosis. Ta M, Flowers SA, Rogers PD. *Ann Pharmacother* 2009; 43: 1696–1700.

Seven cases of CNS blastomycosis successfully treated sequentially with AmB followed by voriconazole are described.

Animal and human studies indicate that high concentrations of voriconazole can be achieved in the CSF and brain tissue. The authors suggest that voriconazole may be considered an azole option for either follow-up therapy after lipid AmB or as salvage therapy in patients intolerant to AmB or other azoles.

Posaconazole: use in the prophylaxis and treatment of fungal infections. Clark NM, Grim SA, Lynch JP. *Semin Respir Crit Care Med* 2015; 36(5): 767–85.

A good review of the use of approved indications for the use of posaconazole by the US Food and Drug Administration as well as the European Medicines Agency. In addition to approved indications, posaconazole as salvage therapy for invasive fungal infections and endemic mycosis including coccidioidomycosis, histoplasmosis, and blastomycosis. It can also be used as a combination agent for difficult-to-treat fungal infections.

GUIDELINES

Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Disease Society of America. Infectious Disease Society of America; Chapman SW, Dismukes WE, Proia LA, et al. *Clin Infect Dis* 2008; 46: 1801–12.

There has been no updated evidence-based guideline since 2008 and this replaced the previous guidelines from 2000. The clinical manifestations of the disease vary from asymptomatic or subclinical infection to acute or chronic pneumonia or disseminated disease, any of which may become fatal. Those infected may have only pulmonary disease, but 25%–40% may develop infection that may be cutaneous, osteoarticular, genitourinary, or CNS disease. Blastomycosis may also affect special populations including immunocompromised hosts (HIV/AIDS, organ transplant recipients, or patients on biologic interventions), pregnant women, and children or the newborn.

Itraconazole is the drug of choice for the treatment of mild-to-moderate pulmonary or disseminated infection. The

recommendation is an initial loading dose of 200 mg three times daily for 3 days, followed by 200 mg once or twice daily for 6–12 months. Serum levels should be measured after 2 weeks to ensure adequate drug exposure.

AmB is the treatment of choice for those with moderately severe to severe pulmonary infection including children and in the immunocompromised. Either the lipid formulation (3–5 mg/kg/day) or AmB deoxycholate (0.7–1 mg/kg/day) is given for 1–2 weeks or until improvement is noted. Itraconazole is then recommended as step-down therapy (loading dose and then 200 mg twice daily for 6–12 months, except in the immunocompromised, who require at least 12 months of treatment or until immunosuppression has been reversed).

For CNS disease, lipid AmB at the dose of 5 mg/kg/day for 4–6 weeks is the recommended treatment, followed by an oral azole (fluconazole 800 mg daily, itraconazole 200 mg two to three times daily, or voriconazole 200–400 mg twice daily), which should be given for at least 1 year and until there is resolution of CSF abnormalities. Despite this recommendation by the Infectious Disease

Society of America Guidelines of either fluconazole or itraconazole for step-down therapy, voriconazole has become the preferred drug for CNS blastomycosis, mainly because voriconazole has better activity against *B. dermatitidis* than fluconazole and it has better CNS penetration than itraconazole.

Immunosuppressed patients are more likely to develop disseminated disease and may have more severe pulmonary symptoms like ARDS. It is therefore recommended that they are treated initially with lipid AmB until clinical response is evident. Then transition to oral itraconazole is appropriate.

AmB is the only drug approved for treatment of blastomycosis in pregnant women. The lipid formulation is the preferred one.

Children with mild-to-moderate blastomycosis should be treated with itraconazole 10 mg/kg/day for 6–12 months. Daily dose should not exceed 400 mg. Moderately severe to severe disease in children should be treated with AmB deoxycholate or lipid AmB.

AmB is the drug of choice for patients who have failed to respond to azole treatment.

Blistering distal dactylitis

Irshad Zaki



Courtesy of Joseph Bikowski, MD

Blistering distal dactylitis (BDD) is a superficial, tender, blistering infection seen in childhood and the early teens. It is usually caused by group A β -hemolytic streptococci, although group B organisms, staphylococci, and, more recently, methicillin-resistant *Staphylococcus aureus* (MRSA) have also been implicated. The distal volar fat pads of the fingers are the most common site of infection, but more extensive involvement of the nailfolds and toes can occasionally occur.

MANAGEMENT STRATEGY

BDD can cause considerable alarm to parents, as large, tense blisters rapidly develop. Despite the absence of constitutional symptoms, patients usually seek help soon after the onset of the infection. The condition does not resolve spontaneously, but prompt treatment results in rapid improvement. *Blisters should be incised to release fluid*, which can vary from clear and watery to frank pus. Subsequent application of topical antibiotics can be helpful, but systemic treatment is usually also required. *Penicillin V* is the treatment of choice for streptococcal infection, but *erythromycin* is an effective alternative for patients allergic to penicillin. It is important to exclude MRSA or immunosuppression for resistant cases.

The differential diagnosis of the condition includes traumatic blisters, herpetic whitlow, staphylococcal bullous impetigo, and the Weber–Cockayne variant of epidermolysis bullosa.

Specific Investigations

- Gram stain of blister fluid
- Culture of blister fluid
- Swab of nasopharynx for bacteriology

A clinically recognizable streptococcal infection. Hays GC, Mullard JE. *Paediatrics* 1975; 56: 129–31.

First large series report describing 13 patients with BDD. Streptococci were found on culture of blister fluid in all cases, and Gram-positive cocci were usually found on Gram staining. This report suggests a link with infection of the nasopharynx, but this has not been confirmed in other case reports.

Blistering distal dactylitis in an adult. Kollipara R, Downing C, Lee M, et al. *J Cutan Med Surg* 2015; 19: 397–9.

Although the majority of cases are in children over the age of 2, this has also been described in adults, particularly if immunosuppressed. Bacteriology should be considered for an isolated distal phalanx blister at any age.

Blistering distal dactylitis. Kowtoniuk R, Bednarek R, Maroon M. *JAMA Dermatol* 2018; 154(12): 1480.

Although this disorder affects the distal digit in most patients, this report demonstrates that it can be more extensive.

First-Line Therapies

• Incision and drainage of blister	C
• Topical antibiotics	C
• Systemic penicillin	C

Is blistering distal dactylitis a variant of bullous impetigo? Scheinfeld NS. *Clin Exp Dermatol* 2007; 32: 314–6.

Good review of literature and treatment. Confirms the importance of incision and drainage, adequate dressings, and the need to consider *S. aureus* as a cause if penicillin is ineffective.

Second-Line Therapies

• Systemic erythromycin	D
• Intravenous vancomycin	D

Blistering distal dactylitis: a manifestation of group A beta-haemolytic streptococcal infection. Schneider JA, Parlette HL. *Arch Dermatol* 1982; 118: 879–80.

Short report of the authors' personal experience, suggesting that this is a relatively common problem. Systemic penicillin and erythromycin were both found to be effective. It is likely that many cases of BDD are wrongly diagnosed as bullous impetigo by clinicians not familiar with this disorder.

MRSA blistering distal dactylitis and review of reported cases. Fretzayas A, Moustaki M, Tsagris V, et al. *Pediatr Dermatol* 2011; 28: 433–5.

First report of BDD due to MRSA infection. This case highlights the importance of culture of blister fluid, as infection with this organism may increase in the future.

Third-Line Therapies

• Amoxicillin/clavulanic acid	D
• Conservative measures for herpetic whitlow	D

A review and report of blistering distal dactylitis due to *Staphylococcus aureus* in two HIV-positive men. Scheinfeld N. *Dermatol Online J* 2007; 13: 8.

S. aureus was found to be the etiologic agent in two HIV-positive patients. The condition improved after treatment with a proprietary mixture of amoxicillin trihydrate and clavulanate potassium. The report highlights that blisters may not always be present and that BDD may present with erosions.

Coexistent infections on a child's distal phalanx: blistering dactylitis and herpetic whitlow. Ney AC, English JC 3rd, Greer KE. *Cutis* 2002; 69: 46–8.

Consider comorbidity if BDD does not respond to antibiotics.

Body dysmorphic disorder (dermatologic non-disease)

Synonyms: Dermatologic non-disease, Body dysmorphic disease, Dysmorphophobia

Richard Fried, Danielle Weitzer



Body dysmorphic disorder (BDD) is an alteration in perception of body image that causes preoccupation with minimal or imagined defect in appearance. The preoccupation can be markedly excessive, causing clinically significant emotional distress and impairment in social, occupational, or other important areas of functioning. Preoccupations commonly involve the face and head, with skin and hair being the most frequent areas of concern. However, any area of the body may be involved. Dermatologic preoccupations are distressing, time consuming, and difficult or impossible for patients to resist. Insight is typically poor and alterations in perception are often to delusional proportion. Most patients have ideas of reference, thinking that others take special notice or mock them for their perceived defect. Repetitive behaviors are present in almost all patients, such as excessive checking or grooming, innumerable consultations with dermatologists and plastic surgeons, constant need for reference and reassurance, and skin manipulations. Risk of suicidal ideation and attempts is high, affecting approximately one-quarter of BDD patients. BDD was reclassified in the DSM-5 under obsessive-compulsive and related disorders.

MANAGEMENT STRATEGY

BDD is common in dermatologic settings with prevalence estimated at 11.9%, 3–53% in cosmetic surgery settings, and 8–37% in those with obsessive-compulsive disorder. Recognition of these patients is extremely important because they typically have psychiatric comorbidities, diminished quality of life, and impairments in psychosocial and vocational function. They are usually poor candidates for cosmetic procedures. Dissatisfaction, anger, and even aggression directed toward the treating clinician have been reported. Patients with BDD often have associated psychiatric disorders including major depression, substance abuse and dependence, social phobia, and obsessive-compulsive disorder. Recent studies with MR imaging have suggested abnormal brain network organization, which may provide some biological basis for the characteristic distortions in self-perception. The majority of these patients also have a personality disorder. Appropriate psychiatric treatment can result in a generally favorable outcome.

Typical body areas of preoccupation include:

- **Face.** Preoccupation with facial itching and burning or obsessive preoccupation with imagined acne, scars, wrinkles, pigmentation, oiliness, redness, paleness, facial vessels, and facial hair are common. Preoccupation with the nose, ears, and pore size is reported. Despite the fact that others do not usually see these minimal or non-existent flaws, patients can spend hours in front of mirrors, preventing them from working or socializing.
- **Scalp.** Dysesthesias (burning or itch) and obsession with imagined hair loss are common.
- **Genital.** Genital size, scrotal, perineal, and perianal burning, as well as vulvar redness and burning are common symptoms. Preoccupation with sexually transmitted disease or neoplastic process is common. Symptoms can be incapacitating.

Hallmarks and Flags for Diagnosis of Body Dysmorphic Disorder

Patients presenting with extreme concern that appears out of proportion to their chief complaint accompanied by a paucity of objective physical findings should raise suspicion that BDD may be present. Obsession, rumination, and extreme psychological distress are striking features. These patients usually report dissatisfaction with previous physicians and describe poor outcomes from past medical and surgical interventions. Skin picking and related behaviors such as excessive tanning, excessive grooming, and relentless need for reassurance are characteristic. Attempts to correct their perceptions are inevitably futile since their perceptual distortions and associated cognitions are deeply entrenched. It can be argued that the distorted perceptions are delusional, which by definition suggests that they are unresponsive to objective logic and persuasion. Patients often wear heavy makeup, hats, sunglasses, scarves, and other clothing to hide their imperfections and perceived ugliness (Table 30.1).

Patients with BDD often make unusual and excessive requests for cosmetic procedures with the belief that the procedure will transform or fix their lives. Poor psychosocial functioning with difficulties in relationships, school, and work is almost always seen. Depression is frequently evident and previous suicide attempts are not infrequent. Bear in mind that there have been instances of violent behavior toward treatment providers.

Clinical interactions and consultations with these patients are typically long, difficult, and emotionally draining. Regardless of the actual length of time spent with them, BDD patients often feel that they were not given adequate time and attention. As already

Table 30.1 Screening questions

1. How much do you currently think about your skin?
2. On an average day, how many hours do you spend thinking about your skin? Please add up all the time that your feature is on your mind and make your best estimate.
3. Do you feel your skin is ugly or very unattractive?
4. How noticeable do you think your skin is?
5. Does your skin currently cause you a lot of distress?
6. How many times a day do you usually check your skin either in a mirror or by feeling it with your fingers?
7. How often do you feel anxious about your skin in social situations? Does it lead to you avoiding social situations?
8. Has your skin affected dating or an existing relationship?
9. Has your skin interfered with your ability to work or study, or your role as a homemaker?

(Adapted from Veale D, Ellison N, Werner TG, et al. Development of a cosmetic procedure screening questionnaire (COPSS) for body dysmorphic disorder. *J Plast Reconstr Aesthet Surg* 2012; 65(4): 530–532.)

stated, it is inadvisable to perform procedures on these patients since less than 10% will be satisfied with the results of medical or surgical interventions.

Selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral psychotherapy remain the treatments of choice. Fluoxetine, fluvoxamine, and citalopram are the best studied agents, but recent evidence suggests that all SSRIs are probably effective. Higher dosing regimens than those used for depression are usually required. For example, fluoxetine and citalopram should be titrated to 60 mg per day while fluvoxamine should be increased to 300 mg per day at monthly intervals. Patients should receive a trial of 12–16 weeks before efficacy is assessed. If one agent fails, another should be substituted since some patients idiosyncratically respond more favorably to one agent over another. SSRIs appear to be more effective than antipsychotic agents despite the fact that BDD can involve severe distortions in self-perception to delusional proportion. Interestingly, only about 20% of patients will become free of their delusional thinking. However, the intrusiveness of the thoughts and distress will diminish sufficiently such that many patients will be able to resume some social and vocational functioning.

Cognitive-behavioral therapy (CBT) is a reality-based, in-the-present therapy that specifically focuses on the affected individual's cognitions and associated emotional experiences. The key elements are known as exposure, response prevention, perceptual retraining, and cognitive restructuring. Exposure consists of having patients expose the perceived defect in social and work situations. Response prevention techniques help patients avoid performance of their repetitive behaviors such as avoidance of others, excessive camouflage, picking, hyperventilating, etc. Perceptual retraining involves the development of a more holistic positive view of appearance. Cognitive restructuring helps patients challenge and eventually change their erroneous beliefs about their appearance. Ideally, treatment of BDD should encompass both CBT and an SSRI.

To initiate treatment or referral, suggest to the patient in a gentle manner that they may have a body image disorder called BDD. Convey your concern regarding the amount of their time being usurped by their preoccupation and their emotional distress. Psychiatric referral is preferable but often not feasible. Dermatologists are encouraged to align themselves, if possible, with mental health professionals who are experienced in treating this entity. Euphemisms for the psychiatric practitioner such as skin-emotion specialist may reduce the stigma of psychiatric referral and may

increase patient acceptance. If referral is not possible, treating with an SSRI may be successful. If suicidal ideation or intent are present, immediate hospitalization is recommended.

Specific Investigations

- Assess for potential suicide risk: emergent referral and appropriate notification if active ideation or intent
- Assess for any evidence of physical or emotional abuse
- Assess for evidence of substance abuse
- Assess for concomitant underlying psychiatric disease, i.e., depression/anxiety/OCD/psychosis, and make an appropriate psychiatric referral
- Appropriately diagnose and acknowledge genuine skin disease, i.e., hair loss, acne, rosacea, psoriasis, eczema, keratosis pilaris, seborrheic keratoses, or dyschromia, and offer legitimate therapies
- Investigate perceived skin changes appropriately to rule out atypical presentations of an underlying organic process if suspicion is present. Perform bacterial, viral, fungal cultures, skin biopsy, serologies, and imaging studies when deemed appropriate

Depression, anxiety, anger, and somatic symptoms in patients with body dysmorphic disorder. Phillips KA, Siniscalchi JM, McElroy SL. *Psychiatr Q* 2004; 75: 309–20.

Seventy-five patients with BDD completed a symptom questionnaire assessing depression, anxiety, somatic/somatization, and anger-hostility. Compared to normal controls, BDD subjects had markedly elevated scores on all four scales, indicating severe distress and psychopathology. When treated with fluvoxamine, all symptoms significantly improved.

Quality of life for patients with body dysmorphic disorder. Phillips KA. *J Nerv Ment Dis* 2000; 188: 170–5.

This is the only published study looking at quality of life (QOL) in BDD patients. These patients were found to have a poorer mental health QOL than has been reported for patients with other severe illnesses such type II diabetes, recent myocardial infarction, or depression. These findings highlight the dramatic impact of a non-disease.

Thirty-three cases of body dysmorphic disorder in children and adolescents. Albertini RS, Phillips KA. *J Am Acad Child Adolesc Psychiatry* 1999; 38: 453–9.

Thirty-three cases were examined. Onset was usually during adolescence but sometimes occurred in childhood. Earlier identification and treatment may avert unnecessary cosmetic and medical interventions as well as suicide.

Gender differences in body dysmorphic disorder. Phillips KA, Diaz S. *J Nerv Ment Dis* 1997; 185: 570–7.

This study looked at a large series of patients with DSM-4 defined BDD and found that one-quarter of patients had attempted suicide. Female patients with severe symptoms are at greater risk.

Body dysmorphic disorder. Ahmed I, Bowman D, Power A. *Medscape* October 3, 2019.

Excellent overview of entity and treatment strategies.

Suicide in dermatological patients. Cotterill JA, Cunliffe WJ. *Br J Dermatol* 1997; 137: 246–50.

Sixteen patients who had committed suicide are described. Most of these patients had acne or BDD. Females with facial complaints and men with facial scarring appeared more at risk for suicide. The authors relate these findings to the possible preventative benefits of early isotretinoin to prevent scarring in patients predisposed to BDD.

Diagnostic Aids

The body dysmorphic disorder symptom scale: development and preliminary validation of a self-report scale of symptom specific dysfunction. Body Image 2016; 17: 82–7. (Medline).

First-Line Therapies

- Selective serotonin reuptake inhibitors **A**
- Cognitive-behavioral therapy **B, C**

Treating body dysmorphic disorder with medication: evidence, misconceptions, and a suggested approach. Phillips KA, Hollander E. Body Image 2008; 5: 13–27.

SSRIs associated with improvement in core BDD symptoms, psychosocial functioning, QOL, suicidality, and other aspects of BDD.

Pharmacotherapy and psychotherapy for body dysmorphic disorder. Ipser JC, Sander C, Stein DJ. Cochrane Database Syst Rev 2009, Jan 21. CD005332.

Supports efficacy of SSRIs.

A randomized placebo-controlled trial of fluoxetine in body dysmorphic disorder. Phillips KA, Albertini RS, Rasmussen SA. Arch Gen Psychiatry 2002; 59: 381–8.

This is the only placebo-controlled BDD pharmacotherapy study. In the 74 patients studied, fluoxetine was significantly more effective than placebo, with a response rate of 53% versus 18%.

Pharmacotherapy relapse prevention in body dysmorphic disorder: a double-blind, placebo-controlled trial. Phillips KA, Keshaviah A, Dougherty DD, et al. Am J Psychiatry 2016; 173: 887–95.

In this trial, 100 BDD subjects were treated with citalopram for 14 weeks with 81% response rate; 58 responders were treated with additional citalopram or placebo for 6 months. The placebo group was 40% versus 18% for citalopram. Study supports ongoing maintenance therapy.

An open label study of venlafaxine in body dysmorphic disorder. Allen A, Hadley SJ, Kaplan A, et al. CNS Spectr 2008; 13: 138–44.

Seventeen patients enrolled, 11 completed 12–16 weeks of venlafaxine minimum 150 mg daily. All 11 patients significantly improved.

Clomipramine versus desipramine crossover trial in body dysmorphic disorder: selective efficacy of a serotonin reuptake inhibitor in imagined ugliness. Hollander E, Allen A, Kwon J, et al. Arch Gen Psychiatry 1999; 56: 1033–9.

This double-blind crossover study of 29 randomized patients found clomipramine (an SSRI) superior to desipramine (a non-SSRI tricyclic antidepressant).

Efficacy and safety of fluvoxamine in body dysmorphic disorder. Phillips KA, Dwight MM, McElroy SL. J Clin Psychiatry 1998; 59: 165–71.

Open-label study of fluvoxamine demonstrated good clinical response in 19 (63%) of 30 patients.

Delusionality and response to open-label fluvoxamine in body dysmorphic disorder. Phillips KA, McElroy SL, Dwight MM, et al. J Clin Psychiatry 2001; 62(2): 87–91.

In this open-label trial, 30 patients with BDD were treated with fluvoxamine for 16 weeks, with 63% of treated patients significantly improved. Important to note that both delusional and non-delusional patients responded similarly.

Change in psychosocial functioning and quality of life of patients with body dysmorphic disorder treated with fluoxetine: a placebo-controlled study. Phillips KA, Rasmussen SA. Psychosomatics 2004; 45: 438–44.

This was a 12-week placebo-controlled study of psychosocial functioning and mental health-related QOL in 60 patients. At baseline, the patients had impaired psychosocial functioning and markedly poor mental health-related QOL. A significant decrease in the severity of BDD was demonstrated along with improvement in functioning and QOL.

Modular cognitive behavioral therapy for body dysmorphic disorder: a randomized controlled trial. Wilhelm S, Phillips KA, Didie E, et al. Behav Ther 2014; 34: 314–27.

A group of 36 adults were treated with 22 sessions of modular CBT, with 81% achieving significant improvement in BDD symptoms, and high levels of satisfaction with treatment were reported.

Cognitive-behavioral body image therapy for body dysmorphic disorder. Rosen JC, Reiter J, Orosan P. J Consult Clin Psycho 1995; 63: 263–9.

Exposure with response prevention was effective in 77% of 27 women treated with cognitive-behavioral group therapy for 8 weeks. Subjects in the treatment group had greater improvement than those in the no-treatment waiting-list control group.

Cognitive-behavioral group therapy for body dysmorphic disorder: a case series. Behav Res Ther 1999; 37: 71–5.

In this case series, 13 BDD patients significantly improved after 12 group therapy sessions.

Body dysmorphic disorder: a cognitive behavioral model and pilot randomized controlled trial. Veale D, Gournay K, Dryden W, et al. Behav Res Ther 1996; 34: 717–29.

Nineteen patients were randomly assigned to CBT or a waiting-list control group. There was significantly greater improvement in BDD symptoms in the CBT group.

Second-Line Therapies

- Additional psychotropic agents and insight-oriented psychotherapy **D, E**
- Visual training programs **E**

Treating body dysmorphic disorder with medication: evidence, misconceptions, and a suggested approach. Phillips KA, Hollander E. Body Image 2008; 5: 13–27. doi: 10.1016/j.bodyim.2007.12.003.

Excellent review of alternative and concomitant psychotropic medications including clomipramine, venlafaxine, buspirone, and pimozide.

An open study of buspirone augmentation of serotonin-reuptake inhibitors in body dysmorphic disorder. Phillips KA. *Psychopharmacol Bull* 1996; 32(1): 175–80.

Thirteen patients with DSM-4 BDD who had not responded, or had responded only partially, to an SRI had buspirone added to the SRI. Six of these subjects (46%) improved. Three who decreased or discontinued buspirone experienced an increase in symptom severity.

The neurobiology of body dysmorphic disorder: a systematic review and theoretical model. Grace SA, Labuschagne I, Kaplan RA, et al. *Neurosci Biobehav Rev* 2017; 83: 83–96.

Nineteen studies utilizing fMRI studies of brain function in BDD patients demonstrated lower activity and poor connectivity between different regions of the occipital lobe for visual processing, suggesting possible opportunity for visual training interventions.

Modifying emotion recognition deficits in body dysmorphic disorder: an experimental investigation. Buhlmann U, Gleiss MJ, Rupf L, et al. *Depress Anxiety* 2011; 28(10): 924–31.

Thirty-four cases of BDD were examined in this study, looking at whether emotional recognition deficits can be improved through a training program. With respect to neutral and scared expressions, BDD participants improved significantly more in the training condition (emotional recognition program), relative to the non-training condition.

Third-Line Therapy	
• Future directions	E

Clinical and electrophysiological outcomes of deep TMS over the medial prefrontal and anterior cingulate cortices in OCD patients. Carmi L, Alyagon U, Barnea-Ygael N, et al. *Brain Stimul* 2018; 11(1): 158–65.

Transcranial magnetic stimulation has already been shown to reduce obsessive-compulsive severity. Obsessive-compulsive severity was believed to be reduced via activation of the medial prefrontal cortex.

Future direction may therefore look at this treatment in terms of BDD because of the shared clinical manifestations with OCD and recent DSM-5 inclusion of BDD under OCD.

Bowen disease and erythroplasia of Queyrat

Shareen Muthiah, Colin A. Morton



INTRODUCTION

Bowen disease (in situ squamous cell carcinoma [in situ SCC]) and erythroplasia of Queyrat (EQ) are forms of intraepidermal squamous cell carcinoma, with the latter located on the penis. Lesions typically present as well-demarcated, erythematous, hyperkeratotic plaques with an irregular border that are persistent and slowly enlarging. Plaques of EQ develop on the glans or inner aspect of the foreskin and can be smooth, scaly or warty. Risk factors for the development of Bowen disease and EQ vary according to site, but include sun exposure, human papilloma virus infection, arsenic exposure, radiation exposure, HIV, or other forms of immunosuppression.

DIAGNOSIS

An initial diagnostic biopsy is recommended, especially for EQ and atypical presentations of Bowen, but many dermatologists will initiate treatment of typical Bowen disease on the basis of clinical diagnosis, aided by dermoscopy.

The specific dermoscopic criteria of Bowen's disease. Zalaudek I, Di Stefani A, Argenziano G. *J Eur Acad Dermatol Venereol* 2006; 20: 361–2.

Dermoscopic features include irregular clusters of coiled 'glomerular vessels' together with a scaly surface characteristic, with

small, pigmented globules and/or homogeneous pigmentation present in pigmented variants.

MANAGEMENT STRATEGY

Curative therapy aims to prevent progression to invasive SCC. SCC arises in approximately 3–5% of typical Bowen disease and about 10% for EQ. Several treatment options are available, and evidence-based guidelines seek to balance efficacy, tolerability, and cosmesis with cost effectiveness. Sexual partners of patients with EQ should be screened for other forms of intraepithelial neoplasia caused by human papillomavirus (HPV) in the genital area.

British Association of Dermatologists' guidelines for the management of squamous cell carcinoma in situ (Bowen's disease) 2014. Morton CA, Birnie AJ, Eedy DJ. *Br J Dermatol* 2014; 170: 245–60.

Quality of evidence for reported treatments for Bowen disease and EQ was reviewed in detail. The strongest evidence was for topical photodynamic therapy (PDT), 5-fluorouracil, and imiquimod, as well as cryotherapy. Non-surgical options are increasingly used and offer advantages for large/multiple lesions. Surgical excision and curettage remain in common use, although with lower-quality evidence available. Similar therapeutic options are available for patients with EQ; however, treatment tolerability is a greater challenge.

Direct surgical excision can be considered if a lesion is small and well defined, especially if there is doubt over possible invasive SCC. Lesion ablation may also be achieved with electrodesiccation and curettage or cryotherapy. Mohs micrographic surgery (MMS) is the surgical treatment of choice in severe/recurrent cases of EQ and indicated for certain sites (e.g., digital Bowen disease) where tissue-sparing benefits are important. Laser and radiotherapy have a more limited evidence base, with poor healing reported after radiotherapy. Several treatment combinations are also reported in the literature but lack a substantial evidence base.

First-Line Therapies

• Photodynamic therapy	A
• Cryotherapy	A
• Electrodesiccation and curettage	B
• Standard excision	B

Interventions for cutaneous Bowen's disease. Bath-Hextall FJ, Matin RN, Wilkinson D, et al. *Cochrane Database Syst Rev* 2013; 6: CD007281.

Review of interventions for SCC in situ by the Cochrane Skin Group identified nine randomized, controlled trials but noted limited data for surgery and topical therapies. Methyl-aminolevulinic acid–photodynamic therapy (MAL-PDT) was shown to be more efficacious than cryotherapy, but equivalent to topical 5-fluorouracil.

ALA-PDT achieved a higher clearance rate compared with 5-fluorouracil, whereas 5-fluorouracil and cryotherapy showed similar efficacy.

Treatments for primary squamous cell carcinoma and squamous cell carcinoma in situ of the skin: a systematic review and network meta-analysis: summary of an agency for healthcare research and quality comparative effectiveness review. Drucker AM, Adam GP, Rofefer V, et al. *J Am Acad Dermatol* 2020; 82: 479–80.

MAL-PDT is more likely to achieve good or better observer-reported cosmesis than a physician's choice of cryotherapy or 5-fluorouracil. Laser plus MAL-PDT provided better clearance than PDT alone or a physician's choice of cryotherapy or topical 5-fluorouracil.

Comparison of topical methyl aminolevulinate photodynamic therapy with cryotherapy or fluorouracil for treatment of squamous cell carcinoma in situ. Morton C, Horn M, Leman J, et al. Arch Dermatol 2006; 142: 729–35.

Estimated complete response rates at 1 year were highest for MAL-PDT ($n\{ts\}=96$) at 80% (two treatments spaced 1 week apart, with the methyl-aminolevulinate applied for 3 hours before red light illumination) compared with cryotherapy ($n\{ts\}=96$) at 67% (a minimum 20-second freeze–thaw cycle) and 5% fluorouracil cream at 69% (4 weeks of treatment applied once a day for the first week, then twice a day), although the three therapies were equivalent at 24 months. MAL-PDT provided superior cosmesis. Given the smaller sample size of 30 lesions treated by 5-fluorouracil in this study where the comparator was chosen by clinician's preference and more limited study data elsewhere, topical 5-fluorouracil has been overall considered a second-line therapy in this chapter.

European guidelines for photodynamic therapy. Part 1: treatment delivery and current indications – actinic keratoses, Bowen's disease, basal cell carcinoma. Morton CA, Szeimies RM, Sidoroff A, et al. J Eur Acad Dermatol Venereol 2019; 33: 2225–38.

Review of the literature observing high efficacy (88–100%) of typical lesions of Bowen disease at 3 months after one or two cycles of MAL-PDT with sustained clearance of 68%–89% over periods of 17–50 months, equivalent to cryotherapy and topical 5-fluorouracil. PDT has been shown effective for large lesions over 3 cm in diameter, clearing 96%, as well as a tissue-sparing option for digital, subungual, and nipple lesions. Enhanced clearance rates have been reported by sequential use of PDT and imiquimod, or by ablative laser assisted MAL-PDT.

Methyl-aminolevulinate photodynamic therapy for the treatment of erythroplasia of Queyrat in 23 patients. Fai D, Romano I, Cassano N, et al. J Dermatolog Treat 2012; 23: 330–2.

Nineteen patients obtained complete clinical remission over an average posttreatment period of 18 months, although local adverse reactions were common during treatment.

Bowen's disease involving the urethra. Yasuda M, Tamura A, Shimizu A, et al. J Dermatol 2005; 32: 210–3.

A case report highlighting the importance of early and definitive surgical treatment of EQ, recognizing the limited options when EQ extends to include the urethral meatus.

Comparison of cryotherapy with curettage in the treatment of Bowen's disease: a prospective study. Ahmed I, Berth-Jones J, Charles-Holmes S, et al. Br J Dermatol 2000; 143: 759–66.

Eighty lesions were randomized to two groups, cryotherapy ($n=36$) or curettage ($n=44$), and followed for a median of 2 years. Curettage produced comparable cure rates with more rapid healing, less pain, and fewer skin complications.

Second-Line Therapies

• 5-Fluorouracil	B
• Imiquimod 5%	B
• Mohs micrographic surgery	B

Topical treatment of Bowen's disease with 5-fluorouracil. Bargman H, Hochman J. J Cutan Med Surg 2003; 7: 101–5.

Only two of 26 biopsy-confirmed lesions recurred up to 10 years after treatment.

Imiquimod 5% cream monotherapy for cutaneous squamous cell carcinoma in situ (Bowen's disease): a randomized, double-blind, placebo-controlled trial. Patel GK, Goodwin R, Chawla M, et al. J Am Acad Dermatol 2006; 54: 1025–32.

Seventy-three percent of 31 patients achieved clinical remission with no recurrence at the 9-month follow-up.

Treatment of Bowen's disease with topical 5% imiquimod cream: retrospective study. Rosen T, Harting M, Gibson M. Dermatol Surg 2007; 33: 427–31.

Forty-two of 49 patients (86%) treated with 5% imiquimod cream once daily for a mean of 9 weeks achieved complete clinical remission at 1.5-year follow-up.

Erythroplasia of Queyrat treated with imiquimod 5% cream. Micali G, Nasca MR, De Pasquale R. J Am Acad Dermatol 2006; 55: 901–3.

Case report of an elderly man with EQ treated with 5% imiquimod with clinical and histologically confirmed cure.

Cutaneous squamous carcinoma in situ (Bowen's disease): treatment with Mohs micrographic surgery. Leibovitch I, Huilgol SC, Selva D, et al. J Am Acad Dermatol 2005; 52: 997–1002.

A case series evaluating 270 cases of Bowen disease treated with MMS with 5-year follow-up demonstrating recurrence rates of approximately 6%. The majority of lesions treated were on the head and neck, and many were recurrent at the time of MMS.

Extensive Bowen's disease of the penile shaft treated with fresh tissue Mohs micrographic surgery in two separate operations. Moritz DL, Lynch WS. J Dermatol Surg Oncol 1991; 17: 374–8.

Third-Line Therapies

• Laser	C
• Radiotherapy	C

Bowen's disease treated by carbon dioxide laser. A series of 44 patients. Covadonga Martinez-Gonzalez M, del Pozo J, Paradelo S, et al. J Dermatolog Treat 2008; 19: 293–9.

A larger retrospective study that used a CO₂ laser in superpulsed mode (2W/cm²) to treat Bowen disease in 44 patients reported clearance after one treatment in 86% of patients.

Radiation therapy for Bowen's disease of the skin. Lukas VanderSpek LA, Pond GR, Wells W, et al. Int J Radiat Oncol Biol Phys 2005; 63: 505–10.

Forty-four cases of Bowen disease treated with radiation therapy were reviewed, demonstrating remission in 42 with three

recurrences at a median follow-up of 2.6 years. A broad range of radiation schedules were used and compared for efficacy and safety with no significant differences in disease remission or recurrence between low- and high-dose regimens.

Bullous pemphigoid

Asli Bilgiç, Dedee F. Murrell



Bullous pemphigoid (BP) is the most common autoimmune blistering disorder. The diagnosis is based on the combination of clinical, histopathological, and immunopathological findings. Currently, direct immunofluorescence (DIF) from perilesional skin (typically showing linear n-serrated deposits of IgG and/or C3 along the dermoepidermal junction) is regarded as the critical test for the diagnosis. However, enzyme-linked immunosorbent assay (ELISA) assessing serum concentrations of circulating auto-antibodies (especially anti-BP180 IgG) has increasing evidence for both diagnosis and monitoring the disease status and response to treatment. The Bullous Pemphigoid Disease Area Index (BPDAI) and the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) are outcome measures used for BP in clinical trials. There is increasing evidence for their use to determine disease severity in a standardized manner.

MANAGEMENT STRATEGY

Always recall that BP patients are generally elderly with comorbidities and all treatments need to be selected to first do no harm. The best evidence for treatment in clinical trials is for moderate-to-severe BP.

Current mortality of BP in non-selected patients is 25–35%; 40% for high-dose oral prednisone and 10% in trials in which over 80% of BP patients were excluded (tetracyclines, methotrexate (MTX) trials).

Superpotent topical corticosteroids have the best randomized controlled-trial (RCT) evidence. Over 1000 patients were reported in validated studies to prove the effectiveness of clobetasol propionate 0.05% cream, 30–40 g per day for severe BP and 20–30 g/day for moderate BP. It is important that the cream is applied all over the body except the face and genitalia, including the blistering and erosions and normal skin. The initial treatment is daily for the first month, every second day for the second month, twice a week for the third month, and once a week in the fourth month. After the fourth month, maintenance once weekly until months 9–12 or stop the treatment. However, due to problems of its practical use in extensive or severe disease, their usage is limited.

In localized or mild BP, superpotent topical steroids are an effective and safer treatment option for BP, as they cause less

serious adverse effects in comparison to high-dose systemic steroids. If topical steroids are not feasible, *oral corticosteroids* may be considered.

Medium doses of oral prednisone (0.5 mg/kg/day) are effective in mild BP with 95% remission rate by day 21. High-dose corticosteroids are effective but should be avoided due to high morbidity and mortality. Low-dose oral prednisone (<0.3 mg/kg) was ineffective for moderate-to-severe BP. If the disease is not controlled by medium-dose corticosteroids, steroid-sparing agents (for severe BP: MTX, azathioprine [AZA], mycophenolate mofetil [MMF]; for mild-to-moderate BP: tetracyclines or dapsone) may be added. *Tetracyclines* may be used initially for patients with many comorbidities or contraindications to conventional immunosuppressants in whom large amounts of potent topical steroids are not practical/affordable. Low doses of *methotrexate* (MTX) at 5 mg/week are ineffective alone or with low doses of prednisone. Median doses of MTX (12.5 mg/week) could be effective when added to potent topical steroids. However, serious side effects are more common when elderly patients are given MTX.

The evidence for adding MMF and AZA from RCTs was not compelling due to lack of statistical difference or insufficient power for demonstrating a steroid-sparing effect. In practice these are often still used for relapsing BP.

Specific Investigations

After the diagnostic lesional and perilesional skin biopsies and BP180/BP230 serology investigations, others to optimize management should be performed.

- Evaluation of medications to rule out drug-induced cases
- Complete physical examination for infections, comorbidities, and underlying malignancy
- Consider patient age and overall medical condition for therapeutic decision-making
- Dietary regulations for glucose intolerance, diabetes, hypertension, or any other metabolic problems
- Screening for tuberculosis, hepatitis B and C, and HIV serology
- Prophylactic vaccinations such as seasonal influenza and pneumococci
- Screening and prophylactic therapy for osteoporosis
- Pregnancy test if relevant prior to any treatment
- Testing glucose 6-phosphate dehydrogenase before dapsone treatment
- Testing thiopurine methyltransferase before azathioprine (AZA) treatment
- Testing serum IgA deficiency for intravenous immunoglobulin (IVIG) therapy

THERAPIES

First-Line Therapies

• Topical clobetasol propionate 0.05%	B
• Systemic corticosteroids	B
• Doxycycline	B
• Tetracycline and nicotinamide	B
• Minocycline	C
• Tetracycline	E

A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. Joly P, Roujeau JC, Benichou J, et al. *N Engl J Med* 2002; 346: 321–7.

In a *non-blinded*, randomized, multicenter trial, Joly et al. enrolled 341 patients with BP. Patients either received topical clobetasol propionate 0.05% cream (a daily dose of 40g applied to the entire surface of the body in patients with extensive disease [bullae >10/day]; 20g/day <10 blisters/day) or oral prednisone (0.5mg/kg/day for moderate BP and 1mg/kg/day for those with extensive disease).

In those with extensive BP (188 patients), topical corticosteroids were superior to oral prednisone in terms of 1-year survival rate and the rate of disease control at 3 weeks.

A comparison of two regimens of topical corticosteroids in the treatment of patients with bullous pemphigoid: a multicenter randomized study. Joly P, Roujeau JC, Benichou J, et al. *J Invest Dermatol* 2009; 129: 1681–7.

In a multicenter, non-blinded, randomized, controlled trial, a total of 312 BP patients (134 moderate and 178 extensive patients) were randomly assigned either to the standard regimen (clobetasol propionate 0.05% cream, 40g per day initially, with corticosteroids [CS] tapering over 12 months) or the mild regimen (10–30g per day), with CS tapering over 4 months. A strong beneficial effect in terms of the risk of death or life-threatening adverse events was found in patients with moderate BP with the mild regimen relative to the standard regimen as well as allowing 70% reduction of the cumulative doses of CS and improved BP patients' outcome.

Treatment of bullous pemphigoid with prednisolone only: 0.75 mg/kg/day versus 1.25 mg/kg/day. A multicenter randomized study. Morel P, Guillaume JC. *Ann Dermatol Venerol* 1984; 11: 925–8.

A total of 46 patients with BP were included in this randomized study comparing the efficacy and safety of two dosages of prednisolone used as a single therapeutic agent: 0.75 mg/kg/day versus 1.25 mg/kg/day for 3 weeks. They found no difference in effectiveness in terms of active lesions after 51 days.

Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: a pragmatic, non-inferiority, randomised controlled trial. Williams HC, Wojnarowska E, Kirtschig G, et al. *UK Dermatology Clinical Trials Network BLISTER Study Group. Lancet* 2017; 389(10079): 1630–8.

This multicenter, parallel-group, randomized, controlled, non-blinded trial examined the efficacy of doxycycline or prednisolone in adults with BP. Local application of adjuvant potent topical corticosteroids (<30g per week) were allowed during weeks 1–3; 132 patients were randomized to doxycycline (200 mg per day) and 121 to prednisolone (0.5 mg/kg/day) for 6 weeks to assess the primary effectiveness. The study concluded that doxycycline is a therapeutic option non-inferior to standard treatment with oral prednisolone in terms of achieving short-term blister control when used with topical steroids limited to the lesions (74% for doxy/91% pred) and significantly safer in terms of rate of serious adverse events and treatment-related death in the long term (56 weeks) (18% doxy vs. 34% pred). There has been significant controversy regarding the methodology because many in the doxycycline initial treatment group switched to the prednisolone group due to lack of efficacy but were analyzed as doxycycline treatment. Furthermore, patients were allowed to use topical steroids and the prednisolone group received an initial fixed prednisolone dose regardless of disease severity. Disease control assessment at 6 weeks was also rather a long time to assess response compared with previous BP studies, which used 3 weeks.

A randomised controlled trial to compare the safety, effectiveness and cost-effectiveness of doxycycline (200mg/day) with that of oral prednisolone (0.5mg/kg/day) for initial treatment of bullous pemphigoid: the Bullous Pemphigoid Steroids and Tetracyclines (BLISTER) trial. Chalmers JR, Wojnarowska E, Kirtschig G, et al. *Health Technol Assess* 2017; 21: 1–90.

A cost-effectiveness analysis of the previous study found no significant difference in terms of costs or quality-adjusted life-years (QALYs) per patient at 1 year between doxycycline-initiated therapy and prednisolone-initiated therapy in patients with low-to-moderate BP. However, prednisolone showed a better quality of life improvement and reduced costs in patients with severe BP.

Nicotinamide and tetracycline therapy of bullous pemphigoid. Fivenson DP, Breneman DL, Rosen GB, et al. *Arch Dermatol* 1994; 130: 753–8.

The efficacy of nicotinamide (500 mg three times daily) and tetracycline (500 mg four times daily) compared with prednisone therapy in 20 patients with BP in a randomized, open-label trial. The combination therapy was not significantly different in efficacy to prednisone and resulted in less toxicity, but the study was underpowered to detect significance, with many dropouts in the tetracycline arm.

Tetracycline, nicotinamide, and lesionally administered clobetasol as a therapeutic option to prednisone in patients with bullous pemphigoid: a comparative, retrospective analysis of 106 patients with long-term follow-up. Kalinska-Bienias A, Kowalczyk E, Jagielski P, et al. *Int J Dermatol* 2019; 58: 172–7.

In this retrospective 3-year clinical study, tetracycline 1.5g daily + nicotinamide 1.2g daily, and 0.05% lesionally administered clobetasol cream (TNC group) were compared with prednisone 0.5 mg/kg daily (P group). One hundred six patients with newly diagnosed BP were divided into two groups: 59 in TNC and 47 in P. TNC was an effective treatment with better survival rates compared with prednisone, especially in advanced-age patients with comorbidities.

Second-Line Therapies

• Azathioprine	B
• Mycophenolate mofetil	B
• Dapsone	B
• Methotrexate	C

An open, multicentre, randomized clinical study in patients with bullous pemphigoid comparing methylprednisolone and azathioprine with methylprednisolone and dapsone. Sticherling M, Franke A, Aberer E, et al. *Br J Dermatol* 2017; 177: 1299–305.

This study compared the efficacy and safety of oral methylprednisolone therapy (0.5 mg/kg/day) in combination with either AZA (1.5–2.5 mg/kg/day) or dapsone (1.5 mg/kg/day) in 54 patients with BP. The combination regimen of either drug with oral methylprednisolone was found to have a relatively low 1-year mortality. The time until complete tapering of methylprednisolone and the cumulative corticosteroid dose were not significantly different. The study was underpowered due to a low number of patients; dapsone was shown to have a higher corticosteroid-sparing potential than AZA.

A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of bullous pemphigoid. Beissert S, Werfel T, Frieling U, et al. *Arch Dermatol* 2007; 143: 1536–42.

The efficacy and safety of oral methylprednisolone plus azathioprine 2 mg/kg/day (AZA group; 38 patients) or oral methylprednisolone plus mycophenolate mofetil 2 g/day (MMF group; 35 patients) in a prospective, multicenter, randomized, non-blinded clinical trial. Although MMF and AZA groups demonstrated similar efficacy and similar cumulative corticosteroid doses to control disease, AZA treatment was associated with faster remission and a lower cumulative dose of methylprednisolone. However, MMF showed a significantly lower liver toxicity profile than AZA.

Treatment of bullous pemphigoid with dapsone: retrospective study of thirty-six cases. Bouscarat F, Chosidow O, Picard-Dahan C, et al. *J Am Acad Dermatol* 1996; 34: 683–4.

In a retrospective study of 36 BP patients treated with dapsone, the response rate was 44% in patients treated with dapsone plus topical steroids versus 20% with dapsone alone. Thus, dapsone alone was less effective than a combination of dapsone and topical steroids.

Methotrexate is safe and efficient as long-term treatment for bullous pemphigoid. Delaunay S, Assikar S, Prudhomme R, et al. *Eur J Dermatol* 2019; 29: 217–8.

In this retrospective study, 51 patients received subcutaneous methotrexate (MTX) (dose range: 7.5–15 mg per week) after topical corticosteroids (clobetasol propionate every day for at least 3 months) out of 329 BP patients diagnosed between 2007 and 2017. Complete remission rate was 90% after 1 month of MTX, and 92% after 3 months. Thus, low-dose MTX with topical steroid can be beneficial for long-term treatment of BP leading to satisfactory control of the disease while being safe.

Combined treatment with low-dose methotrexate and initial short-term superpotent topical steroids in bullous pemphigoid: an open, multicentre, retrospective study. Du-Thanh A, Merlet S, Maillard H, et al. *Br J Dermatol* 2011; 165: 1337–43.

In a clinical record-based retrospective analysis, the effectiveness and safety of a combined regimen of initial short-term superpotent topical steroids and MTX followed by long-term MTX alone was evaluated in 70 BP patients. All patients showed complete clinical remission. Long-term disease control was achieved by 76%; however, 24% of patients experienced at least one relapse during subsequent treatment with MTX alone and 16% had drug-related adverse effects.

Third-Line Therapies

• Intravenous immunoglobulin (IVIG)	B
• Rituximab	C
• Omalizumab	C
• Chlorambucil + prednisolone	C
• Pulse intravenous corticosteroids	D
• Cyclophosphamide + pulse intravenous corticosteroids	D
• Dupilumab	D
• Cyclophosphamide	E
• Ciclosporin	E
• Dimethyl fumarate	E
• Etanercept	E
• Daclizumab	E
• Ustekinumab	E
• Secukinumab	E

A randomized double-blind trial of intravenous immunoglobulin for bullous pemphigoid. Amagai M, Ikeda S, Hashimoto T, et al. *Bullous Pemphigoid Study Group. J Dermatol Sci* 2017; 85: 77–84.

High-dose IVIG (IVIG; 400 mg/kg/day for 5 days) in resistant BP patients was assessed using a disease activity score (DAS) modified from the pemphigus disease area index (PDAI) on day 15. Twenty-nine patients were randomized to IVIG and 27 to placebo along with an oral steroid tapering. Although there was no significant difference between the IVIG and placebo groups, the IVIG group demonstrated lower scores than the placebo group at all observation points throughout the study period. Furthermore, a significant difference in the severe cases (DAS ≥ 40) between the treatment groups was shown during the early stages after treatment.

First-line combination therapy with rituximab and corticosteroids provides a high complete remission rate in moderate-to-severe bullous pemphigoid. Cho YT, Chu CY, Wang LF. *Br J Dermatol* 2015; 173: 302–4.

In a retrospective case-control study, patients with generalized BP (moderate to severe) treated with systemic treatments were evaluated. In the first-line combination therapy ($n=13$) (the regimen included four weekly infusions of 500 mg rituximab [RTX] and corticosteroids, with a starting dose of prednisolone of 0.5 mg/kg/day), the corticosteroids dose was tapered rapidly after the disease was controlled within a total duration of <6 months. The comparison group ($n=19$) consisted of patients from the same period receiving a similar starting dose of prednisolone for at least 6 months. This study was the first to use rituximab as a first-line treatment in BP and demonstrated a significantly better rate of complete remission than conventional steroid treatment. Results also showed similar and even lower rates of infection and mortality than conventional treatment although infection was the most important cause of mortality in the study. To conclude, the combination therapy of RTX and steroid is effective and relatively safe for moderate-to-severe BP.

Rituximab and omalizumab for the treatment of bullous pemphigoid: a systematic review of the literature. Kremer N, Snast I, Cohen ES, et al. *Am J Clin Dermatol* 2019; 20: 209–16.

A systematic review was carried out in order to evaluate the safety and efficacy of the use of RTX and omalizumab for the treatment of BP. Thirty-five publications including 84 patients (62 received rituximab and 22 received omalizumab) were analyzed. Complete response rates for RTX and omalizumab were compatible with the rates of 85% and 84%, respectively. Furthermore, there was no significant change in terms of adverse effects (24% in RTX and 20% in omalizumab). However, the RTX group had a lower (29%) relapse rate than with omalizumab (80%).

There are more than 11 case reports apart from this systematic review showing the efficacy of omalizumab.

Abdat R, Waldman RA, de Bedout V, et al. *J Am Acad Dermatol* 2020 [Epub ahead of print].

This recent multi-institutional study included 13 patients with BP who were treated with dupilumab (using the dosing regimen approved for atopic dermatitis: 600 mg SC initially followed by 300 SC every other week). They suggested that dupilumab might be an additional treatment for recalcitrant BP.

Daclizumab: a novel therapeutic option in severe bullous pemphigoid. Mockenhaupt M, Grosber M, Norgauer J. *Acta Dermatol Venereol* 2005; 85: 65–6.

Daclizumab (1 mg/kg per infusion given every 2 weeks) was used in a 52-year-old patient with diffuse BP who failed with combination treatment. The patient had six infusions of daclizumab and succeeded in complete resolution of lesions at week 2 and remained on prednisolone 5 mg/day and azathioprine 50 mg/day.

Treatment of bullous pemphigoid with low-dose oral cyclophosphamide: a case series of 20 patients. Gual A, Iranzo P, Mascaró JM Jr. *J Eur Acad Dermatol Venereol* 2014; 28: 814–8.

A retrospective study evaluated low-dose oral cyclophosphamide (50–100 mg/day) in refractory BP already taking systemic steroids; 11/19 (58%) had a complete response. Cyclophosphamide (CFM) was used as first-line corticosteroid-sparing treatment in 8/19 (40%) cases, as second-line treatment in eight (40%) patients, and as third-line therapy in the remaining three (15%) patients. Clinical remission was achieved in 8/19 and partial remission in 4/19 (21%). The main adverse effects were bone marrow suppression (in 12 patients), gastrointestinal intolerance (in one patient), and death because of heart failure (not attributed to CFM), and another patient developed acute myeloid leukemia 1.5 years after CFM therapy.

Cyclosporin in the treatment of bullous pemphigoid: preliminary study. Barthélémy H, Thivolet J, Cambazard F, et al. *Ann Dermatol Venereol* 1986; 113: 309–13.

Seven BP patients received cyclosporin (CyA) at 6 to 8 mg/kg/day. CyA was used alone in four patients, and used with a combination of steroids in three patients during relapses. Out of four patients using CyA alone, two had failures and two had successful outcomes. Researchers suggested that CyA had no beneficial effect in the acute phase and in the long term CyA could be potentially nephrotoxic in elderly people.

Successful management of bullous pemphigoid with dimethyl fumarate therapy: a case report. Bilgic-Temel A, Das S, Murrell DF. *Int J Womens Dermatol* 2019; 5: 179–80.

A 69-year-old woman affected by both multiple sclerosis for 35 years and BP (unsuccessful treatment with first-line therapies) was able to taper off corticosteroids with dimethyl fumarate (DMF) at

a dose of 120 mg twice per day for 7 days and then increased to 240 mg twice per day maintained for over a year. DMF is now under evaluation with an investigator-initiated prospective controlled trial in patients with BP to determine the efficacy and safety of adjuvant DMF (<http://www.erare.eu/financed-projects/dpem>).

Treatment of coexisting bullous pemphigoid and psoriasis with the tumor necrosis factor antagonist etanercept. Yam-auchi PS, Lowe NJ, Gindi V. *J Am Acad Dermatol* 2006; 54(3 Suppl 2): S121–2.

A 64-year-old man with psoriasis more than 12 years and coexisting BP was treated with etanercept 50 mg weekly with systemic prednisone after using mycophenolate mofetil (1 g twice daily) as initial therapy, then using prednisone alone at a dose of 60 mg daily. When the prednisone dose decreased to 20 mg/day, due to a flare, the etanercept dosage was increased to 50 mg twice weekly. BP lesions subsequently resolved, and prednisone was discontinued eventually.

A successful treatment with ustekinumab in a case of relapsing bullous pemphigoid associated with psoriasis. Loget J, Plée J, Antonicelli F, et al. *J Eur Acad Dermatol Venereol* 2017; 31: e228–30.

The patient had complete remission of recalcitrant BP and psoriasis after ustekinumab, an anti-IL 12/23 monoclonal antibody (45 mg subcutaneously at weeks 0 and 4, and then every 12 weeks). Although sparse psoriatic lesions persisted, complete remission was achieved, and serum anti-BP180 autoantibodies became negative.

Secukinumab decreased circulating anti-BP180-NC16a autoantibodies in a patient with coexisting psoriasis vulgaris and bullous pemphigoid. Kamata M, Asano Y, Shida R, et al. *J Dermatol* 2019; 46: 216–7.

A 69-year-old man with a 40-year history of psoriasis and recent diagnosis of BP who received secukinumab, an anti-interleukin (IL)-17 antibody, was shown to be effective in decreasing the required prednisolone dose and further decreased the anti-BP180-NC16a autoantibody level.

33

Burning mouth syndrome (glossodynia)

Ashley N. Privalle, Rochelle R. Torgerson



Primary burning mouth syndrome (BMS) is a rare, chronic, debilitating disease characterized by intraoral burning in the absence of systemic disease or identifiable abnormalities on physical examination and laboratory testing. Current evidence suggests that altered neurophysiology of the central or peripheral nervous system as well as immune-mediated, hormonal, and psychological factors may play an etiopathogenic role. The diagnosis of primary BMS is a clinical diagnosis of exclusion. Various medical conditions and medications can induce oral burning, a condition referred to as *secondary BMS*. Secondary BMS improves with treatment of the underlying condition(s).

MANAGEMENT STRATEGY

A detailed history and physical examination should be completed to identify all alternative or correctable causes of oral burning. Correctable, associated factors may be local, systemic, or psychological.

Local Factors

Local factors include xerostomia (age, medication, radiotherapy); direct irritation (oral care products, tobacco); mechanical trauma (rough dental restorations, poorly fitting dental prostheses); parafunctional habits (bruxism, tongue thrusting); microbial infection or colonization (candidiasis, herpetic, fusospirochetal); geographic or fissured tongue; mucocutaneous diseases (lichen planus, pemphigus, pemphigoid); and allergic or irritant contact stomatitis (flavorings, food additives, dental materials, cosmetic products).

Systemic Factors

Systemic factors include nutritional deficiency states; autoimmune disease (Sjögren syndrome); gastrointestinal disease (gastroesophageal reflux); neurologic disease (trigeminal neuralgia, acoustic neuroma, Parkinson disease, glossopharyngeal neuralgia); medication(s); and endocrinopathies (hypothyroidism, diabetes).

Psychological Factors

Psychological factors include anxiety (including cancerophobia), depression, adjustment disorder, and psychosocial stressors.

Specific Investigations

Laboratory evaluation should be directed by the history and physical examination findings. If burning persists after eliminating or treating potential local, systemic, and psychological factors, a working diagnosis of primary BMS is adopted. Although consensus on treatment for primary BMS is lacking, many have found success with multimodal approaches resembling those used for the treatment of chronic, neuropathic pain.

A population-based study of the incidence of burning mouth syndrome. Kohorst JJ, Bruce AJ, Torgerson RR, et al. *Mayo Clin Proc* 2014; 89(11): 1545–52.

Annual age- and sex-adjusted incidence of BMS of 11.4 per 100,000 person-years.

Burning mouth syndrome. Jaaskelainen SK, Woda A. *Cephalalgia* 2017; 37: 627–47.

A review of BMS including evidence of neurophysiologic alterations in the peripheral or central nervous system.

Psychiatric comorbidity in patients with burning mouth syndrome. Bogetto F, Maina G, Ferro G, et al. *Psychosom Med* 1998; 60: 378–85.

In a case-control study of 102 patients with BMS, 59.8% had concomitant psychiatric disorders.

Burning mouth syndrome. Torgerson RR. *Dermatol Ther* 2010; 23: 291–8.

Multiple possible etiologies of BMS, including neuropathic, exocrine dysfunction, taste disturbance, mucosal atrophy, and psychological illness are reviewed (Tables 33.1–33.3).

Burning mouth syndrome: a comparative cross-sectional study. Rabiei M, Leili EK, Alizadeh L. *Contemp Clin Dent* 2018; 9: S256–60.

Age and sex are significant risk factors for development of BMS. Menopause, candidiasis, psychological disorders, job status, dentures, and dry mouth were more common in patients with BMS.

Burning mouth syndrome. Bender SD. *Dent Clin North Am* 2018; 62: 585–96.

BMS is a multifactorial condition, including interaction of psychological and neurophysiologic factors.

Table 33.1 Specific investigations**History**

Oral symptoms	Timing, quality, duration, location, alleviating/exacerbating factors
Medications	Causative: efavirenz, ACE inhibitors, ARBs, omeprazole, topiramate, TNF- α inhibitors
Dental	Prostheses, recent procedures, dentifrices, topical medicaments, oral care products
Parafunctional habits	Bruxism, tongue thrusting
Review of symptoms	Weakness, headache, fatigue, concentration, sleep disturbance, arthralgia

Physical examination

Oral	Complete oral examination, including head and neck (remove any dental prostheses)
Nodal	Adenopathy
Musculoskeletal	Temporomandibular joint
Neurologic	Cranial nerve exam

Table 33.2 Laboratory evaluation

Hematologic	Complete blood count, ferritin, serum folate, cobalamin (+ methylmalonic acid, homocysteine)
Metabolic	Serum thiamine, riboflavin, pyridoxine, zinc (+ alkaline phosphatase), magnesium
Endocrinologic	Glycosylated hemoglobin, thyrotropin (+ free thyroxine)
Immunologic	Antinuclear factor (+ Ro/SSA, La/SSB)
Dermatologic	Biopsy (+ direct immunofluorescence) if visible abnormality on oral examination
Microbiology testing	Herpes simplex (polymerase chain reaction [PCR]); varicella zoster (PCR); candidiasis (swab from site of pain for direct examination and culture); human immunodeficiency virus screening

Table 33.3 Consultations

Otolaryngology	Nasopharyngoscopy
Gastroenterology	Esophagogastroduodenoscopy
Oral/maxillofacial	Periapical radiographs, magnetic resonance imaging
Mental health	Psychiatry consultation
Neurology	Neurologic examination, magnetic resonance imaging
Hypersensitivity testing	Epicutaneous patch testing (preservatives, oral flavors, metals, adhesives, food-related allergens)

First-Line Therapies

- Acknowledge and validate patient symptoms and experience; reassure **E**
- Avoid contact irritants (alcohol-based oral rinses, caustic mouthwashes, flavored dentifrices, acidic foods, carbonated beverages) **E**
- Treat xerostomia (sialagogues, artificial oral lubricants) **D**
- Discontinue or change causative medications (ACE inhibitor, ARB, selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor, benzodiazepine, non-nucleoside reverse-transcriptase inhibitor, PPI, anticonvulsant, anticholinergics, TNF- α inhibitors) **E**
- Replace thiamine, riboflavin, pyridoxine, folate, cobalamin, iron, zinc, ascorbic acid, magnesium **C**
- Manage concomitant psychiatric illness **C**
- Assess and address parafunctional habits (bruxism, tongue thrusting) **E**
- Assess oral prostheses and dental work **C**
- Imidazole/azole therapy (presence of functional pain) **C**
- Assess and address oral hygiene **E**
- Address sleep quality **B**

Patients complaining of a burning mouth. Further experience in clinical assessment and management. Main DM, Basker RM. Br Dent J 1983; 154: 206–11.

A high rate of intraoral burning attributable to shortcomings in denture design.

Glossodynia from Candida-associated lesions, burning mouth syndrome, or mixed causes. Terai H, Shimahara M. Pain Med 2010; 11: 856–60.

Seventy-two of 95 (75.7%) patients with functional glossodynia improved with imidazole therapy (25 mg gel four times a day for 2–4 weeks).

Drug-induced burning mouth syndrome: a new etiologic diagnosis. Salort-Llorca C, Minguez-Serra MP, Silvestre FJ. Med Oral Patol Oral Cir Bucal 2008; 13: E167–70.

Antihypertensive medications that interact with the renin-angiotensin system are the most frequent cause of drug-associated BMS. Efavirenz, clonazepam, venlafaxine, fluoxetine, and sertraline were also associated.

Proton pump inhibitors. Scully C. Br Dent J 2010; 208: 147.

A case report of BMS-like symptoms that resolved after discontinuing omeprazole.

Topiramate-induced burning mouth syndrome. Friedman DI. Headache 2010; 50: 1383–5.

A case report of BMS that resolved after discontinuing topiramate. Symptoms recurred upon rechallenge.

Burning mouth syndrome associated with tumor necrosis factor (TNF)- α inhibitor. Gambardella A, Licata G, De Rosa A, et al. Int J Dermatol 2020; 59: e70–1.

A case report of BMS following initiation of etanercept that resolved after discontinuation.

Burning mouth syndrome: results of screening tests for vitamin and mineral deficiencies, thyroid hormone, and glucose levels – experience at Mayo Clinic over a decade. Verenzuela CSM, Davis MDP, Bruce AJ, et al. *Int J Dermatol* 2017; 56: 952–6.

The most common laboratory abnormalities in patients with BMS included deficiencies in vitamins D₃, B₂, B₆, and B₁ and zinc and elevations of blood glucose and TSH.

The association between burning mouth syndrome and sleep disturbance: a case-control multicentre study. Adamo D, Sardella A, Varoni E, et al. *Oral Dis* 2018; 24: 638–49.

Seventy-nine percent of patients with BMS reported poor sleep quality. Anxiety and depression were strongly correlated with sleep quality.

Second-Line Therapies

• Topical capsaicin	A
• Topical clonazepam	B
• Low-dose clonazepam	A
• Amitriptyline	B
• Paroxetine	D
• Milnacipran	D
• Duloxetine	E
• Low-dose olanzapine	E
• Low-dose pregabalin	D
• Cognitive behavioral therapy	B
• Gabapentin	A
• Alpha lipoic acid (contradictory information)	A
• Bupivacaine lozenge	A

Application of a capsaicin rinse in the treatment of burning mouth syndrome. Silvestre FJ, Silvestre-Ranil J, Tamarit-Santafé C, et al. *Med Oral Patol Oral Cir Bucal* 2012; 17: e1–4.

A randomized, double-blind, crossover study of topical capsaicin rinse (0.02%) or placebo three times daily found reduced pain scores among capsaicin-treated, but not placebo-treated, patients with BMS.

Topical clonazepam in stomatodynia: a randomised placebo-controlled study. Gremeau-Richard C, Woda A, Navez ML, et al. *Pain* 2004; 108: 51–7.

Forty-eight patients with BMS received either 'suck and spit' clonazepam (1 mg) or placebo three times daily for 14 days. Patients receiving topical clonazepam had a greater reduction in pain scores.

Outcome predictors affecting the efficacy of clonazepam therapy for the management of burning mouth syndrome (BMS). Ko JY, Kim MJ, Lee SG, et al. *Arch Gerontol Geriatr* 2012; 55: 755–61.

One hundred patients with BMS took clonazepam (0.5 mg) once or twice daily for 4 weeks. Patients with fewer psychological symptoms, higher initial pain scores, and the presence of xerostomia or taste disturbance experienced greater therapeutic efficacy.

Therapeutic dose of amitriptyline for older patients with burning mouth syndrome. Suga T, Takenoshita M, Watanabe T, et al. *Neuropsychiatr Dis Treat* 2019; 15: 3599–607.

Seventy-six percent of 187 patients with BMS treated with amitriptyline (starting dose 5–10 mg/day increased by 5–10 mg weekly or biweekly, as tolerated) showed improvement in pain scores. Older patients required lower therapeutic doses.

An open-label, noncomparative, dose escalation pilot study of the effect of paroxetine in treatment of burning mouth syndrome. Yamazaki Y, Hata H, Kitamori S, et al. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009; 107: e6–11.

Out of 52 BMS patients, 42 (80.8%) responded to paroxetine (10–30 mg daily) over 12 weeks. Nineteen (70.4%) had a complete response by the end of the treatment period. The effects were dose dependent.

Milnacipran dose-effect study in patients with burning mouth syndrome. Kato Y, Sato T, Katagiri A, et al. *Clin Neuropharmacol* 2011; 34: 166–9.

An open-label, dose-escalation pilot study of milnacipran in 56 patients with BMS. The response rate was 67.9% and 50.8% for daily dosages of 90 mg and 60 mg, respectively.

Burning mouth syndrome responsive to duloxetine: a case report. Mignogna MD, Adamo D, Schiavone V, et al. *Pain Med* 2011; 12: 466–9.

Report of one case of BMS responsive to duloxetine (60 mg daily).

Two cases of burning mouth syndrome treated with olanzapine. Ueda N, Kodama Y, Hori H, et al. *Psychiatry Clin Neurosci* 2008; 62: 359–61.

Two cases of BMS responsive to olanzapine treatment (2.5–5.0 mg daily).

Five patients with burning mouth syndrome in whom an antidepressant (serotonin-noradrenaline reuptake inhibitor) was not effective, but pregabalin markedly relieved pain. Ito M, Tokura T, Yoshida K, et al. *Clin Neuropharmacol* 2015; 38: 158–61.

Pregabalin (50–150 mg/day) was effective in treating five patients who previously did not respond to SNRIs.

Cognitive therapy in the treatment of patients with resistant burning mouth syndrome: a controlled study. Bergdahl J, Anneroth G, Perris H. *J Oral Pathol Med* 1995; 24: 213–5.

A randomized trial in resistant BMS found cognitive therapy superior to an attention program.

Combination of alpha lipoic acid and gabapentin, its efficacy in the treatment of burning mouth syndrome: a randomized, double-blind, placebo controlled trial. López-D'alessandro E, Escovich L. *Med Oral Patol Oral Cir Bucal* 2011; 16: e635–40.

One hundred twenty patients with BMS were randomized to receive alpha lipoic acid (ALA) (600 mg/day), gabapentin (300 mg/day), or a combination of both reported improvement in 55%, 50%, and 70% of cases, respectively, compared with placebo (15%).

Alpha lipoic acid efficacy in burning mouth syndrome. A controlled clinical trial. Palacios-Sánchez B, Moreno-Lopez LA, Cerero-Lapiedra R, et al. *Med Oral Patol Oral Cir Bucal* 2015; 20: e435–40.

Sixty BMS patients were randomized to receive ALA 600 mg daily (200 mg every 8 hours) or placebo. ALA was statistically superior to placebo.

Alpha lipoic acid in burning mouth syndrome: a randomized double-blind placebo-controlled trial. Cavalcanti DR, da Silveira FR. *J Oral Pathol Med* 2009; 38: 254–61.

ALA failed to provide a therapeutic benefit.

Effect of a local anesthetic lozenge in relief of symptoms in burning mouth syndrome. Tredal C, Jacobsen CB, Mogensen S, et al. *Oral Dis* 2016; 22: 123–31.

A randomized, double-blinded control crossover trial of 18 patients with BMS demonstrated reduced pain with bupivacaine lozenges three times daily without improvement in taste alterations or xerostomia.

Third-Line Therapies	
• Avoid contact allergens	D
• Low-level laser therapy	B
• Mandibular nerve block	E

Type 3 burning mouth syndrome: psychological and allergic aspects. Lamey PJ, Lamb AB, Hughes A, et al. *J Oral Pathol Med* 1994; 23: 216–9.

In 33 patients with BMS and intermittent symptoms at atypical sites, 65% were found to have positive patch tests to food flavorings or additives. Symptoms improved in 80% with allergen avoidance.

Burning mouth syndrome and contact dermatitis. Powell A, Nelson KN, Awosika O, et al. *Dermatitis* 2020; 31: 238-43.

Addition of bakery and dental series will include allergens that may otherwise be missed in patients with type 3 BMS.

Low-level laser therapy in patients with burning mouth syndrome: a double-blind, randomized, controlled clinical trial. Spanemberg JC, Segura-Egea JJ, Rodriguez-de Rivera-Campillo E, et al. *J Clin Exp Dent* 2019; 11: e162–9.

Twenty-one BMS patients randomly assigned to twice-weekly sessions with low-level diode laser ($\lambda = 808 \text{ nm} \pm 5 \text{ nm}$; fluence = 1.97 J/cm^2 ; time = 15 seconds per spot) demonstrated significant improvement in pain scores compared to placebo.

Mandibular nerve block for long-term pain relief in a case of refractory burning mouth syndrome. Kassem H, Alexandre L, Urits I, et al. *Pain Ther* 2020 [Epub ahead of print].

One patient reported 70% improvement 1 month following therapeutic injection of the mandibular division of the left trigeminal nerve with a mixture of lidocaine and 10 mg/mL dexamethasone.

Calcinosis cutis

Jasmine Mann, Rabindranath Nambi, Ian H. Coulson



Calcinosis cutis is a rare disease of aberrant calcium deposition in the skin and subcutaneous tissue. There are five major types:

- Idiopathic: occurs without tissue injury or metabolic defect (e.g., idiopathic scrotal calcinosis)
- Dystrophic: (most common form) secondary to local tissue damage or alterations in collagen, elastin, or subcutaneous fat but normal calcium and phosphate levels (e.g., in autoimmune connective tissue diseases, post trauma or infection)
- Metastatic: abnormal calcium and/or phosphate metabolism leading to precipitation of calcium salts in normal tissue (hyperparathyroidism, sarcoidosis, chronic kidney failure, malignant neoplasms)
- Iatrogenic: secondary to a treatment or procedure (such as extravasation of calcium or phosphate infusions)
- Calciophylaxis: calcific vasculopathy that occurs in the setting of end-stage kidney disease

Other rare variants of calcinosis cutis that have been described include calcinosis cutis circumscripta, calcinosis universalis, tumoral calcinosis, transplant-associated calcinosis cutis, and milia-like idiopathic calcinosis cutis (usually associated with Down syndrome). Firm white or yellow dermal lesions may ulcerate and extrude a gritty material. It most commonly involves the extensor aspect of joints, particularly the fingers, but can also involve large areas of the body. Stiffening of the skin can limit joint mobility and function, and fingertip lesions may be painful.

MANAGEMENT STRATEGY

The first step in management is to identify any underlying cause, as the subtype influences the approach to treatment. Principles of treatment are to treat an underlying disease, reduce calcium deposits, minimize inflammation, and physical removal of deposits.

Dystrophic calcification occurs in approximately 25% of patients with systemic sclerosis (SSc) and 10%–40% of patients with juvenile dermatomyositis, but is rare in systemic lupus erythematosus. Examination and investigations for connective tissue disease are therefore strongly recommended. Skin

biopsy can help to distinguish cutaneous calcification from ossification.

Elevated interleukin-1 levels, along with interleukin-6, interleukin-1 β , and tumor necrosis factor- α (TNF- α), are found in patients with juvenile dermatomyositis. Mannose-binding lectin levels were significantly increased in SSc patients with calcinosis. It is positively associated with positive anticentromere, anti-PM/Scl, and anticardiolipin antibodies in SSc patients with calcinosis.

A number of malignancies have been implicated in causing metastatic calcification (e.g., leukemia and multiple myeloma). However, successful treatment of the underlying cause does not always have an impact on calcinosis cutis, which frequently requires other treatment modalities. There are no large studies for the treatment of calcinosis cutis, and most therapies are based on case reports or small case series.

Spontaneous extrusion of calcium salts may occur; this may need surgical encouragement. General measures to improve blood flow to extremities, such as avoiding smoking, stress, and cold exposure, are crucial. *Diltiazem*, *colchicine*, and *minocycline* have shown success, mostly in dystrophic calcinosis cutis associated with dermatomyositis. In particular, *colchicine* and *minocycline* have been reported to reduce the frequency of ulceration and inflammation associated with cutaneous calcinosis in patients with limited SSc. The mechanism of action may be mainly through inhibition of matrix metalloproteinases and antiinflammatory effects.

Other beneficial therapies for calcinosis cutis associated with connective tissue disease include: *intralesional corticosteroids*, *aluminum hydroxide supplements*, *bisphosphonates*, *probenecid*, *intravenous immunoglobulin*, *topical sodium thiosulfate*, *carbon dioxide laser vaporization*, and *extracorporeal shock wave lithotripsy*.

Warfarin has been advocated in both dermatomyositis and SSc-associated calcinosis for small, calcified deposits. *Topical sodium metabisulfite*, *infliximab*, and *apremilast* are recent approaches that have been tried. Surgical removal can be of benefit for idiopathic calcinosis cutis, large lesions, and lesions as a result of calciophylaxis.

Specific Investigations

- Full blood count
- Urea and creatinine
- Serum calcium and phosphate
- Parathyroid hormone levels
- Vitamin D levels
- Serum electrophoresis
- Muscle enzymes: creatine kinase, lactate dehydrogenase (LDH), aldolase
- Connective tissue disease screen: antinuclear antibodies (ANAs) and other autoantibodies
- Skin biopsy
- Plain radiographs
- Bone scintigraphy
- Computed tomography and magnetic resonance imaging (MRI)

First-Line Therapies

• No treatment/self-healing	E
• Diltiazem	C
• Intralesional corticosteroid/oral prednisolone	E

Self-healing dystrophic calcinosis following trauma with transepidermal elimination. Pitt AE, Ethington JE, Troy JL. *Cutis* 1990; 45: 28–32.

A case of dystrophic calcinosis after trauma that resolved over 8 weeks with spontaneous transepidermal elimination.

Calcinosis cutis: part II. Treatment options. Reiter N, El-Shabrawi L, Leinweber B, et al. *J Am Acad Dermatol* 2011; 65: 15–22.

Calcinosis cutis in dermatomyositis has been successfully treated with diltiazem (2–4 mg/kg/day), with lower doses being ineffective. Surgical excision or curettage is the treatment of choice in idiopathic calcinosis cutis, especially scrotal calcinosis. It is also effective for small, digital calcified skin lesions. A 16-year-old boy with morphea profunda developed small, calcified deposits on both arms, his chest, and left thigh. He was treated with ceftriaxone 2 g/day intravenously for 20 days, and the calcification diminished within weeks.

A case of juvenile dermatomyositis with severe calcinosis and successful treatment with prednisone and diltiazem. Jiang X, Yi Q, Liu D, et al. *Int J Dermatol* 2011; 50: 74–7.

A 12-year-old boy with calcinosis secondary to juvenile dermatomyositis received diltiazem at a dose of 30 mg/day, resulting in obvious softening and radiologic regression and functional improvement at 4 months.

Calcinosis cutis occurring in association with autoimmune connective tissue disease: the Mayo Clinic experience with 78 patients, 1996 to 2009. Balin SJ, Wetter DA, Andersen LK, et al. *Arch Dermatol* 2012; 148: 455–62.

Nine of 17 patients with autoimmune connective tissue disorders showed partial response to treatment with diltiazem at the dose of <480 mg/day. This is recommended as first-line treatment. Eight patients were treated with colchicine (<1.2 g/day), resulting in one patient showing complete response and two patients showing partial response. Six patients received minocycline (200 mg/day). Only one patient showed partial response, two patients did not respond, and the response was unknown in three patients. Four patients were treated with warfarin with only one patient partially responding. Out of the 11 patients who received surgical excision alone, all 11 responded, with eight having a complete response. Another 17 patients had surgical and medical treatment with complete response in 14 patients, partial response in two patients, and no response in one patient.

Localized calcinosis in juvenile dermatomyositis: successful treatment with intralesional corticosteroids injection. Al-Mayouf SM, Alsonbul A, Alismail K. *Int J Rheum Dis* 2010; 13: e26–8.

A 10-year-old boy with juvenile dermatomyositis had calcinosis of his left elbow. It was treated with Depo-Medrol 80 mg and xylocaine 1% under ultrasound guidance with significant improvement.

Severe calcinosis cutis with cutaneous ulceration in juvenile dermatomyositis. Meher BK, Mishra P, Sivaraj P, et al. *Indian Pediatr* 2014; 51: 925–7.

A 7-year-old girl with severe calcinosis cutis with ulceration improved, with healing of the ulcer and resolution of nodules, after 1 month of oral prednisolone (1 mg/kg/day) and methotrexate (10 mg/week).

Second-Line Therapies

• Colchicine	E
• Minocycline	E
• Bisphosphonates	D
• Probenecid	E
• Aluminum hydroxide	D

Treatment of cutaneous calcinosis in limited systemic sclerosis with minocycline. Robertson LP, Marshall RW, Hickling P. *Ann Rheum Dis* 2003; 62: 267–9.

In an open-label study, eight out of nine patients with limited cutaneous SSc prescribed minocycline 50 mg or 100 mg daily showed definite improvement. The frequency of ulceration and inflammation associated with the calcinosis deposits decreased with treatment. A reduction in calcinosis size was evident but less dramatic, with improvement occurring by 5 months. The mean duration of treatment was 3.5 years.

See also Balin et al. earlier regarding colchicine and minocycline.

Dramatic improvement of subcutaneous calcinosis by intermittent, high-dose etidronate plus cimetidine in a patient with juvenile dermatomyositis. Wakabayashi T, Sasaki N, Chinen N, et al. *Case Rep Rheumatol* 2015, Article ID 817592, 3 pages, 2015.

A 17-year-old boy with juvenile dermatomyositis and bilateral extensive lower limb calcinosis extending into the subcutaneous tissue and muscle showed marked improvement with intermittent six monthly high-dose etidronate (800 mg/day for 3 months) and cimetidine for over 5 years.

Effectiveness of the treatment with intravenous pamidronate in calcinosis in juvenile dermatomyositis. Marco Puche A, Calvo Penades I, Lopez Montesinos B. *Clin Exp Rheumatol* 2010; 28: 135–40.

Three children with juvenile dermatomyositis received treatment with intravenous pamidronate at 1 mg/kg/day on 3 consecutive days every 3 months. In all three cases calcinosis significantly decreased and even totally cleared in one of them.

Improvement of calcinosis using pamidronate in a patient with juvenile dermatomyositis. Martillotti J, Moote D, Zemel L. *Pediatr Radiol* 2014; 44: 115–8.

A 7-year-old girl with juvenile dermatomyositis developed severe calcinosis, despite an extensive medication regimen. Three administrations of intravenous pamidronate (1 mg/kg/dose every month for 3 months) produced significant improvement in calcinosis, pain, and function, leading to remission less than 1 year after induction of therapy.

Efficacy of probenecid for a patient with juvenile dermatomyositis complicated with calcinosis. Nakamura H, Kawakami A, Ida H, et al. *J Rheumatol* 2006; 33: 1691–3.

An 11-year-old boy with juvenile dermatomyositis developed calcinosis of both legs. Probenecid was used to reduce calcinosis, resulting in remarkable improvement of calcinosis accompanied by normalization of serum phosphorus level.

Large subcutaneous calcification in systemic lupus erythematosus: treatment with oral aluminium hydroxide administration followed by surgical excision. Park YM, Lee SJ, Kang H, et al. *J Korean Med Sci* 1999; 14: 589–92.

A 22-year-old woman with systemic lupus erythematosus developed soft tissue calcification with ulceration, infection, and abscess formation. She was treated with aluminum hydroxide 600 mg three times a day with reduction in size and softening of the deposits after 9 months.

Calcinosis cutis in juvenile dermatomyositis responsive to aluminum hydroxide treatment. Nakagawa T, Takaiwa T. *J Dermatol* 1993; 20: 558–60.

A case of calcinosis cutis in juvenile dermatomyositis was successfully treated with oral aluminum hydroxide; near-complete clearance was observed after 8 months of therapy.

The use of these agents in patients with renal insufficiency may result in aluminum toxicity.

Third-Line Therapies

• Warfarin	D
• Ceftriaxone	E
• Rituximab	E
• Intravenous immunoglobulin	D
• Intralesional sodium thiosulfate	D
• Topical sodium thiosulfate	D
• Topical sodium metabisulfite	E
• Surgery	C
• Carbon dioxide laser	E
• Extracorporeal shock wave lithotripsy	D
• Infliximab	D
• Apremilast	E

Low dose warfarin treatment for calcinosis in patients with systemic sclerosis. Cukierman T, Elinav E, Korem M, et al. *Ann Rheum Dis* 2004; 63: 1341–3.

Three patients with disseminated subcutaneous calcinosis were treated with low doses of warfarin (1 mg/day) for 1 year. Two patients (relatively small lesions up to 2 cm in diameter) had complete resolution within 2 months. The other patient (larger and longer-standing lesions reaching up to 5 cm) did not respond to treatment. None of the patients showed a prolongation of prothrombin time, partial thromboplastin time, or an increased tendency for bleeding.

See also Reiter et al. earlier regarding ceftriaxone.

Rituximab-induced regression of CREST-related calcinosis. de Paula DR, Klem FB, Lorencetti PG, et al. *Clin Rheumatol* 2013; 32: 281–3.

A 54-year-old woman with limited cutaneous scleroderma and calcinosis in her hands had complete resolution 7 months after the first infusion of rituximab (four weekly infusions 375 mg/m²).

Treatment of systemic sclerosis-associated calcinosis: a case report of rituximab-induced regression of CREST-related calcinosis and review of the literature. Daoussis D, Antonopoulos I, Liossis SN, et al. *Semin Arthritis Rheum* 2012; 41: 822–9.

This patient with frequently ulcerating and painful extensive CREST-related calcinosis received two rituximab courses (consisting of four weekly infusions, 375 mg/m² each); calcinosis significantly improved and pain disappeared.

Intravenous immunoglobulin for treatment of dermatomyositis-associated dystrophic calcinosis. Galimberti F, Li Y, Fernandez AP. *J Am Acad Dermatol* 2015; 73: 174–6.

In a retrospective analysis of dermatomyositis-associated calcinosis in an institution, five out of eight patients showed clinical improvement of calcinosis after IV immunoglobulin (1–3 g/kg over 2 days monthly).

Calcinosis cutis associated with amyopathic dermatomyositis: response to intravenous immunoglobulin. Peñate Y, Guillermo N, Melwani P, et al. *J Am Acad Dermatol* 2009; 60: 1076–7.

A 55-year-old female with amyopathic dermatomyositis and progressive dystrophic calcinosis on the limbs with ulceration and pain failed to respond to various immunosuppressants and diltiazem. She had treatment with intravenous immunoglobulin (IVIG) (2 g/kg/month) at a dose of 0.4 g/day for 5 consecutive days, in combination with a reduced dose of prednisolone. After five courses of IVIG the dermal calcifications reduced, both clinically and radiologically, and became asymptomatic.

Intralesional sodium thiosulfate treatment for calcinosis cutis in the setting of lupus panniculitis. Gunasekera NS, Maniar LE, Lezcano C, et al. *JAMA Dermatol* 2017; 153(9): 944–5.

A 40-year-old female with systemic lupus erythematosus with calcified subcutaneous nodules on her abdomen, arms, and legs was treated with intralesional sodium thiosulfate solution at a concentration of 12.5 g/50 mL, injected into individual calcified lesions, using 0.5 mL/cm(diameter) and injecting every 5–10 mm. After this treatment was repeated one or two times per lesion at subsequent appointments, the patient noticed softening and decreased size of the lesions over the next 16 months, with no new inflammatory lesions, and resolution of deep calcified lesions.

Treatment of skin calcifications with intra-lesional injection of sodium thiosulphate: a case series. Baumgartner-Nielsen J, Olesen AB. *Acta Derm Venereol* 2016; 96: 257–8.

A case series of six consecutive patients with calcifications due to systemic sclerosis or nephrogenic systemic fibrosis were treated with intralesional injections of sodium thiosulfate, 150 mg/mL. A total of eight lesions on the extremities in six female patients were treated with a total of 21 injections of sodium thiosulfate for up to a 4-week period, using doses ranging from 12.5 mg to 275 mg at each treatment. The size of the lesions was, on average, reduced by 67% by week 4 and by 90% by week 12. Complete remission was obtained in 50% of patients by week 12 and 80% reduction in baseline lesion size was achieved in the remaining 50% by week 12.

Topical sodium thiosulfate for calcinosis cutis associated with autoimmune connective tissue diseases: the Mayo Clinic experience, 2012–2017. Ma JE, Ernste FC, Davis MD, et al. *Clin Exp Dermatol* 2019; 44: 189–92.

A case series of 28 patients showed clinical improvement in 19 patients. Two had unknown response and seven had no response. One patient had pain with application and two had skin irritation but, overall, it was relatively well-tolerated.

Topical sodium metabisulfite for the treatment of calcinosis cutis: a promising new therapy. Del Barrio-Díaz P, Moll-Manzur C, Álvarez-Veliz S, et al. *Br J Dermatol* 2016; 175: 608–11.

Four female patients with calcinosis cutis showed decrease in size, erythema, and pain after 6 weeks of topical 25% sodium metabisulfite twice daily.

See also Reiter et al earlier regarding surgical excision.

High-speed burr debulking of digital calcinosis cutis in scleroderma patients. Lapner MA, Goetz TJ. *J Hand Surg Am* 2014; 39(3): 503–10.

A retrospective analysis of nine patients with scleroderma who underwent debulking surgery using a high-speed micro-burr to soften and express calcific material in digits was performed. After 2 years' follow-up, four patients were very or somewhat satisfied with the procedure and two patients had no recurrence, but there were seven cases of recurrence. Patient satisfaction appeared inversely correlated to the number of digits involved.

Scrotal calcinosis: two case reports. Karray O, Dhaoui A, Boulma R, et al. *J Med Case Rep* 2017; 11(1): 312.

Case reports of two North African patients with scrotal calcinosis. Complete excision resulted in good aesthetic and functional outcomes and, 5 years postoperatively, patients have no sign of recurrence.

Surgical debridement of painful fingertip calcinosis cutis in CREST syndrome. Saddic N, Miller JJ, Miller OF 3rd, et al. *Arch Dermatol* 2009; 145: 212–3.

A 58-year-old woman with CREST syndrome underwent 2-mm curettage. There was immediate pain relief, and 7 months after the procedure, calcinosis had not recurred.

See also Balin et al. earlier. Surgical excision of large, discrete, and symptomatic lesions can be beneficial to patients.

A dystrophic calcinosis cutis case treated with CO₂ laser. Kutlubay Z, Yardimci G, Gokler G, et al. *J Cosmet Laser Ther* 2014; 16: 144–6.

A 12-year-old boy with 2- to 4-mm calcinosis on his right knee was treated with eight to 10 passes with a CO₂ laser (Candela CO2RE) at a wavelength of 10,600 nm, in classical mode, 3- to 5-mm spot size, fluence of 5 mJ, and pulse duration of 0.104 ms. There was resolution and no recurrence after 3 months.

Therapy of calcinosis cutis using erbium-doped yttrium aluminum garnet laser treatment. Meissner M, Ochsendorf F, Kaufmann R. *Dermatol Surg* 2010; 36: 727–8.

Patients with subcutaneous nodules smaller than 2 cm in diameter were given local anesthesia, then the skin over the mass was opened using a focused erbium-doped yttrium aluminum garnet (Er:YAG) beam (5 J/cm², 5 mm diameter, 5 Hz). The chalky material was then removed with a swab or curette. Reepithelialization and cosmetic recovery were seen at 2–3 weeks and 14 weeks, respectively.

Treatment of calcinosis cutis by extracorporeal shock-wave lithotripsy. Sultan-Bichat N, Menard J, Perceau G, et al. *J Am Acad Dermatol* 2012; 66: 424–9.

A single center study, including eight consecutive patients (with 10 calcinosis cutis lesions) who underwent three extracorporeal shock wave lithotripsy sessions at 3-week intervals for 6 months. At the end of this treatment period the median area had decreased by more than 50% in three calcinosis cutis lesions, with pain scores decreasing significantly in five patients and analgesia consumption decreasing in three patients, with no difference in results according to the underlying causal disease.

Effectiveness of infliximab in the treatment of refractory juvenile dermatomyositis with calcinosis. Riley P, McCann LJ, Maillard SM, et al. *Rheumatology* 2008; 47: 877–80.

Intravenous infliximab was initially given at a dose of 3 mg/kg to five patients with dermatomyositis-associated calcinosis. Further doses were then given at weeks 2, 6 and every 8 weeks thereafter. Between 8 and 30 months after starting infliximab, improvements were seen in all five patients, as shown by positive changes in physician visual analog scale, Childhood Myositis Assessment Score (CMAS), Childhood Health Assessment Questionnaire (CHAQ), joint range of movement, and, in some, regression of calcinosis and skin signs.

Apremilast as an adjuvant therapy for calcinosis cutis. Qiblawi SH, Fivenson DP. *JAAD Case Reports* 2019; 874–6.

Two patients with calcinosis cutis resistant to multiple treatments started on apremilast, with improvement after 2 months. One had recurrent infections on apremilast and had to stop; the other remained on treatment for over 16 months and continued to have slow improvement of deep ulcerated lesions on the legs.

Calciphylaxis

Kevin Young Chao, Reid Oldenburg, Taraneh Paravar



From Weenig RH. Pathogenesis of calciphylaxis: Hans Selye to nuclear factor kappa-B. J Am Acad Dermatol 2008; 58(3): 458–471.

Calciphylaxis (or calcific uremic arteriolopathy) is a life-threatening condition, which most often occurs in patients with end-stage renal disease, although non-uremic calciphylaxis also occurs. It is characterized by calcification of the medial layer of arterioles and subintimal fibrosis, which progresses to thrombotic occlusion and cutaneous necrosis. Calciphylaxis presents with tender purpuric retiform plaques, nodules, or ulcers most commonly on the lower extremities.

MANAGEMENT STRATEGY

Calciphylaxis has a mortality of up to 80%, which underscores the importance of early diagnosis via skin biopsy and aggressive treatment. The pillars of treatment for calciphylaxis are monitoring for infection, aggressive wound care, calcium chelation, and addressing underlying metabolic imbalance.

Sepsis is the leading cause of death in calciphylaxis, which necessitates consistent surveillance for wound infection including consideration of tissue and wound cultures, *monitoring for systemic signs of infection*, and prompt initiation of *antibiotics when necessary*. Early and aggressive *debridement of necrotic tissue* is important to remove a potential nidus of infection.

Intravenous sodium thiosulfate (STS) is used to remove calcium deposits by chelation. STS is currently considered a standard of care. *Intralesional STS* has also been used.

Addressing the underlying metabolic dysregulation is critical. Serum calcium should be decreased by *discontinuing calcium and vitamin D supplementation*. Hyperphosphatemia must be reduced with dietary phosphorus restriction and usage of non-calcium-based phosphate binders. *Discontinuation of vitamin K antagonists (VKA)* such as warfarin is critical to promote vitamin K-dependent production of matrix Gla protein, a potent inhibitor of arterial calcification. In renal failure, the use of *low-calcium dialysate* to

solubilize calcium into the intravascular space is helpful. *Bisphosphonates* can be used to decrease arterial calcification.

Hyperparathyroidism may be treated with *cinacalcet* with continued surveillance of parathyroid hormone levels. *Parathyroidectomy* is an option for recalcitrant hyperparathyroidism, but risks and benefits of surgery must be weighed.

Patients should be evaluated for hypercoagulability and autoimmune conditions. Hyperbaric oxygen therapy and negative pressure wound therapy also have potential utility.

Multi-interventional therapy is important in calciphylaxis management.

Specific Investigations

- Skin biopsy
- Serum calcium, phosphorus, parathyroid hormone, 25-hydroxyvitamin D, vitamin K, albumin
- Wound/tissue cultures
- Hypercoagulation evaluation (PT, PTT, protein C/S, antithrombin III, and antiphospholipid antibodies)
- Bone scintigraphy

Calciphylaxis: risk factors, diagnosis, and treatment. Nigwekar SU, Kroshinsky D, Nazarian RM, et al. Am J Kidney Dis 2015; 66: 133–46.

Literature review of calciphylaxis.

The role of bone scintigraphy in the diagnosis of calciphylaxis. Paul S, Rabito CA, Vedak P, et al. JAMA Dermatol 2017; 153: 101–3.

In a retrospective case-control study of calciphylaxis and control patients, bone scintigraphy had a sensitivity of 89% and a specificity of 97%.

First-Line Therapies

• Debridement of necrotic tissue and aggressive wound care	C
• Discontinuation of calcium and vitamin D supplementation	C
• Decrease serum phosphorus	C
• Discontinue vitamin K antagonists (VKA)	C
• Treatment of low serum albumin	C
• IV sodium thiosulfate (STS)	C
• Cinacalcet	C
• Pamidronate	D
• Monitoring for infection	C

Calciphylaxis epidemiology, risk factors, treatment and survival among French chronic kidney disease patients: a case-control study. Gaisne R, Péré M, Menoyo V, et al. BMC Nephrol 2020; 21: 63.

Retrospective cohort study of 89 calciphylaxis patients (70 dialysis and 19 non-dialysis). Higher serum albumin, surgical debridement, treatment with STS, treatment with sevelamer, and VKA discontinuation were associated with better survival.

A nationally representative study of calcific uremic arteriopathy risk factors. Nigwekar S, Zhao S, Wenger J, et al. J Am Soc Nephrol 2016; 27: 3421–9.

Retrospective review of 1030 patients found diabetes, high body mass index (BMI), hypercalcemia, hyperphosphatemia, vitamin D treatment, and warfarin were associated with increased odds of developing calciphylaxis.

Multi-intervention management of calcific uremic arteriopathy in 24 patients. Harris C, Kiaii M, Lau W, et al. Clin Kidney J 2018; 11: 704–9.

Retrospective analysis of 24 patients with calciphylaxis, all of whom received IV STS (12.5–25 g three times weekly), intensive hemodialysis, wound care, and medication discontinuation, some of whom received hyperbaric oxygen and cinacalcet. The majority showed complete or partial response to therapy and seven showed no response.

Use of sodium thiosulfate in a multi-interventional setting for the treatment of calciphylaxis in dialysis patients. Emanuel Z, Matthias K, Andreas V, et al. Nephrol Dial Transplant 2013; 28: 1232–40.

Retrospective cohort study of 27 calciphylaxis patients that were treated with STS. Complete or partial remission was achieved in 70%.

The effect of cinacalcet on calcific uremic arteriopathy events in patients receiving hemodialysis: The EVOLVE Trial. Floege J, Kubo Y, Floege A, et al. Clin J Am Soc Nephrol 2015; 10: 800–7.

Randomized placebo-controlled study of cinacalcet with conventional therapies for chronic kidney disease-mineral and bone disorder found that prophylactic cinacalcet (30–180 mg daily) resulted in 69%–75% risk reduction in calciphylaxis.

The use of cinacalcet for the treatment of calciphylaxis in patients with chronic kidney disease: a comprehensive review. Deen J, Schaidler H. Australas J Dermatol 2019; 60: e186–94.

Review of 41 patients from 26 publications. Of these patients, 12 received cinacalcet monotherapy and 29 received combination therapy. Combination therapy yielded complete response in 18 of 29 cases and partial response in six of 29 cases, with a total response rate of 82.8%. Monotherapy yielded similar results.

Non-uraemic calciphylaxis successfully treated with pamidronate infusion. Truong D, Riedhammer MM, Zinszer K. Int Wound J 2019; 16: 250–5.

This is one of several reports of the successful use of pamidronate as calciphylaxis therapy. Pamidronate disodium 30 mg infusions every 2 weeks for a total of four infusions led to resolution in a patient with calciphylaxis over 6 months.

Second-Line Therapies	
• Intralesional sodium thiosulfate (STS)	D
• Parathyroidectomy (for patients with elevated parathyroid hormone)	C
• Hyperbaric oxygen therapy	C
• Low-calcium dialysate	D
• Negative pressure wound therapy	E
• Vitamin K supplementation in patients who are deficient	E

Intralesional sodium thiosulfate for the treatment of calciphylaxis. Strazzula L, Nigwekar SU, Steele D, et al. JAMA Dermatol 2013; 149: 946–9.

Four patients with calciphylaxis treated with 1–4 mL of intralesional STS (250 mg/mL) in areas of clinically active disease had complete resolution of ulcers with only transient localized discomfort during injection. This and other cases utilized 1–4 mL every 1–2 weeks.

Survival, risk factors, and effect of treatment in 101 patients with calciphylaxis. McCarthy JT, El-Azhary RA, Patzelt MT, et al. Mayo Clin Proc 2016; 91: 1384–94.

Calciphylaxis patients with hyperparathyroidism treated with subtotal parathyroidectomy had improved 6-month and overall survival. Surgical debridement was also associated with improved survival.

Hyperbaric oxygen in the treatment of calciphylaxis: a case series and literature review. An J, Devaney B, Ooi KY, et al. Nephrology (Carlton) 2015; 20: 444–50.

Retrospective analysis of patients with calciphylaxis associated with renal disease. In total, 34 received a full course of hyperbaric oxygen therapy with or without parathyroidectomy or STS, with 58% showing improvement and over half demonstrating complete healing.

Successful treatment of severe calciphylaxis in a hemodialysis patient using low-calcium dialysate and medical parathyroidectomy: case report and literature review. Wang HY, Yu CC, Huang CC. Ren Fail 2004; 26: 77–82.

This and other cases report successful calciphylaxis treatment with low-calcium dialysate.

Nonuraemic calciphylaxis: response to treatment with pamidronate and negative pressure therapy. Lorriaux A, Chaby G, Dhaille F, et al. Clin Exp Dermatol 2015; 40: 52–5.

Two cases of non-uraemic calciphylaxis responded to IV pamidronate 30 mg every 2 weeks with negative pressure therapy with improvement in wounds and pain after several months.

Calciphylaxis in a dialysis patient successfully treated with high-dose vitamin K supplementation. Christiadi D, Singer R. Clin Kidney J 2018; 11: 528–9.

Case report of a hemodialysis patient with calciphylaxis and undetectable vitamin K levels who received vitamin K supplementation with lesion resolution.

Third-Line Therapies	
• Rheopheresis	D
• Myo-inositol hexaphosphate	C
• Prednisone (for patients without ulcerations only)	C
• Renal transplantation	E
• Heparin	D
• Tissue plasminogen activator	D

Rheopheresis: a new therapeutic approach in severe calciphylaxis. Robert T, Lionet A, Bataille S, et al. Nephrology (Carlton) 2020; 25: 298–304.

Retrospective study of eight cases of calciphylaxis that failed STS and VKA discontinuation and were treated with 2–3 weekly sessions of rheopheresis with hemodialysis. Complete remission was obtained in five patients over 114–196 days.

Improvement in wound healing, pain, and quality of life after 12 weeks of SNF472 treatment: a phase 2 open-label study of patients with calciphylaxis. Brandenburg VM, Sinha S, Torregrosa JV, et al. *J Nephrol* 2019; 32: 811–21.

Open-label, single-arm study of 14 calciphylaxis patients who received standard care and intravenous myo-inositol hexaphosphate, which inhibits formation of hydroxyapatite crystals, three times per week for 12 weeks. Seven of nine patients with ulcerated lesions improved.

Calciphylaxis is usually nonulcerating: risk factors, outcome and therapy. Fine A, Zacharias J. *Kidney Int* 2000; 61: 2210–7.

Review of 36 patients who presented with calciphylaxis without ulcerations demonstrated improvement from steroid therapy (prednisone 30–50 mg orally daily for 3–8 weeks) in 80% of cases. Contraindications to steroid therapy include ulceration anywhere or high risk of infection.

Resolution of calciphylaxis after urgent kidney transplantation in 3 patients with end-stage kidney failure. Nordheim E, Dahle DO, Syse IM, et al. *Transplant Direct* 2016; 2: e113.

Three case reports of patients with prior failed kidney transplants demonstrate complete resolution of calciphylaxis within 4 months of receiving kidney transplantation.

Calciphylaxis with evidence of hypercoagulability successfully treated with unfractionated heparin: a multidisciplinary approach. Carter A, Ortega-Loayza AG, Barrett J, et al. *Clin Exp Dermatol* 2016; 41: 275–8.

This and other case reports note successful use of unfractionated heparin or low molecular weight heparin for calciphylaxis.

Retrospective analysis of tissue plasminogen activator as an adjuvant treatment for calciphylaxis. el-Azhary RA, Arthur AK, Davis MDP, et al. *JAMA Dermatol* 2013; 149: 63–7.

Retrospective study of calciphylaxis treated with adjunctive low-dose tissue plasminogen activator suggests benefit. Bleeding was a complication.

Capillaritis (pigmented purpuric dermatoses, purpura pigmentosa)

Cord Sunderkötter, Thomas A. Luger



Capillaritis (a generic term for the various pigmented purpuric dermatoses) presents with the common feature of orange-red macules with peripheral purpuric spots resembling grains of cayenne pepper. As they progress, the macules partially coalesce and acquire a yellowish-brown color. Also called Schamberg purpura, capillaritis is a chronic dermatosis with relapses and remissions. Pigmented purpuric dermatoses are characterized histologically by erythrocyte extravasation and perivascular infiltration with T lymphocytes. Lesions develop a characteristic brown to orange color due to hemosiderin deposits in macrophages. These conditions may also present with additional, distinctive, and sometimes overlapping morphological patterns, which have given rise to several descriptive or eponymous names: papules in pigmented purpuric lichenoid dermatosis (of Gougerot and Blum) or in the rarely described granulomatous pigmented purpura (non-necrotizing granulomata with concomitant lymphocytic infiltrate); eczematous spongiosis with pruritus in eczematoid-like purpura; annular forms with telangiectases and central clearing in purpura annularis telangiectodes (Majocchi disease); and often solitary, ochre-golden plaques or patches with band-like infiltrates including a grenz zone in lichen aureus. Sites of predilection are mostly both lower extremities. A form of unilateral linear capillaritis or involvement of other areas of the skin are rare. Pigmented purpuric dermatoses also occur in children, albeit less frequently than in adults.

The etiology of capillaritis is not known. The reason for extravasation of erythrocytes is not an inflammatory fibrinoid necrosis of vessel walls (no vasculitis). Possible pathophysiological factors that can be addressed therapeutically are recruitment or activation of lymphocytes, increased venous pressure, increased vascular permeability, or vascular fragility due to subtle defects in the extracellular matrix.

MANAGEMENT STRATEGY

Diagnostic hallmarks are the yellow-brown or orange patches with superimposed pinpoint cayenne pepper spots, which represent petechiae and persist with diascopy. Thus, biopsies are warranted when in doubt.

Dermoscopic examination shows a coppery-red to brownish diffuse coloration of the background, round to oval red dots, globules or patches, and gray dots (probably accumulation of hemosiderin-containing macrophages) and a partial network of interconnected pigmented lines.

The main differential diagnoses are petechiae in thrombocytopenia ($<10.000\text{--}20.000/\text{mm}^3$) and small vessel vasculitis; a discerning criterion from the latter would be a palpable infiltrate (palpable or retiform purpura) when present, but there are courses or variants of small vessel vasculitis with petechial maculae only (e.g., IgA vasculitis or recurrent macular vasculitis in hypergammaglobulinemia [hypergammaglobulinemic purpura of Waldenström]).

Thus, biopsies are warranted when in doubt. Allergic contact dermatitis (e.g., in response to textile or azo dyes) may be purpuric or hemorrhagic, but with intense pruritus. The pigmented purpuric dermatitis-like variant of mycosis fungoides also needs to be excluded. Suspicion would be raised by poikiloderma, pruritus, coalescing plaques, and a duration of more than 1 year. Exclusion of mycosis fungoides may require repeated biopsies. Linear morphea was seen to develop in the same anatomic distribution as prior lichen aureus, warranting follow-up especially in pediatric patients.

Capillaritis has a benign course and therefore must be differentiated from these more serious diseases.

Usually there is no need for treatment unless the patient has pruritus or suffers from cosmetic disfigurement.

Detection and avoidance of possible eliciting agents should always be attempted. Reported causes include:

- Drugs (14% in one series), e.g., non-steroidal antiinflammatory drugs (NSAIDs) (acetaminophen, acetylsalicylic acid), bromine-containing drugs, carbamazepine, meprobamate, chlorthalidone, furosemide, nitroglycerine, interferon- α , raloxifene (selective estrogen receptor modulator), thiamine (vitamin B1), sildenafil, or topical 5-fluorouracil. As a rule, drug-induced capillaritis is more generalized and does not usually present with epidermal involvement or lichenoid infiltrate; its onset is around 10 days after intake of the suspected drug.
- Dietary supplements or ingredients: reported triggers include creatine or coca cola and apple-cherry fruit spritzer, as well as ingredients of an energy drink (vitamin B complex, caffeine, taurine).
- Chronic infections such as viral hepatitis B or C (though relation is questionable) or odontogenic infections.

When the etiology remains obscure, therapy has to be empirical. Local corticosteroids, calcineurin inhibitors, or ultraviolet (UV) 311 nm (preferred to psoralen plus UVA [PUVA]) have been tried. Increased venous pressure (particularly in the legs) or exercise are not direct causes but can aggravate capillaritis. In these cases, compression stockings may be helpful.

There is some evidence for increased vascular permeability or vascular fragility due to subtle defects in the extracellular matrix. This may explain reported responses to *bioflavonoids* (which may be due to inhibition of elastase and hyaluronase and of leukocyte activation), *ascorbic acid* (antioxidant effects and perhaps reduction of vascular permeability), and *calcium dobesilate* (reduction of microvascular permeability in part by antioxidant properties).

Specific Investigations

- Careful drug history
- Look for signs of chronic infection or rheumatoid arthritis
- Exclude chronic venous insufficiency and purpuric contact eczema (e.g., by modified patch test performed at the site of skin lesions to look after a petechial reaction to, e.g., azo dyes)
- Dermoscopy
- Hematology (complete blood count)
- C-reactive protein
- Optional: immunoglobulins, protein electrophoresis
- Histology
- In granulomatous variant: triglycerides and cholesterol

Purpura simplex (inflammatory purpura without vasculitis): a clinicopathologic study of 174 cases. Ratnam KV, Su WP, Peters MS. *J Am Acad Dermatol* 1991; 25: 642–7.

A retrospective review of 174 cases. A correlation between purpuric reaction and drugs was observed in 14%. Of the 87 patients who were followed up, 67% appeared to eventually have clearing of lesions.

Pigmented purpuric dermatosis: clinicopathologic characterization in a pediatric series. Coulombe J, Jean SE, Hatami A, et al. *Pediatr Dermatol* 2015; 32: 358–62.

A retrospective chart review of 17 children. Pigmented purpuric dermatosis resolved in 13 cases with a median duration <1 year, in five of them without treatment; those cases treated with topical corticosteroids improved in 75% and those with narrowband ultraviolet B in 100%. No associated disease or drug exposure were found.

The pathological spectrum and clinical correlation of pigmented purpuric dermatosis – a retrospective review of 107 cases. Huang Y-K, Lin C-K, Wu Y-H. *J Cutan Pathol* 2018; 45: 325–32.

This study described the wide pathological spectrum of pigmented purpuric dermatosis among Asians.

Progression of pigmented purpura-like eruptions to mycosis fungoides: report of three cases. Barnhill RL, Braverman IM. *J Am Acad Dermatol* 1988; 19: 25–31.

Initial eruptions, resembling pigmented purpuric dermatitis both clinically and histologically, developed into histologically definite mycosis fungoides in a follow-up period averaging 8.4 years.

Drug-induced purpura simplex: clinical and histological characteristics. Pang BK, Su D, Ratnam KV. *Ann Acad Med Singapore* 1993; 22: 870–2.

A prospective study of 183 patients with purpura simplex was carried out. Of these, 27 cases were confirmed to be drug induced as the purpura cleared within 4 months of withdrawal of medications. NSAIDs, diuretics, meprobamate, and ampicillin were the commonest offenders.

Pigmented purpura dermatosis and viral hepatitis: a case-control study. Ehsani AH, Ghodsi SZ, Nourmohammad-Pour P, et al. *Australas J Dermatol* 2013; 54: 225–7.

A prospective case-control study with 60 pigmented purpuric dermatosis (PPD) patients and 230 randomly selected controls. The prevalence of hepatitis B surface antigen (HBsAg) in PPD patients and the controls were 3% and 4.3%, respectively; the prevalence of hepatitis C virus (HCV) was 1.7% vs. 1.3%. Thus, direct involvement of hepatitis B (HBV) or HCV in pathogenesis of PPD is not certain.

Chronic pigmented purpura associated with odontogenic infection. Satoh T, Yokozeki H, Nishioka K. *J Am Acad Dermatol* 2002; 46: 942–4.

Appearance of purpuric spots in five patients ceased after treatment for periodontitis, pulpitis, or both.

Capillaritis associated with interferon-alfa treatment of chronic hepatitis C infection. Gupta G, Holmes SC, Spence E, et al. *J Am Acad Dermatol* 2000; 43: 937–8.

Pigmented purpuric dermatosis after taking a dietary supplement. Unal E, Ergül G. *Cutan Ocul Toxicol* 2015; Nov 10: 1–3.

Dermoscopic finding in pigmented purpuric lichenoid dermatosis of Gougerot-Blum: a useful tool for clinical diagnosis. Park MY, Shim WH, Kim JM, et al. *Ann Dermatol* 2018; 30: 245–7.

Nomenclature of Cutaneous Vasculitis: Dermatologic Addendum to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Sunderkötter C, Zelger B, Chen KR, et al. *Arthritis Rheumatol* 2018; 70(2): 171–84.

Capillaritis or pigmented purpura dermatosis are no genuine vasculitis (and would also not present a so-called lymphocytic vasculitis if it exists).

Linear morphea overlying site of previous lichen aureus in a pediatric patient. Johnston M, Benson P, Morley K. *Pediatr Dermatol* 2019; 36(4): e91–2.

First-Line Therapies

• Oral bioflavonoids and ascorbic acid	C
• Local corticosteroids initially in cases of pruritus/eczematoid or itching purpura	D
• Narrowband UVB (or PUVA)	D
• Calcium dobesilate	D
• Compression stocking when aggravated by increased venous pressure	E

We recommend rutoside and ascorbic acid as our therapy of choice, because it is efficacious especially in early disease and because it has fewer potential side effects than UV light or topical corticosteroids.

Early treatment with rutoside and ascorbic acid is highly effective for progressive pigmented purpuric dermatosis. Schober SM, Peitsch WK, Bonsmann G, et al. *J Dtsch Dermatol Ges* 2014; 12: 1112–9.

A retrospective review on 35 patients treated with 1000 mg ascorbic acid and 2 × 50 mg rutoside (a form of bioflavonoid,

often available without prescription). The mean treatment duration was 8.2 months: 71.4% of the participants experienced complete clearance and 20.0% an improvement of more than 50%. Nine (25.1%) relapsed after discontinuation; in seven treatment was successfully reinitiated. Only three participants reported mild adverse effects. Participants with shorter disease duration showed better and faster therapeutic success, and lower risk of recurrence.

Treatment of progressive pigmented purpura with oral bioflavonoids and ascorbic acid: an open pilot study in 3 patients. Reinhold U, Seiter S, Ugurel S, et al. *J Am Acad Dermatol* 1999; 41: 207–8.

First report on this treatment; complete clearance of skin lesions after 4 weeks of treatment.

Venoprotective drugs in pigmented purpuric dermatoses: a case report. Gupta A, Sardana K, Kishan Gautam R. *A case report. J Cosmet Dermatol* 2019 [Epub ahead of print].

Successful treatment with a fixed dose combination of diosmin 450 mg, hesperidin 50 mg (micronized purified flavonoid fraction [MFPP]), *Euphorbia prostrata* extract 100 mg, and calcium dobesilate 500 mg once a day. Relapse after discontinuation was responsive to the same medication.

PUVA therapy in lichen aureus. Ling TC, Goulden V, Goodfield MJ. *J Am Acad Dermatol* 2001; 45: 145–6.

One case of lichen aureus that responded dramatically to photochemotherapy (PUVA).

Treatment of pigmented purpuric dermatoses with narrow-band UVB: a report of six cases. Fathy H, Abdelgaber S. *J Eur Acad Dermatol Venereol* 2011; 25: 603–6.

Successful treatment was achieved in all six patients after 24–28 treatments and maintenance of nine treatments. Two patients who showed flare of their lesions were efficiently controlled with further 14 treatments.

Calcium dobesilate (Cd) in pigmented purpuric dermatosis (PPD): a pilot evaluation. Agrawal SK, Gandhi V, Bhattacharya SN. *J Dermatol* 2004; 31: 98–103.

Nine male patients (seven with Schamberg disease and one each with lichenoid dermatosis of Gougerot and Blum and lichen aureus) were given calcium dobesilate 500 mg twice daily for 2 weeks initially, and then 500 mg once daily for 3 months. No new lesions occurred within 2 weeks, and itching ceased in all patients. The improvement of existing lesions 1 year after cessation of therapy was moderate in 11.11% and mild in 66.67% of cases; 22.22% did not show any improvement.

Second-Line Therapies

• Pentoxifylline	E
• Topical calcineurin inhibitors	E
• Advanced fluorescence technology (AFT) of broadband pulsed light	D

Successful treatment of Schamberg's disease with pentoxifylline. Kano Y, Hirayama K, Orihara M, et al. *J Am Acad Dermatol* 1997; 36: 827–30.

Three patients with Schamberg disease were treated with pentoxifylline 300 mg daily for 8 weeks. A significant response was observed within 2–3 weeks. One patient had recurrence after discontinuation, but promptly responded to resumption of therapy.

Resolution of lichen aureus in a 10-year-old child after topical pimecrolimus. Böhm M, Bonsmann G, Luger TA. *Br J Dermatol* 2004; 150: 519–20.

A 10-year-old boy with lichen aureus, resistant to topical corticosteroids for 4 months. A significant improvement was observed within 3 weeks of treatment with pimecrolimus cream twice daily.

Unlike topical corticosteroids, topical immunomodulators do not cause fragility of blood vessels, which is an advantage when treating this group of diseases.

Treatment of Schamberg's disease with advanced fluorescence technology. Manolagos DA, Weiss J, Glick B, et al. *J Drugs Dermatol* 2012; 11: 528–9.

Favorable treatment of five patients with Schamberg disease using AFT pulsed light, a broadband pulsed light platform device as used for non-ablative treatment of, for example, photodamaged skin.

Third-Line Therapies

• Colchicine	E
• Ciclosporin	E
• Methotrexate	E

The authors would recommend neither ciclosporin nor methotrexate because of the severity of possible adverse events or side effects and because of the benign nature of capillaritis.

Schamberg's disease: case report with therapeutic success by using colchicine. Cavalcante MLLL, Masuda PY, Brito FF, et al. *An Bras Dermatol* 2017; 92(2): 246–8.

Capillaritis improved after 2 months of colchicine 0.6 mg twice daily and cleared after 4 months.

Cat scratch disease

Floriane Kouby, Olivier Chosidow



Cat scratch disease (CSD) is a benign, usually self-limited disease caused by *Bartonella henselae* (formerly *Rochalimaea henselae*), a Gram-negative pleomorphic rod. The primary lesion consists of a 0.5- to 1-cm papule or pustule, which may undergo ulceration, and adjacent unilateral lymphadenopathy is the hallmark of the disease. Atypical manifestations, including retinitis/neuroretinitis, Parinaud syndrome (granulomatous conjunctivitis and preauricular adenopathy), neuritis, encephalitis, hepatosplenic disease, osteomyelitis, erythema nodosum, and endocarditis, develops in 5%–20% of patients with the disease.

Atypical manifestations of cat-scratch disease, United States, 2005–2014. Nawrocki C, Max R, Marzec N, et al. Emerg Infect Dis. 2020; 26: 1438–46.

Using US nationwide insurance claims data, authors identified and characterized 224 atypical cases of cat scratch disease during 2005–2014 and estimated an average annual incidence of 0.7 cases/100,000 population. Ocular (48.7%), hepatosplenic (24.6%), and neurologic (13.8%) manifestations were common. Atypical cat scratch occurred most often in females 10–14 years of age.

MANAGEMENT STRATEGY

As there is a paucity of data showing a clear benefit of antimicrobial therapy in the treatment of patients with mild-to-moderate CSD, these patients should be managed with *conservative, symptomatic treatment*. The lymphadenopathy associated with CSD is self-limiting and resolves in 2–4 months; therefore, most patients can be managed with *observation* until involution of the node.

For patients with systemic symptoms and/or complications, antibiotic therapy should be instituted. *Azithromycin* (500 mg on day 1, followed by 250 mg on days 2–5) is the only antibiotic that has been shown in a double-blind, placebo-controlled evaluation to be beneficial to immunocompetent patients with CSD. In a retrospective analysis of 202 patients with CSD who had been on at least 3 days of antimicrobial therapy, only four antibiotics

(rifampin, ciprofloxacin, gentamicin, and trimethoprim-sulfamethoxazole) provided clinical benefit.

In immunosuppressed patients, infection with the CSD bacillus can produce a spectrum of disease, from classic CSD to bacillary angiomatosis, peliosis, or septicemia (see Chapter 21, Bacillary angiomatosis). Antimicrobial treatment for such patients is beneficial and clearly indicated. Lesions and symptoms respond rapidly to erythromycin 500 mg four times daily or doxycycline 100 mg twice daily. In patients with AIDS, therapy should be administered for at least 3 months.

Of note, *B. henselae* has rarely been isolated from patients with CSD; however, patients who are immunosuppressed may be culture positive. A single dose of oral antibiotics will rapidly sterilize blood and lesional cultures.

Specific Investigations

- Serology
- Polymerase chain reaction (PCR)-based techniques
- Histopathology
- Culture

CSD may be diagnosed presumptively in patients with typical signs and symptoms and a compatible exposure history. The *Bartonella* species are difficult to culture, and serology is the best initial test and can be performed by indirect fluorescent assay or enzyme-linked immunosorbent assay. Although more sensitive than culture, serologic tests lack specificity because many asymptomatic persons may have positive serology because of previous (often asymptomatic) exposure. *B. henselae* DNA may be detected by PCR or culture of lymph node aspirates or blood. Lymph node biopsy is not indicated routinely but should be considered if the diagnosis is unclear.

Evaluation of sensitivity, specificity and cross-reactivity in *Bartonella henselae* serology. Vermeulen MJ, Verbakel H, Notermans DW, et al. J Med Microbiol 2010; 59: 743–5.

The combined use of (Houston strain) indirect fluorescence antibody assay (IFA), IgM, and IgG improves sensitivity with significant reduction of specificity. Erroneous diagnosis of CSD can have a major impact for the patient, so IgG results must be interpreted with caution.

Development of a specific and sensitive enzyme-linked immunosorbent assay as an in vitro diagnostic tool for detection of *Bartonella henselae* antibodies in human serum. Jost M, Latz A, Ballhorn W, et al. J Clin Microbiol 2018; 56: e01329–e18.

The authors report the development of enzyme-linked immunosorbent assay (ELISA)-detecting human anti-*B. henselae* antibodies from serum samples. By the use of well-characterized human sera from the strictly quality-controlled serum library of the German National Consiliary Laboratory for *Bartonella* infections, the sensitivity of this ELISA was 100% for PCR-proven infections and 76% for clinically-suspected infections with a specificity of 93%.

***Bartonella henselae* DNA in seronegative patients with cat-scratch disease.** Yanagihara M, Tsuneoka H, Tanimoto A, et al. Emerg Infect Dis 2018; 24: 924–5.

Real-time PCR was used to detect *Bartonella henselae* DNA in 7.9% (5/63) of blood specimens from seronegative patients suspected of cat scratch disease. The combined use of serologic tests and real-time PCR to analyze blood specimens is recommended.

Bartonella-associated infections. Spach DH, Koehler JE. Infect Dis Clin North Am 1998; 12: 137–55.

Early in the disease course, lymphoid hyperplasia and arteriolar proliferation are prominent. Subsequently, granulomas appear. Late in the disease, multiple stellate microabscesses are prominent.

Combined application of immunohistochemistry and Warthin–Starry silver stain on the pathologic diagnosis of cat scratch disease. Peng J, Fan Z, Zheng H, et al. Appl Immunohistochem Mol Morphol 2020.

In this review of 46 cases of paraffin-embedded lymphadenitis with histologic and/or clinical suspicion of CSD, 80.4% of cases were positive for *B. henselae* by immunohistochemistry (IHC) and 52.5% by the Warthin–Starry silver stain (WS) method. Moreover, a positive percentage of *B. henselae* was 97.8%, which was detected by the combined application of IHC and WS. The combination of IHC and WS exhibited high sensitivity (97.8%) with good concordance (86.5%).

First-Line Therapy

- Symptomatic treatment

A

Treatment outcomes of human bartonellosis: a systematic review and meta-analysis. Prutsky G, Domecq JP, Mori L, et al. Int J Infect Dis 2013; 17: e811–9.

Two studies evaluating antibiotic therapy in CSD. The first was a randomized controlled trial comparing azithromycin with placebo, and the second was a non-randomized observational study comparing trimethoprim-sulfamethoxazole, ciprofloxacin, gentamicin, and rifampin with no treatment. These two studies did not show a statistically significant effect in terms of cure rate or time to achieve cure.

Second-Line Therapy

- Azithromycin

A

Prospective randomized double blind placebo-controlled evaluation of azithromycin for treatment of cat-scratch disease. Bass JW, Freitas BC, Freitas AD, et al. Pediatr Infect Dis J 1998; 17: 447–52.

Seven of 14 azithromycin-treated patients (500 mg on day 1, followed by 250 mg on days 2–5) showed an 80% reduction in initial lymph node volume compared with one of 15 placebo-treated controls during the first 30 days of observation. After 30 days there was no significant difference in resolution rates.

This is the only controlled clinical trial of an antibiotic for the therapy of CSD; the use of all other antibiotics is based on anecdotal reports.

Third-Line Therapies

- Erythromycin
- Doxycycline
- Rifampin
- Ciprofloxacin
- Gentamicin
- Trimethoprim-sulfamethoxazole
- Surgical intervention

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Antibiotic therapy for cat-scratch disease: clinical study of therapeutic outcome in 268 patients and a review of the literature. Margileth AM. Pediatr Infect Dis J 1992; 11: 474–8.

In 60 patients with CSD with systemic symptoms, one of four antibiotics was effective at least 72% of the time. Patients who received rifampin (10–20 mg/kg daily for 7–14 days), ciprofloxacin (20–30 mg/kg daily for 7–14 days), gentamicin (5 mg/kg daily intravenously in divided doses every 8 hours for at least 3 days), or trimethoprim-sulfamethoxazole (6–8 mg/kg of trimethoprim component 2–3 times daily for 7 days) had a shorter mean duration of posttreatment illness than those who received either no antibiotics or antibiotics thought to be ineffective.

Recommendations for the treatment of human infections caused by *Bartonella* species. Rolain JM, Brouqui P, Koehler JE, et al. Antimicrob Agents Chemother 2004; 48: 1921–33.

Even if azithromycin is the authors' first-line treatments for CSD, combination of doxycycline (10 mg twice daily) with rifampin (300 mg twice daily) could be an alternative. This combination has been successful in treating patients with retinitis or central nervous system disease.

When CSD lymph nodes suppurate, needle aspiration results in rapid pain alleviation.

Effectiveness of antibiotic therapy in pediatric patients with cat scratch disease. Shorbatli LA, Koranyi KI, Nahata MC. Int J Clin Pharm 2018; 40:1458–61.

In a group of 175 children, 102 were treated with azithromycin and 18 with trimethoprim-sulfamethoxazole (TMP-SMX). There was no statistically significant difference in the effectiveness based on CSD resolution or improvement between azithromycin and TMP-SMX groups ($p=0.56$).

Cat-scratch disease of the head and neck in a pediatric population: surgical indications and outcomes. Munson PD, Boyce TG, Salomao DR, et al. Otolaryngol Head Neck Surg 2008; 139: 358–63.

In children, failure of medical therapy in cases that presented as persistent lymphadenopathy often were accompanied by violaceous skin changes, extreme tenderness to palpation, and even chronic drainage. In this subgroup of patients the benefit of surgical intervention and concurrent tissue examination outweighed the risk.

Acknowledgments

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Cellulite

Doris M. Hexsel, Bruce E. Katz, Camile L. Hexsel



Cellulite consists of surface relief alterations with depressed and raised areas, located mainly on the thighs and buttocks but also on other areas. Depressed lesions are due to the presence of fibrous septa that pull the skin surface down; raised areas result from the projection of underlying fat to the skin surface. In addition, cellulite is aggravated by progressive skin laxity, localized fat deposition, and obesity. Treatments do not cure cellulite but can improve its appearance. Unfortunately, some studies lack blinding or controls and objective measurements.

MANAGEMENT STRATEGY

Diagnosis: Clinical

Specific Treatments

- Subcision, which targets the subcutaneous septa that pull the skin down and addresses cellulite depressions
- Devices and treatments that target the dermis and thus improve flaccidity and projection of fat and devices that target localized fat
- Weight control to a normal body mass index (BMI)
- Oral and topical treatments

Specific Investigations

- Physical examination: patient in standing position with relaxed gluteus muscles. Determine morphologic characteristics to help guide treatment option selection:
 - Presence and depth of cellulite depressions
 - Presence of localized fat and obesity
 - Presence of flaccidity and fat herniation
- Pretreatment and posttreatment photographs (relaxed gluteus muscles)
- Scales: a validated photonumeric scale, cellulite severity scale (CSS), and dimple scales for pre- and posttreatment objective assessment
- Preoperative investigations for subcision: prothrombin time (PT), partial thromboplastin time (PTT), and international normalization ratio (INR); history of coagulation disorders; use of medications that alter blood coagulation

A validated photonumeric cellulite severity scale. Hexsel DM, Dal'forno T, Hexsel CL. *J Eur Acad Dermatol Venereol* 2009; 23: 523–8.

A validated photonumeric severity quantitative and qualitative scale of five key morphologic aspects of cellulite. Each item is graded from 0 to 3; their sum allows a final classification of cellulite as mild, moderate, and severe.

Validated assessment scales for cellulite dimples on the buttocks and thighs in female patients. Hexsel D, Fabi SG, Sattler G, et al. *Dermatol Surg* 2019; 45 (Suppl 1): S2–11.

The cellulite dimple grading scales provide 5-point photonumeric assessments of cellulite severity at rest and in a dynamic state. Overall inter-rater reliability and intra-rater reliability of the scales were both 'almost perfect' (at rest) and 'substantial' (dynamic).

Side-by-side comparison of areas with and without cellulite depressions using magnetic resonance imaging. Hexsel DM, Abreu M, Rodrigues TC, et al. *Dermatol Surg* 2009; 35: 1471–7.

Cellulite depressions were associated to the presence of underlying fibrous septa perpendicular to the skin surface ($n=30$).

First-Line Therapies

• Subcision	B
• Devices	B
• Weight control	B

Effect of weight loss on cellulite: gynoid lipodystrophy. Smalls LK, Hicks M, Passeretti D, et al. *Plast Reconstr Surg* 2006; 118(2): 510–6.

Twenty-eight subjects with visible cellulite recruited from a weight loss program and eight weight-stable subjects without visible cellulite completed a study in which 17 subjects' cellulite improved and nine worsened.

Subcision: a treatment for cellulite. Hexsel DM, Mazzuco R. *Int J Dermatol* 2000; 39: 539–44.

Based on clinical assessment of pre- and posttreatment standardized photographs on 232 patients, subcision was shown to be efficacious in the treatment of high-grade cellulite. It specifically targets major cellulite depressions by sectioning the underlying fibrous septa and consequently forming new connective tissue.

Magnetic resonance imaging of cellulite depressed lesions successfully treated by subcision. Hexsel D, Dal Forno T, Hexsel C, et al. *Dermatol Surg* 2016; 42: 693–6.

A 7-month follow-up of moderate-to-severe cellulite-depressed lesions treated with subcision showing evident reduction in CSS grading (number and depth of the treated lesions) in the two assessed patients. The subdermal portion of the septum underlying the treated lesion was absent after subcision.

A multicenter pivotal study to evaluate tissue stabilized-guided subcision using the Cellfina device for the treatment of cellulite with 3-year follow-up. Kaminer MS, Coleman WP 3rd, Weiss RA, et al. *Dermatol Surg* 2017; 43(10): 1240–8.

Fifty-five women with moderate-to-severe cellulite underwent one treatment with a vacuum-assisted tissue stabilized-guided subcision (TS-GS). Assessments by subject photographs, CSSs, GAIS (Global Aesthetic Improvement Scale), and subject satisfaction showed significant improvements lasting up to 1 year; 94% of subjects had at least 1-grade improvement in the CSS (mean change of 2 points; $p < 0.0001$). At 3 years posttreatment, more than 91% of patients sustained improvement.

Multicenter study of vacuum-assisted precise tissue release for the treatment of cellulite in a cohort of 112 Italian women assessed with cellulite dimples scale at rest. Stefania G, Bruno B, Luigi CP, et al. *J Cosmet Laser Ther* 2019; 21(7–8): 404–7.

A retrospective study of one treatment with TS-GS for cellulite ($n = 122$). The mean score of Merz Aesthetics cellulite dimple grading scale decreased from 2.6 ± 0.9 to 0.9 ± 0.6 ($n = 112$; $p < .01$) after 1 year, and 96.4% of the subjects improved at least 1 point in cellulite dimple scale.

Treatment of dimpling from cellulite. Amore R, Amuso D, Leonardi V, et al. *Plast Reconstr Surg Glob Open* 2018; 6(5): e1771.

Multicenter observational study ($n = 200$) of one treatment with manual subcision with Celluerase, a microsurgical blade with two cutters and a gauge of 19 G $\times$ 30 mm. Results were assessed by two physicians using a scale from 0 to 10 where 0 is 'no result at all' and 10 is 'the best result achievable'. The average score was 8.1 and the subjective improvement average score 7.8.

Collagenase Clostridium histolyticum for the treatment of edematous fibrosclerotic panniculopathy (cellulite): a randomized trial. Sadick NS, Goldman MP, Liu G, et al. *Dermatol Surg* 2019; 45(8): 1047–56.

A collagenase *Clostridium histolyticum* (CCH) is thought to enzymatically disrupt fibrous septae. A double-blind placebo-controlled multicenter trial, in which 843 women received three injection sessions to the buttocks at 3-week intervals. CCH significantly improved cellulite compared to placebo considering a two-level composite response in the photonumeric cellulite severity scale (PCSS) assessment. Significant subject satisfaction on the GAIS was also observed.

Treatment of cellulite using a 1440-nm pulsed laser with one-year follow-up. DiBernardo BE. *Aesthet Surg J* 2011; 31: 328–41.

Ten women with cellulite on their thighs received a single treatment with a 1440-nm pulsed laser. Mean skin thickness (as shown by ultrasound) and skin elasticity increased. Subjective physician evaluations indicated improvement in the appearance of cellulite.

Quantitative and qualitative evaluation of efficacy of a 1440 nm Nd:YAG laser with novel bi-directional optical fiber in the treatment of cellulite as measured by 3-dimensional surface imaging. Katz BE. *J Drugs Dermatol* 2013; 12: 1224–30.

Fifteen women with cellulite were treated with a 1440-nm pulsed laser with side-firing fiber. There was improvement in cellulite in 68% of subjects on photographic evaluation by two independent observers, revealing good-to-excellent results, and significant improvement in 65% of subjects assessed by three-dimensional surface imaging.

Microfocused ultrasound with visualization and calcium hydroxylapatite for improving skin laxity and cellulite appearance. Casabona G, Pereira G. *Plast Reconstr Surg Glob Open* 2017; 5(7): e1388.

Twenty women with skin laxity and moderate-to-severe cellulite on the buttocks and thighs were treated with MFU-V using 4 MHz and 7 MHz transducers (25 lines/transducer/site) and immediately followed by subdermal calcium hydroxylapatite injection (1 mL/buttock or thigh). Two blinded evaluators reported improvements compared with baseline for each item on the cellulite severity scale ($p < 0.001$) with a 4.5-point improvement in mean overall score ($p < 0.001$).

Effectiveness of the electromagnetic shock wave therapy in the treatment of cellulite. Modena DAO, Nogueira da Silva C, Delinocente TCP, et al. *Dermatol Res Pract* 2019; 2019: 8246815.

Comparative and prospective longitudinal study ($n = 27$) showed significant improvement in CSS between baseline and after 10 treatments, and follow-up of 3 months for gluteus (7.2 ± 2.8 to 6.6 ± 2.7 and 5.5 ± 2.2 to 5.3 ± 1.6 ; $p < 0.0087$) and posterior thigh (7.2 ± 2.9 to 6.4 ± 2.6 and 5.7 ± 2.3 to 5.2 ± 1.5 ; $p < 0.0031$).

Acoustic wave therapy for cellulite, body shaping and fat reduction. Hexsel D, Camozzato FO, Silva AF, et al. *J Cosmet Laser Ther* 2017; 19(3): 165–73.

Prospective, single-center, open study ($n = 25$). The mean CSS grading reduced from 11.1 at baseline to 9.5 at 12 weeks ($p < 0.001$) posttreatment.

The effectiveness of anticellulite treatment using tripolar radiofrequency monitored by classic and high-frequency ultrasound. Mlosek RK, Woźniak W, Malinowska S, et al. *J Eur Acad Dermatol Venerol* 2012; 26: 696–703.

Randomized, controlled study in which 28 women with cellulite grade I to III underwent eight treatments with radiofrequency; 17 women were in the placebo group. Nürnberger–Müller scale was reduced in 89.3% in the treatment group and no statistically significant changes were observed in the placebo group.

Unipolar radiofrequency treatment to improve the appearance of cellulite. Alexiades-Armenakas M, Dover JS, Arndt KA. *J Cosmet Laser Ther* 2008; 10: 148–53.

Randomized, blinded, split-design study ($n = 10$) of excessive localized fat and cellulite (grades II–IV) on the thighs evaluated up to six unilateral treatments (number of treatments at the investigator's discretion; mean: 4.22, range: 3–6) at 2-week intervals.

with unipolar RF. Blinded photographic evaluations of a quantitative four-point cellulite grading scale demonstrated improvements in mean grading scores for the treated leg versus the control side: 11.2% in dimple density, 10.7% in dimple distribution, 2.5% in dimple depth, and $8 \pm 2.8\%$ mean score improvement.

A multicenter study of cellulite treatment with a variable emission radio frequency system. Van der Lugt C, Romero C, Ancona D, et al. *Dermatol Ther* 2009; 22: 74–84.

The buttocks of 50 patients were treated with bipolar RF technology at $6\text{ J}/\text{cm}^2$ for 12 weekly sessions on each buttock, with the treatment end point of 42°C external skin temperature. Based on the photography at baseline and at the 2-month assessment, the blinded independent clinicians' assessment of the cellulite appearance demonstrated that results were apparent in 66% of patients.

Reduction in thigh circumference and improvement in the appearance of cellulite with dual-wavelength, low-level laser energy and massage. Gold MH, Khatri KA, Hails K, et al. *J Cosmet Laser Ther* 2011; 13: 13–20.

In this controlled, multicenter study, 83 subjects with mild-to-moderate cellulite received eight treatments with a device comprising a low-level, dual-wavelength diode laser (650 nm and 915 nm), combined with heat induction and mechanical massage by suction, in one thigh with the untreated contralateral thigh serving as a control. There was subjective clinical improvement of the appearance of cellulite when comparing pretreatment and posttreatment photographs.

A single center, randomized, comparative, prospective clinical study to determine the efficacy of the VelaSmooth system versus the Triactive system for the treatment of cellulite. Nootheti PK, Magpantay A, Yosowitz G, et al. *Lasers Surg Med* 2006; 38: 908–12.

Twenty female patients were treated biweekly for 6 weeks with randomization to infrared (IR) light (680–1550 nm) with bipolar radiofrequency (RF) and mechanical massage by vacuum suction on one side, and diode lasers (808/810 nm) combined with mechanical massage, suction, and localized cooling on the other side. In both treatment groups, 25% of the patients had improvement in the appearance of cellulite. The rates of improvement in roughness and of perceived change in cellulite grade were not statistically different ($p > 0.05$) between the two treatment arms.

Prospective multicenter clinical trial of a temperature-controlled subcutaneous microneedle fractional bipolar radiofrequency system for the treatment of cellulite. Alexiades M, Munavalli G, Goldberg D, et al. *Dermatol Surg* 2018; 44(10): 1262–71.

Open clinical trial to assess the effects of minimally invasive bipolar fractional RF system ($n = 50$). Blinded physician evaluations revealed a procedural success rate of 93% at 6-month follow-up.

Second-Line Treatments

• Mesotherapy	B
• Carboxytherapy	B
• Mesolipolysis	B

Efficacy of intradermal mesotherapy in cellulite reduction – conventional and high-frequency ultrasound monitoring results. Sylwia M, Krzysztof MR. *J Cosmet Laser Ther* 2017; 19(6): 320–24.

Twenty-one women received six treatments with polyaminoacidic gel, $\alpha\text{-D-(+)}$ glucopyranose, 1-4 glycosidic, ethylenediaminetetraacetic sodium, amino acid buffer system with bicarbonate-sodium corrector, osmolarity regulator at 6–7-day intervals. Improvements: Nürnberger–Müller's scale ($p = 0.002$); reduction in thigh circumference, subcutaneous tissue thickness, and surface area of a subcutaneous tissue fascicle ($p \leq 0.0005$).

Evaluation and efficacy of carbon dioxide therapy (carboxytherapy) versus mesolipolysis in the treatment of cellulite. Eldsouky F, Ebrahim HM. *J Cosmet Laser Ther* 2018; 20(5): 307–12.

Randomized blind study of one group receiving carboxytherapy and the other mesolipolysis using phosphatidylcholine for 6 weeks, one weekly session. Improvement in cellulite grading scale ($p < 0.001$) were observed in both groups. Results persisted for 6 months in 66.7% of cases treated with carboxytherapy and in 65.8% treated with mesolipolysis. Regression of results occurred in 33.3% and 34.2% of the cases, respectively.

Third-Line Therapies

• Topical retinol, caffeine, and ruscogenin	B
• Occluded topical caffeine with extracts of green tea, black pepper seed, citrus, ginger, and cinnamon	B
• Topical retinol	C
• Topical caffeine	B
• Topical phosphatidylcholine gel and light-emitting diode (LED)	C

A double-blind evaluation of the activity of an anticellulite product containing retinol, caffeine, and ruscogenin by a combination of several noninvasive methods. Bertin C, Zunino H, Pittet JC, et al. *J Cosmet Sci* 2001; 52: 199–210.

A placebo-controlled, double-blind study ($n = 46$) evaluated a topical anticellulite product that combined *retinol* microcapsules, *caffeine*, *Centella asiatica*, *L-carnitine*, *Esculoside*, and *ruscogenin*. The product was more effective than placebo in reducing cellulite appearance.

A two-center, double blinded, randomized trial testing the tolerability and efficacy of a novel therapeutic agent for cellulite reduction. Rao J, Gold MH, Goldman MP. *J Cosmet Dermatol* 2005; 4: 93–102.

In this placebo-controlled study, 34 women with moderate cellulite used a cream (caffeine, green tea extract, black pepper seed extract, citrus extract, ginger root extract, cinnamon bark extract, and capsicum annum resin) under occlusion with bio-ceramic-coated neoprene shorts. Dermatologists noted greater improvement in the treated group in 68% of subjects (prestudy vs. poststudy photographs).

Topical retinol improves cellulite. Kligman AM, Pagnoni A, Stoudmayer T. *J Dermatol Treat* 1999; 10: 119–25.

This placebo-controlled study ($n = 19$) demonstrated improvement in cellulite on the side treated with topical *retinol* 0.3% on the thighs for 6 months in 63.1% of the patients compared with the untreated side by clinical dermatologic evaluation.

The effectiveness and safety of topical PhotoActiv phosphatidylcholine-based anticellulite gel and LED (red and near-infrared) light on grade II–III thigh cellulite: a randomized,

double-blinded study. Sasaki GH, Oberg K, Tucker B, et al. J Cosmet Laser Ther 2007; 9: 87–96.

Placebo-controlled, double-blinded study. Nine subjects with grade II–III thigh cellulite were randomly treated twice daily with a phosphatidylcholine-based anticellulite gel on one thigh. Twice weekly, each thigh was exposed for a 15-minute treatment with LED array (660nm and 950nm) for 24 treatments; 89% of the treated thighs were downgraded to a lower cellulite grade by clinical examination, digital photography, and pinch test assessment. After 18 months, 63% of responsive thighs reverted back to baseline grading.

Cellulite reduction by modified Thai herbal compresses: a randomized double-blind trial. Ngamdokmai N, Waranuch N, Chootip K, et al. J Evid Based Integr Med 2018; 23: 2515690X18794158.

Double-blind, randomized, placebo-controlled paired trial. Twenty-one women received both herbal and placebo compress treatments for cellulite in one or other leg for 8 weeks. The actively treated leg presented significant reduction in CSS grading. Significant difference between the CSS scores (active vs. placebo) was observed. At week 11, the CSS score increased ($p=0.001$ vs. previous visit) and treatment effects dissipated.

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Cellulitis and erysipelas

Colleen Gabel, Lauren Ko, Daniela Kroshinsky



Cellulitis is an infection of the deep dermis and subcutaneous tissue thought to occur after pathogen entry into the dermis through breaks in the skin. In erysipelas, superficial infection gives rise to an edematous, palpable, well-demarcated, often advancing, edge. These infections are often grouped together and included in the larger category of skin and skin-structure infections (SSSIs). The causative organism is commonly group A streptococcus, though many organisms have been isolated, including *Staphylococcus*, *Haemophilus influenzae*, and, more rarely, *Aeromonas hydrophila*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa*, as well as fungi and Gram-negative rods. Fulminating and necrotic cellulitis and fasciitis may occur rarely, usually in relation to immunosuppression or atypical organisms, and are accompanied by a high mortality rate.

MANAGEMENT STRATEGY

The management of SSTIs should initially assess illness severity and determine the appropriate treatment setting (i.e., outpatient vs. hospital), identifying the organism responsible when indicated, and then directing antimicrobial therapy. Underlying and predisposing conditions should be treated to prevent recurrence.

In the United States, the Infectious Diseases Society of America (IDSA) has published treatment guidelines for non-purulent and purulent SSTIs; however, there is little agreement on regimen. As published by Raff and Kroshinsky (2016), the following is derived in combination from the IDSA 2014 guidelines, Johns Hopkins antibiotic guidelines, and results from the literature for non-purulent cellulitis (Box 39.1) and purulent cellulitis (Box 39.2). Systemic inflammatory response syndrome (SIRS) is identified by two or more symptoms including fever or hypothermia, tachycardia, tachypnea, and change in blood leucocyte count.

For both non-purulent and purulent cellulitis, the following definitions apply:

- Mild cellulitis – cellulitis without systemic signs of infection
- Moderate cellulitis – cellulitis in a patient who meets 1 point of the following criteria: heart rate greater than 90/min; temperature greater than 38°C or lower than 36°C; respiratory rate greater than 20/min; or white blood cell count greater than 12,000 cells/mm³ or fewer than 4000 cells/mm³

- Severe cellulitis – cellulitis in a patient with any of the moderate cellulitis criteria and hypotension, rapid progression, or immunocompromise

Mild non-purulent cellulitis should be treated with amoxicillin/clavulanate, cephalexin, dicloxacillin, penicillin VK, or, in cases of true penicillin allergy, clindamycin to provide antistreptococcal coverage.

The same agents used for mild cellulitis may be used in cases of moderate cellulitis. Intravenous antibiotics such as cefazolin, ceftriaxone, and penicillin G should be considered in patients who fail oral therapy or meet two or more SIRS criteria. Clindamycin may be used in penicillin allergy.

Patients with severe non-purulent cellulitis should receive broad coverage therapy. Intravenous vancomycin with piperacillin/tazobactam, imipenem, or meropenem may be used. If necrotizing infection is suspected, urgent surgical evaluation

Box 39.1 Non-purulent cellulitis

Mild – Oral therapy with amoxicillin/clavulanate, cephalexin, dicloxacillin, penicillin VK

Moderate – If 1 SIRS criterion present, oral antibiotics as for mild cellulitis. If ≥ 2 SIRS criteria or treatment failure with oral antibiotics, intravenous cefazolin, ceftriaxone, penicillin G

Severe – Intravenous vancomycin plus piperacillin/tazobactam, imipenem, or meropenem. Consider surgical evaluation for necrotizing process with culture and sensitivity. If *S. pyogenes* or methicillin-susceptible *Staphylococcus aureus* (MSSA) is suspected, intravenous cefazolin, cefotaxime, ceftriaxone, or penicillin G. If treatment failure or suspected methicillin-resistant *Staphylococcus aureus* (MRSA), intravenous vancomycin, clindamycin, linezolid, daptomycin, ceftaroline, telavancin, or tigecycline

Box 39.2 Purulent cellulitis (purulent drainage or pustules in the absence of an abscess)

For all, perform I&D.

Mild – If suspected MSSA, oral cephalexin, dicloxacillin, or amoxicillin/clavulanate. If suspected MRSA, oral TMP-SMX, doxycycline, or minocycline. Cover with cephalexin or penicillin if streptococcal coverage also needed

Moderate – If 1 SIRS criteria present, as above for suspected MSSA or suspected MRSA. If ≥ 2 SIRS criteria and suspected MSSA, intravenous oxacillin, nafcillin, or cefazolin. If ≥ 2 SIRS criteria and suspected MRSA, intravenous vancomycin, clindamycin, or linezolid

Severe – Culture and sensitivity plus consideration of surgical evaluation for necrotizing disease with culture and sensitivity of any surgically obtained tissue. Empiric broad coverage with intravenous vancomycin, clindamycin, linezolid, daptomycin, ceftaroline, telavancin, or tigecycline. If MSSA culture positive, deescalate to intravenous oxacillin, nafcillin, cefazolin, or ceftriaxone. If MRSA culture positive, continue broad-spectrum coverage

Adapted from Raff AB, Kroshinsky D. Cellulitis: a review. JAMA 2016;316(3):3253–7.

with cultures and sensitivities should be sought. If streptococcal toxic shock syndrome is suspected, penicillin G and clindamycin should be used.

Other risk factors that should prompt broad-spectrum coverage with vancomycin or linezolid include cases secondary to penetrating trauma, active injection drug use, or evidence of MRSA infection or colonization. Patients who cannot receive vancomycin may be treated with oral linezolid. Severely immunocompromised patients should receive broad-spectrum coverage.

Purulent cellulitis should be accompanied by culture and sensitivity testing. Cases of purulent cellulitis are more likely to be *S. aureus*, and patient risk factors for MRSA may guide empiric antibiotic choice. Risk factors for MRSA include athletes, children, men who have sex with men, prisoners, military recruits, residents of long-term care facilities, individuals with previous MRSA exposure, and intravenous drug use.

Mild purulent cellulitis therapy is based on suspicion for methicillin-sensitive *S. aureus* (MSSA) versus MRSA. If MSSA is suspected, consider cephalexin, dicloxacillin, amoxicillin/clavulanate, or clindamycin if there is a penicillin allergy. If MRSA is suspected, trimethoprim-sulfamethoxazole, doxycycline, or minocycline should be used. If both streptococcal and staphylococcal organisms are suspected, cephalexin or penicillin should be added to therapy, with clindamycin or linezolid for penicillin-allergic patients.

Moderate purulent cellulitis in patients meeting only one SIRS criterion may be treated with the same initial therapy as mild non-purulent disease, with empiric therapy selected based on suspicion for MSSA versus MRSA. Intravenous antibiotics should be considered if patients meet two or more SIRS criteria. For suspected MSSA, agents of choice include cefazolin, oxacillin, or nafcillin. For suspected MRSA, vancomycin, clindamycin, or linezolid should be used.

Empiric MRSA coverage with intravenous vancomycin, clindamycin, linezolid, daptomycin, or ceftaroline should be used in patients with severe cellulitis. If necrotizing cellulitis is suspected, surgical evaluation with culture and sensitivity should be obtained.

Newer antibiotic agents include telavancin, tedizolid, dalbavancin, and oritavancin. These agents may be considered; however, they currently have limited clinical applications. Second-line therapies for cellulitis discussed below are limited in clinical practice due to cost and concern for adverse effects.

Sites of entry for infection should be sought and should be treated, such as tinea pedis and chronic skin ulcers. Lymphedema can be associated with recurrence of cellulitis and so should be managed with long-term compression and elevation, when possible.

The use of long-term antibiotics for the prevention of recurrent cellulitis has produced conflicting evidence but may be considered for at least 3–4 recurrent cases/year once underlying risk factors have been mitigated. There are no supporting data for antibiotic prophylaxis for MRSA cellulitis.

Specific Investigations

- Blood cultures – not routinely done in uncomplicated patients due to low yield
- Swabs of any purulent exudate, pustules, or wounds
- Ultrasound to assess for a drainable fluid collection if clinical exam indeterminate for abscess
- Skin scrapings for mycology

The IDSA recommends against performing routine blood or tissue cultures, except in cases of malignancy on chemotherapy, severe cell-mediated immunodeficiency, neutropenia, animal bites, or immersion injuries. Routine use of procalcitonin to diagnose or evaluate cellulitis is not recommended.

Ultrasound may be helpful in identifying abscesses.

In the case of SSTIs of the lower leg, skin scrapings from toe web spaces, sides of feet, or toenail subungual debris may be taken for mycologic examination. Facial erysipelas should warrant sinus radiographs to exclude underlying sinusitis. Crepitus should prompt the clinician to the presence of either *Clostridia* or non-spore-forming anaerobes, either alone or mixed with other organisms, and warrants surgical consultation and/or imaging.

Procalcitonin and cellulitis: correlation of procalcitonin blood levels with measurements of severity and outcome in patients with limb cellulitis. Brindle RJ, Ijaz A, Davies P. *Biomarkers* 2019; 24(2): 127–30.

Procalcitonin levels are not recommended in the evaluation or confirmation of limb cellulitis and is a poor predictor of improvement.

Clinical practice. Skin and soft-tissue infections caused by methicillin-resistant *Staphylococcus aureus*. Daum RS. *N Engl J Med* 2007; 357(4): 380–90.

In cases of purulent cellulitis, culture and sensitivity testing should be performed to guide therapy, with empirical antibiotic selection based on patient risk factors for MRSA infection.

Clinical usefulness of imaging and blood cultures in cellulitis evaluation. Ko L, Garza-Mayers AC, St. John J, et al. *JAMA Intern Med* 2018; 178(7): 994–6.

Radiologic imaging and blood cultures are not recommended for routine use in evaluation and treatment of cellulitis and may contribute significant cost to the healthcare system.

Methicillin-resistant *S. aureus* infections among patients in the emergency department. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. *N Engl J Med* 2006; 355: 666–74.

A study of 422 patients in the United States who presented with purulent SSTIs found that swabs showed 59% had MRSA, 17% had methicillin-sensitive *S. aureus*, and 2.9% had β -hemolytic *Streptococcus*, demonstrating importance of swabs in such cases.

Clinical practice. Skin and soft-tissue infections caused by methicillin-resistant *Staphylococcus aureus*. Daum RS. *N Engl J Med* 2007; 357(4): 380–90.

Risk factors for MRSA colonization include household and day-care contacts of a patient with MRSA infection, children, soldiers, incarceration, men who have sex with men, athletes, infectious drug use, and previous MRSA infection.

Effect of dermatology consultation on outcomes for patients with presumed cellulitis: a randomized clinical trial. Ko LN, Garza-Mayers AC, St. John J, et al. *JAMA Dermatol* 2018; 154(5): 529–36.

This randomized clinical trial demonstrated that inpatient dermatology consultation may improve outcomes by identifying misdiagnosed cases of cellulitis and decreasing length of antibiotic treatment, improving antibiotic stewardship.

First-Line Empiric Therapies for Mild, Non-Purulent Cellulitis

• Cephalexin	A
• Dicloxacillin	A
• Penicillin VK	A
• Amoxicillin with clavulanic acid	A
• Clindamycin	B

First-Line Therapies for Mild Purulent Cellulitis – MSSA

• Cephalexin	A
• Dicloxacillin	A
• Amoxicillin with clavulanic acid	A
• Clindamycin	B

First-Line Therapies for Mild Purulent Cellulitis – MRSA

• TMP-SMX	A
• Doxycycline	A
• Minocycline	A
• Clindamycin	B
• Linezolid	B

Cellulitis. Fabre V, Bartlett, JC. Johns Hopkins ABX Guide, The Johns Hopkins University, 2019. Johns Hopkins Guide: www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540106/all/Cellulitis.

Informs the above treatment recommendations for purulent and non-purulent cellulitis.

The course, costs and complications of oral versus intravenous penicillin therapy of erysipelas. Jorup-Ronstrum C, Britton S, Gavlevik A, et al. *Infection* 1984; 12: 390–4.

In this study of 60 patients there appeared to be no appreciable benefit from intravenous rather than oral therapy with penicillin for erysipelas, and so oral therapy is recommended if there are no associated complications with the infection.

Interventions for cellulitis and erysipelas. Kilburn SA, Featherstone P, Higgins B, et al. *Cochrane Database Syst Rev* 2010; 16: CD004299.

A Cochrane review in 2010 could not recommend any particular antibiotic regimen for cellulitis and erysipelas due to the large variation in treatment regimens studied.

Efficacy of oral beta-lactam versus non-beta-lactam treatment of uncomplicated cellulitis. Madaras-Kelly KJ, Remington RE, Oliphant CM, et al. *Am J Med* 2008; 121(5): 419–25.

A multicenter, retrospective cohort study of outpatients treated for uncomplicated cellulitis found no significant difference in failure rates when comparing oral beta-lactams with non-β-lactams, with increased discontinuation in the non-β-lactam group because of adverse events.

Effect of cephalexin plus trimethoprim-sulfamethoxazole vs. cephalexin alone on clinical cure of uncomplicated cellulitis:

a randomized clinical trial. Moran GJ, Krishnadasan A, Mower WR, et al. *JAMA* 2017; 317(20): 2088–96.

In this multicenter, double-blind, randomized superiority trial in five US emergency departments of uncomplicated cellulitis treatment, clinical resolution of cellulitis was not significantly different in patients treated with cephalexin plus trimethoprim-sulfamethoxazole compared to cephalexin alone.

Clinical trial: comparative effectiveness of cephalexin plus trimethoprim-sulfamethoxazole versus cephalexin alone for treatment of uncomplicated cellulitis: a randomized controlled trial. Pallin DJ, Binder WD, Allen MB, et al. *Clin Infect Dis* 2013; 56(12): 1754–62.

A multicenter, double-blind, randomized controlled trial comparing the use of cephalexin to cephalexin and trimethoprim-sulfamethoxazole for cases of non-purulent, uncomplicated cellulitis demonstrated no benefit to the addition of antibiotics against community-acquired MRSA.

Risk factors for nonpurulent leg cellulitis: a systematic review and meta-analysis. Quirke M, Ayoub F, McCabe A, et al. *Br J Dermatol* 2017; 177(2): 382–94.

A systematic literature search revealed increased risk of non-purulent cellulitis associated with previous cellulitis, wounds, current leg ulcers, lymphedema, excoriation, tinea pedis, and obesity.

Cellulitis: a review. Raff AB, Kroshinsky D. *JAMA* 2016; 316: 325–37.

A review article from 2016 advises the above treatment regime based on the IDSA guidelines and Johns Hopkins Guidelines, as well as randomized controlled trials.

Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Stevens DL, Bisno AL, Chambers HF, et al. *Clin Infect Dis* 2014; 59(2): 147.

These updated guidelines serve as a basis for the antibiotic regimes suggested above.

Management of invasive group A streptococcal infections. Waddington CS, Snelling TL, Carapetis JR. *J Infect* 2014; 69(Suppl 1): S63–9.

Patients with cellulitis and signs of shock should receive penicillin G and clindamycin for potential streptococcal toxic shock syndrome.

Second-Line Therapies

• Linezolid	A
• Daptomycin	A
• Vancomycin	A
• Oritavancin	B
• Telavancin	B
• Tedizolid	B
• Dalbavancin	B
• Imipenem/cilastatin	B

ATLAS trials: efficacy and safety of telavancin compared with vancomycin for the treatment of skin infections. Barriere SL. *Future Microbiol* 2010; 5(12): 1765–73.

Telavancin is FDA-approved for the treatment of complicated SSTIs caused by susceptible Gram-positive bacteria, including

MRSA. Telavancin 10 mg/kg once daily is non-inferior to vancomycin; however, there is a risk of nephrotoxicity.

Single-dose oritavancin in the treatment of acute bacterial skin infections. Corey GR, Kabler H, Mehra P, et al. *N Engl J Med* 2014; 370(23): 2180–90.

A single dose of oritavancin has been shown to be as effective as twice-daily intravenous vancomycin administered for 7–10 days.

Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: The ESTABLISH-1 Randomized Trial. Prokocimer P, De Anda C, Fang E, et al. *JAMA* 2013; 309(6): 559–69.

A once-daily oral dose of 200 mg tedizolid phosphate for 6 days was non-inferior to 600 mg oral linezolid every 12 hours for 10 days in early clinical response at 48–72 hours.

Twice daily intramuscular imipenem/cilastatin in the treatment of skin and soft tissue infections. Sexton DJ, Wlodaver CG, Tobey LE, et al. *Chemotherapy* 1991; 37: 26–30.

Of 102 patients enrolled in this study with mild to moderately severe SSTIs, 74 were evaluable, with 20 having cellulitis, 23 wound infections, and 31 abscesses. Imipenem/cilastatin was given intramuscularly using doses of 500 mg or 750 mg 12-hourly. In this study there was no assessment by type of infection, but 82% were cured and 16% improved. Eight patients reported minor side effects.

Randomized comparison of linezolid (PNU-100766) versus oxacillin-dicloxacillin for treatment of complicated skin and soft tissue infections. Stevens DL, Smith LG, Bruss JB, et al. *Antimicrob Agents Chemother* 2000; 12: 3408–13.

Hospitalized adult patients were randomized to receive linezolid (600 mg intravenously) every 12 hours or oxacillin (2 g intravenously) every 6 hours; after sufficient clinical improvement, patients were switched to the respective oral agents (linezolid 600 mg orally every 12 hours or dicloxacillin 500 mg orally every 6 hours). The clinical cure rates were 88.6% and 85.8%, respectively.

Comparative efficacy of antibiotics for the treatment of acute bacterial skin and skin structure infections (ABSSSI): a systematic review and network meta-analysis. Thom H, Thompson JC, Scott DA, et al. *Curr Med Res Opin* 2015; 31: 1539–51.

This meta-analysis of 52 trials concluded that there is equivalence of clinical efficacy between vancomycin, daptomycin, linezolid, and the novel antimicrobial agent oritavancin. However, they noted the heterogeneity of the available evidence and the need for further research.

Linezolid versus vancomycin for skin and soft tissue infections. Yue J, Dong BR, Yang M, et al. *Cochrane Database Syst Rev* 2013; 7(7): CD008056.

A 2013 Cochrane review comparing oral linezolid with intravenous vancomycin for the treatment of SSTIs demonstrated that linezolid had better clinical and microbiological cure rates overall as well as for MRSA infections.

Prophylaxis

• Low-dose oral penicillin	A
• Intramuscular weekly penicillin	C
• Treatment of predisposing factors	E

The experience of intramuscular benzathine penicillin for prophylaxis of recurrent cellulitis: a cohort study. Chen HM, Li YL, Liu YM, et al. *J Microbiol Immunol Infect* 2017; 50(5): 613–8.

A retrospective study of 72 patients with a history of recurrent cellulitis who had received intramuscular benzathine penicillin at a 4-week interval demonstrated a reduced incidence rate of recurrent cellulitis.

Interventions for the prevention of recurrent erysipelas and cellulitis. Dalal A, Eskin-Schwartz M, Mimouni D, et al. *Cochrane Database Syst Rev* 2017; 6.

A total of six trials were assessed in this systematic review, concluding that antibiotics may be effective in reducing recurrence, incidence, and time to next episode of lower limb cellulitis (moderate-certainty evidence) for the duration that the antibiotic is prescribed (low-certainty evidence).

Cellulitis and erysipelas. Morris A. *Clin Evid* 2004; 12: 2268–74.

Although there is a consensus that successful treatment of predisposing factors such as leg edema, tinea pedis, and traumatic wounds reduces the risk of developing cellulitis, there are no randomized controlled trials or observational studies to support this.

Antibiotic prophylaxis for preventing recurrent cellulitis: a systematic review and meta-analysis. Oh CC, Ko HC, Lee HY, et al. *J Infect* 2014; 69: 26.

This meta-analysis concluded that antibiotic prophylaxis can prevent recurrent cellulitis but that further research is needed to establish indication, choice of drug, and dosage regimens.

Penicillin to prevent recurrent leg cellulitis. Thomas KS, Crook AM, Nunn AJ, et al. *N Engl J Med* 2013; 368(18): 1695–703.

A double-blind, randomized, controlled trial of 274 patients treated either with low-dose oral penicillin (250 mg twice daily) or placebo for 12 months, finding a reduced recurrence risk during the time of prophylaxis administration, but not in subsequent no-prophylaxis follow-up.

Chancroid

Iris A. Hagans, Glenn C. Newell



Chancroid is an ulcerative disease of the skin caused by the Gram-negative, facultative, anaerobic coccobacillus *Haemophilus ducreyi*. Chancroid is typically considered a sexually transmitted genital ulcer disease; however, it is increasingly identified as a cause of non-genital ulcerative skin lesions, especially in endemic areas. The incidence is decreasing worldwide; however, chancroid should be suspected in any ulcerative skin lesion especially in travelers returning from high-risk areas, including Africa, the Caribbean basin, and Southwest Asia.

Chancroid typically presents as a painful, ragged, deep ulcer 3–20 mm in diameter without induration, often beginning with papules that may pustulate and subsequently break down into the classic ulcer. There may be surrounding erythema, and the base is often covered with a yellow-gray exudate.

Genital lesions may be single, but can be multiple as a result of autoinoculation (kissing lesions). Painful lymphadenitis occurs in 30%–60% of genitally infected patients, and approximately one quarter of patients with lymphadenopathy may develop a suppurative bubo.

DIAGNOSIS AND MANAGEMENT STRATEGY

Diagnosis on clinical criteria alone is difficult. The painful genital ulcer of chancroid can easily be confused with genital herpes or secondarily infected syphilis, and non-genital ulcerative lesions have been misdiagnosed as yaws in both adults and children.

A presumptive diagnosis of chancroid can be made with consistent epidemiologic history, one or more painful genital or skin ulcers with negative laboratory tests for herpes simplex virus (HSV) and syphilis. In genital lesions, coinfection with either of these diseases occurs in as many as 10% of patients, further complicating diagnosis.

A definitive diagnosis may be made by culturing the exudates from the ulcer base or by aspiration of a bubo. Gram stain of the ulcer base in chancroid may show Gram-negative coccobacilli in a 'school of fish' appearance. Special culture media should be used, and the specimen should be handled by laboratories familiar with *H. ducreyi*. It should be noted that sensitivity of culture as shown by DNA amplification techniques can be as low as 75%.

Nucleic acid amplification tests (NAATs) show higher positivity rates than culture and do not depend on live bacteria, making the test especially useful. However, only a few laboratories have established NAATs for the diagnosis of chancroid. Polymerase chain reaction testing has the advantage of simultaneous testing of *H. ducreyi* along with *T. pallidum* and HSV.

Concurrent HIV infection can alter the manifestations of chancroid. HIV prolongs the incubation period of *H. ducreyi* and prevents proper healing of the ulcers. As HIV can increase the number of genital ulcers and non-genital ulcers are frequently found, the diagnosis is often confused with HSV. Treatment guidelines for patients coinfecting with HIV are the same as for those without HIV, but closer follow-up and a potentially longer course of therapy may be recommended, as there are increased treatment failures with HIV coinfection. Additionally, chancroid has been noted to increase the susceptibility to HIV, probably by disrupting mucosal integrity. Patients should be tested for HIV at the time of chancroid diagnosis and should be retested for HIV 3 months after the diagnosis of chancroid if initial testing was negative.

Treatment should be started once a presumptive diagnosis is made and it is not necessary to wait for laboratory confirmation. Single-dose azithromycin or ceftriaxone are considered the preferred treatment regimens. These offer the advantage of improved adherence rates, though there is a scarcity of data regarding treatment success and antimicrobial resistance, in part due to limited testing and most cases occurring in resource-poor areas. Improvement occurs rapidly with a decrease in symptoms typically noted within 3 days and visual ulcer healing beginning within 7 days, though scarring can occur. Of note, uncircumcised men may have a higher risk of infection and may take longer to cure. Patients should be reevaluated within a week of treatment and if no improvement is noted the diagnosis should be reconsidered and adherence should be assessed. Additionally, HIV coinfection should be ruled out and consideration regarding antimicrobial resistance should be made. Patients should abstain from sexual contact and sexual partners should also be examined and treated.

Specific Investigations

- Gram stain of ulcer base or bubo aspirate
- Culture of ulcer base or bubo aspirate
- NAATs
- Syphilis serology
- HIV serology

First-Line Therapies

• Azithromycin 1 g orally (one dose)	A
• Ceftriaxone 250 mg intramuscularly (one dose)	A

2017 European guideline for the management of chancroid. Lautenschlager S, Michael Kemp M, Christensen JJ, et al. Int J STD AIDS 2017; 28: 324–9.

A comprehensive review of chancroid diagnosis and management. The authors note that while the first-line therapies above have generally acceptable response rates, treatment failures have been noted in HIV positive patients.

Macrolides for treatment of *Haemophilus ducreyi* infection in sexually active adults. Romero L, Huerfano C, Grillo-Ardila CF. Cochrane Database Syst Rev 2017(12): CD012492.

A systematic review of seven randomized, controlled studies to evaluate the effectiveness of macrolides for the treatment of

H. ducreyi infections. The authors determined that, based on low quality evidence, azithromycin can be considered a first-line therapy for the treatment of *H. ducreyi* infections due to its single-dose administration compared with erythromycin, which requires a longer course. There was little data regarding the safety and effectiveness of using macrolides to treat *H. ducreyi* in patients with HIV.

Single-dose azithromycin for the treatment of *Haemophilus ducreyi* skin ulcers in Papua New Guinea. González-Beiras C, Kapa A, Vall-Mayans M, et al. Clin Infect Dis 2017; 65: 2085–90.

A community-based cohort study on a single island in Papua New Guinea, in which 246 patients with skin or genital ulcers were tested for *H. ducreyi* and *Treponema pallidum* subspecies *pertenue* (the causative agent of yaws) via lesional polymerase chain reaction (PCR) swab and given 1 g of azithromycin orally. Ulcers were examined 14 days later. Healing rates were 88.5% in the *H. ducreyi* group, 78.4% in the yaws group, and 74.4% in the PCR-negative group. Of the patients with *H. ducreyi*-positive lesions, 94.7% had improved ulcers and all patients with non-healed *H. ducreyi* lesions converted to *H. ducreyi* PCR negative.

Second-Line Therapies

- Ciprofloxacin 500mg orally twice a day for 3 days **B**
- Erythromycin 500mg orally three times a day for 7 days **B**

Epidemiology of *Haemophilus ducreyi* infections. González-Beiras C, Marks M, Chen CY, et al. Emerg Infect Dis 2016; 22: 1–8.

This is a systematic review to assess the global epidemiology of *H. ducreyi* infections between 1980 and 2014. There was a clear decrease in the percentage of genital ulcers caused by *H. ducreyi* during this time, though several studies demonstrated that it is a significant cause of chronic skin ulceration.

Incision and drainage versus aspiration of fluctuant buboes in the emergency department during an epidemic of chancroid. Ernst AA, Marvez-Valls E, Martin DH. Sex Transm Dis 1995; 22: 217–20.

Evacuation of buboes has historically been recommended to prevent fistula formation, and needle aspiration was previously the procedure of choice. This study compared incision and drainage with packing with needle aspiration of suppurative buboes during an epidemic in Louisiana. No difference in cure rate was seen; however, aspirated buboes required reaspiration in six out of 15 patients. As such, the authors recommended considering incision and drainage as an alternative to needle aspiration.

***Haemophilus ducreyi*: from sexually transmitted infection to skin ulcer pathogen.** Lewis DA, Mitjá O. Curr Opin Infect Dis 2016; 29: 52–7.

The authors of this review discuss recent investigations discerning yaws from chancroid as the culprit for chronic skin ulceration in endemic countries. They suggest that chancroid should be considered in the evaluation of chronic limb ulceration.

***Haemophilus ducreyi* as a cause of skin ulcers in children from a yaws-endemic area of Papua New Guinea: a prospective cohort study.** Lancet Glob Health 2014; 2: e235–41

This study evaluated the prevalence and characteristics of chancroid and yaws on an island in Papua New Guinea and compared the characteristics of the skin lesions of these two diseases. *H. ducreyi* lesions tended to be larger and more superficial whereas yaws and yaws/chancroid coinfections tended to present with more circular lesions with central granulating tissue and indurated edges.

Class I *Haemophilus ducreyi* strain containing a class II *hgbA* allele is partially attenuated in humans: implications for HgbA vaccine efficacy trials. Leduc I, Fortney KR, Janowicz DW, et al. Infect Immun 2019; 87:e00112–9.

H. ducreyi was shown to colonize 20% of asymptomatic children in an endemic area and has been detected on flies and fomites. These environmental reservoirs are thought to contribute to the development of non-genital *H. ducreyi* skin lesions and have subsequently made *H. ducreyi* a target for vaccination. Preliminary studies are being performed to explore models for *H. ducreyi* vaccine development.

Chilblains

Antonios Kanelleas, Spyridon Schoinas



Chilblains (synonyms: *perniosis*, *pernio*) are localized, inflammatory lesions that are caused by exposure to cold, damp, non-freezing conditions. The pathogenesis is unknown, but chilblains are thought to represent an abnormal inflammatory response of vascular origin (vasospasm) to cold.

The onset is usually in the autumn or winter, with women, children, and the elderly being most frequently affected.

Lesions occur acutely as single or multiple erythematous to blue-violaceous macules, papules, or nodules. They are usually accompanied by pruritus, burning sensation, or pain and rarely in severe cases may blister or ulcerate. The lesions are often symmetrical with a predilection for fingers, toes, heels, nose, and ears.

Chilblains usually resolve spontaneously within 1–3 weeks, although they may be prolonged in elderly patients.

Perniosis may be idiopathic or represent a clinical manifestation of systemic diseases (connective tissue disorders, cold-induced syndromes, hematological malignancies) or eating disorders (anorexia nervosa, poor nutrition). During the COVID-19 pandemic pernio-like lesions, called ‘Covid toes’, occurred and were attributed to an associated coagulopathy.

MANAGEMENT STRATEGY

Clinical findings and history suggest the diagnosis and further investigations are seldom required. However, in patients with atypical and/or persistent lesions and in the elderly, investigations should be performed for underlying causes. The condition must be distinguished from *chilblain lupus*, a form of cutaneous lupus in which lesions develop in cold but tend to persist and ulcerate, and from *lupus pernio*, which is a form of cutaneous sarcoidosis that usually affects the face/nose.

The treatment of perniosis remains unsatisfactory.

For chilblains with no underlying pathology, preventive measures such as adequate clothing and heating and insulation, avoidance of cold, and avoidance of smoking are important.

Treatment includes use of vasodilator *calcium channel blockers* (*nifedipine* 20–60 mg daily, *diltiazem* 60–120 mg TID), which have been shown to be effective in the treatment and

prophylaxis of perniosis in patients with idiopathic acral perniosis and in those with low body weight. *Pentoxifylline* provides a safe alternative approach. A range of *topical vasodilators* and other treatments have been deployed with a largely anecdotal evidence base.

Specific Investigations

Investigations are not routinely required in typical cases, but consider:

- CBC
- Autoimmune profile (ANA, complement)
- Antiphospholipid antibodies
- Cryoglobulins
- Cold agglutinins
- Cryofibrinogen
- Histology and immunofluorescence
- Vascular assessment in the elderly
- Serum protein electrophoresis

Chilblains. Nyssen A, Benhadou F, Magnée M, et al. *Vasa* 2020; 49(2): 133–40.

A comprehensive literature review regarding differential diagnosis and management of chilblains.

Chilblain lupus erythematosus – a review of literature. Hedrich CM, Fiebig B, Hauck FH, et al. *Clin Rheumatol* 2008; 27: 949–54.

This article reviews the clinical presentation, pathogenesis, diagnosis, and management of chilblain lupus erythematosus.

Pernio as the presenting sign of blast crisis in acute lymphoblastic leukemia. Park KK, Tayebi B, Uihlein L, et al. *Pediatr Dermatol* 2018; 35(1): e74–5.

A case of a 5-year-old girl with pernio as the presenting symptom of acute B-cell lymphoblastic leukemia.

Anorexia nervosa associated with acromegaloïd features, onset of acrocyanosis and Raynaud’s phenomenon and worsening of chilblains. Rustin MH, Foreman JC, Dowd PM. *J Roy Soc Med* 1990; 83: 495–6.

Two patients are reported who developed severe perniosis in association with anorexia nervosa.

Acute perniosis in elderly people: a predictive sign of systemic disease? Guadagni M, Nazzari G. *Acta Derm Venereol*. 2010; 90(5): 544–5.

In this letter to the editor, the authors present seven cases of elderly patients in which perniosis was associated with an underlying disease in six out of the seven patients.

Childhood pernio and cryoproteins. Weston WL, Morelli JG. *Pediatr Dermatol* 2000; 17: 97–9.

A 10-year retrospective study in a pediatric clinic identified eight patients with perniosis, four of whom had cryoglobulins or cold agglutinins and two who had positive rheumatoid factor.

First-Line Therapies

• Conservative management	C
• Avoidance of further cold injury	E
• Calcium channel blockers	B

Clinical characteristics, etiologic associations, laboratory findings, treatment, and proposal of diagnostic criteria of perniosis (chilblains) in a series of 104 patients at Mayo Clinic, 2000 to 2011. Cappel JA, Wetter DA. Mayo Clin Proc 2014; 89: 207–15.

Conservative treatments (e.g., warming, drying, and smoking cessation) provided complete response in 23 (82%) of the 28 patients for whom follow-up data were available.

The treatment of chilblains with nifedipine: the results of a pilot study, a double-blind placebo-controlled randomized study and a long-term open trial. Rustin MH, Newton JA, Smith NP, et al. Br J Dermatol 1989; 120: 267–75.

Ten patients with severe recurrent acral perniosis were treated with 20 mg of nifedipine or placebo daily in a double-blind, crossover trial for 12 weeks total. No patients developed new lesions while on treatment, and 70% were clear after a mean of 8 days. In the open study, 34 patients received up to 60 mg of nifedipine daily for 2 months; this was shown to be effective in reducing the healing time and symptoms of lesions.

Diltiazem vs. nifedipine in chilblains: a clinical trial. Patra AK, Das AL, Ramadasan P. Indian J Dermatol Venereol Leprol 2003; 69: 209–11.

The authors compared two groups of patients with chilblains. Group A (12 patients) was treated with diltiazem 60 mg TID and group B (24 patients) with nifedipine 10 mg TID until complete relief and then 20 mg twice daily for maintenance. They concluded that nifedipine has greater efficacy than diltiazem (80%–90% of patients from group B showed relief by the 14th day of treatment).

Nifedipine vs placebo for treatment of chronic chilblains: a randomized controlled trial. Souwer IH, Bor JH, Smits P, et al. Ann Fam Med 2016; 14(5): 453–9.

Contrary to other papers the authors could not confirm that nifedipine was superior to placebo.

Assessing the effectiveness of topical betamethasone to treat chronic chilblains: a randomised clinical trial in primary care. Souwer IH, Bor JH, Smits P, et al. Br J Gen Pract 2017; 67(656): e187–93.

The authors concluded that there was no clinically or statistically significant difference between treatment with topical betamethasone valerate cream and placebo. Therefore, topical steroids *cannot be recommended* in the treatment of chronic chilblains.

Second-Line Therapies

• Topical nitroglycerine	C
• Pentoxifylline	A
• Topical 2% hexyl nicotinate cream	E
• Minoxidil 5% lotion	E
• Acidified nitrate cream	E
• Tamoxifen	E

Topical nitroglycerine in perniosis/chilblains. Verma P. Skinmed 2015; 13: 176–7.

An uncontrolled study on 0.2% nitroglycerine ointment: 18 of 22 patients had regression of lesions within a week.

Treatment of primary perniosis with oral pentoxifylline (a double-blind placebo-controlled randomized therapeutic trial). Al-Sudany NK. Dermatol Ther 2016; 29: 263–8.

Pentoxifylline 400 mg TID for 3 weeks proved superior to placebo in a double-blind trial undertaken in Iraq.

Treatment of perniosis with oral pentoxifylline in comparison with oral prednisolone plus topical clobetasol ointment in Iraqi patients. Noaimi AA, Fadheel BM. Saudi Med J 2008; 29: 1762–4.

Forty patients with chilblains were randomly divided into two equal groups. Group A received oral prednisolone 0.5 mg/kg/day BD and topical clobetasol ointment for 2 weeks. Patients in group B received pentoxifylline tablets 400 mg TID for 2 weeks. In group B, 5 of 9 patients (55.5%) who completed the study showed a significant improvement, compared with 3 of 11 patients (27.2%) in group A.

Chilblains. Dowd PM, Blackwell V. In: Lebowitz M, Heymann W, Berth-Jones J, et al., eds. Treatment of Skin Disease: Comprehensive Therapeutic Strategies, 2nd edn. Chicago: Mosby, 2006; 39–40.

These authors reported use of 2% hexyl nicotinate in aqueous cream preparation and minoxidil 5% lotion applied three times a day in patients with chilblains and Raynaud phenomenon, and acidified nitrite cream (3% salicylic acid and 3% potassium nitrate) TID in patients with chilblains intolerant of calcium channel blockers. Low-dose (5 mg daily) tamoxifen proved useful in anorexia-associated perniosis.

Third-Line Therapies

• Non-steroidal antiinflammatory drugs	E
• Prednisolone	E
• Hydroxychloroquine	E
• Intense pulsed light	E

Major cluster of chilblain cases in a cold dry Western Australian winter. Larkins N, Murray KJ. J Paediatr Child Health 2013; 49: 144–7.

Thirty-two patients with perniosis are described. Most received some form of treatment including non-steroidal antiinflammatory drugs, prednisolone, or nifedipine, but most improved spontaneously with warmer weather or responded to cold protection advice.

Successful treatment of perniosis with hydroxychloroquine. Yang X, Perez OA, English JC 3rd. J Drugs Dermatol 2010; 9: 1242–6.

In this retrospective study, hydroxychloroquine improved symptoms in four out of five patients with perniosis.

Chondrodermatitis nodularis helicis chronicus

Walayat Hussain



Chondrodermatitis is a benign condition; the chief indication for treatment is pain causing sleep disturbance. Asymptomatic areas of chondrodermatitis do not require active intervention. The use of a pressure-relieving sponge or cushion can provide a good first-choice alternative to surgery.

MANAGEMENT STRATEGY

Chondrodermatitis usually occurs on the lateral portion of the ear on the preferred sleeping side. It is generally caused by the weight of the head on the pillow causing direct pressure and frictional irritation of the cartilage of the ear. Surgery or injury to the ear may leave irregular spicule(s) of cartilage that become a focus for sleep-related pressure. Chondrodermatitis affects the most protuberant part of the ear – most frequently the helix in men and the antihelix in women. Individuals who can only adopt one sleeping position due to arthritis or vertigo, for example, are particularly vulnerable. Requests for patients to ‘change their sleeping position’ are therefore impractical. Patients should be reassured that chondrodermatitis is not skin cancer. If there is any diagnostic uncertainty, a biopsy is warranted. Conservative treatment, such as lidocaine (lignocaine) gel, nitroglycerin gel, a potent topical corticosteroid, self-adhesive foam dressing, or a pressure-relieving cushion may be tried. If sleep is unaffected, further intervention is not necessary unless cosmesis is a concern.

Numerous surgical strategies have been described to treat chondrodermatitis. Whichever surgical technique is adopted, unless the subsequent underlying area of cartilage is smooth, without protuberant foci, the condition will inevitably recur. Although there is no ‘need’ for skin or ulcer excision, this is often undertaken as part of the chosen technique. Other destructive therapies have been advocated but tend to be less effective.

Specific Investigations

- None required
- Biopsy only if diagnostic uncertainty exists (specifically to exclude skin cancer)

First-Line Therapies

- Reassurance that chondrodermatitis is not skin cancer **B**
- Conservative management **B**
- Pressure-relieving cushion or sponge **B**
- Topical corticosteroids **B**
- Intralesional corticosteroids **B**
- Topical nitroglycerin **C**

Treatment of chondrodermatitis nodularis helicis and conventional wisdom? Beck MH. Br J Dermatol 1985; 113: 504–5.

Topical corticosteroids (betamethasone valerate 0.1% and 3% clioquinol cream) used twice a day for up to 6 weeks resolved the condition in all patients.

This was a small case series of only five patients, with limited (eight week) follow-up only.

Intralesional triamcinolone for chondrodermatitis nodularis: a follow-up study of 60 patients. Cox NH, Denham PF. Br J Dermatol 2002; 146: 712–3.

A retrospective analysis of 60 patients with chondrodermatitis nodularis helicis (CNH) treated with 0.1 mL intralesional triamcinolone acetonide 10 mg/mL or triamcinolone hexacetonide 5 mg/mL showed good response on 43% of helix and 31% of antihelix lesions.

This author's experience is that topical or intralesional steroids provide only temporary benefit in a minority of patients. Although their use is still advocated by clinicians, this author has stopped using this approach in favor of topical nitroglycerin or surgery.

The usefulness of 0.2% topical nitroglycerin for chondrodermatitis nodularis helicis. Sanz-Motilva V, Martorell-Calatayud A, Gutiérrez García-Rodrigo C, et al. Actas Dermosifiliogr 2015; 106: 555–61.

Ninety-three percent of 29 patients treated showed clinical improvement with a mean follow-up of 5.9 months. There were fewer side effects using the 0.2% preparation compared with the original 2% ointment.

Perichondrial arteriolar constriction inducing ischemia is implicated in the etiology of chondrodermatitis. This author has found the use of nitroglycerin ointment (0.2%) to be very effective in managing the condition non-surgically. Side effects such as headache are rare with the 0.2% preparation. Asking patients solely to not sleep on the affected side is impractical as a chronic, underlying condition often necessitates that the patient ends up on the side of the chondrodermatitis. The use of a pressure-relieving device as an adjunct to any intervention is of benefit to lessen the chances of recurrence.

Auricular pressure relieving cushions for chondrodermatitis nodularis helix. Allen DL, Swinson PA, Arnstein PM. J Maxillofac Prosthet Tech 1998; 2: 5–10.

Thirty-five of 46 patients treated in this way had complete resolution of their symptoms.

Effective treatment of chondrodermatitis nodularis chronica helix using a conservative approach. Moncrieff M, Sassoon EM. Br J Dermatol 2004; 150: 892–4.

A simple-to-construct ear cushion design was used, made up of a bath sponge with the center removed and held in place with a head band. Thirteen out of 15 patients followed for 1 month responded.

The author (no conflicts of interest) has directed patients to use a similar pressure-relieving device, which is commercially available (CNH ear protector, Delasco.com), with good results.

Management of chondrodermatitis nodularis chronica helix using a “doughnut pillow”. Sanu A, Koppa R, Snow DG. J Laryngol Otol 2007; 121: 1096–8.

Patients used a doughnut-shaped pillow made of orthopedic ‘memory foam’. This distributes the weight of the recumbent head more evenly and is designed to relieve the pressure on the affected ear. Thirteen of 23 (56%) patients treated remained pain free after a 1-year follow-up.

Management of chondrodermatitis nodularis helix by auricular pressure-relieving device: a retrospective study. Belgi A, Logan RA. Br J Dermatol 2007; 157(Suppl 1): 68.

Seventy-eight patients with CNH used a custom-made ear pressure-relieving device designed and built by the local maxillofacial technicians. Of these, 48 patients responded to a questionnaire examining the outcome. Only 7 found it helpful (15%); 20 reported no benefit (42%) and 20 reported some benefit (42%).

Management of chondrodermatitis helix by protective padding: a series of 12 cases and a review of the literature. Timoney N, Davison PM. Br J Plast Surg 2002; 55: 387–9.

Fourteen patients with CNH were prospectively enrolled and used protective padding of the ear at night. Most patients were rapidly relieved of their symptoms, although healing was frequently prolonged.

Chondrodermatitis nodularis chronica helix: a conservative therapeutic approach by decompression. Kuen-Spiegel M, Ratzinger G, Sepp N, Fritsch P. J Dtsch Dermatol Ges 2011; 9: 292–6.

Using a self-made bandage of foam plastic applied during the night, 11 out of 12 patients reported substantial reduction of pain within the first month and were pain free after an average of 1.75 months.

Self-adhering foam: a simple method for pressure relief during sleep in patients with chondrodermatitis nodularis helix. Travelute CR. Dermatol Surg 2013; 39: 317–9.

An inexpensive method using a self-adhering foam sponge (Reston Foam 3M, St Paul, MN) placed on the back of the ear and used nightly for several months was described as effective for helix and antihelix lesions.

Various types of ear cushions are described. They all share the same aim, that is, to transfer the weight of the sleeping head from the ear to the surrounding scalp. Authors report a wide range of benefits with between 15% and 80% of patients not requiring surgery. This author advocates the use of some form of pressure relief as an adjunct to any

non-surgical approach as in his experience the outcomes are favorable, and the benefits of treatment maintained.

Second-Line Therapy

- Surgical excision of cartilage

B

The treatment of chondrodermatitis nodularis with cartilage removal alone. Lawrence CM. Arch Dermatol 1991; 127: 530–5.

Cartilage excision without skin removal resulted in cure rates of 84% for helix and 75% for antihelix lesions. Local anesthesia with lidocaine and epinephrine (adrenaline) reduced bleeding and improved the visibility without ear skin necrosis. On the helix, the skin was reflected back from a helix rim incision to expose the cartilage. On the antihelix, a medially based skin flap was raised to expose cartilage. After exposed cartilage excision, all remaining cartilage edges were left smooth and gently shelving up to the uninvolved cartilage to prevent recurrences that may develop on rough or protuberant cartilage edges. Cartilage excision alone is not disfiguring, and further cartilage edges can be removed if recurrences occur.

This comprehensive article laid the foundation for cartilage excision (without skin removal) in the surgical management of chondrodermatitis of the helix and antihelix.

Treatment of chondrodermatitis nodularis with removal of the underlying cartilage alone: retrospective analysis of experience in 37 lesions. de Ru JA, Lohuis PJ, Saleh HA, et al. J Laryngol Otol 2002; 116: 677–81.

Most otolaryngologists treat patients with chondrodermatitis nodularis by wedge excision. This can leave the patient with an asymmetric, deformed ear. The authors described their results after changing to removal of cartilage alone. In a mean follow-up of 30 months, all 34 patients remained symptom free, and only one required revisional surgery.

Wedge excision should not be used in the surgical management of chondrodermatitis – it is unnecessarily destructive and results in marked unwarranted ear asymmetry.

Twelve years’ experience of simplified surgical treatment of chondrodermatitis nodularis by cartilage trimming and sutureless skin closure. Hussain W, Chalmers RJ. Br J Dermatol 2009; 160: 116–8.

After skin incision, mosquito forceps were used to ‘nibble’ away fragments of cartilage to leave a smooth cartilage contour without the need for full exposure of the cartilage edge. Skin nodules or ulcers are not excised but are left to resolve spontaneously. Tape strips were used for skin closure. Thirty-two of 34 (94%) patients with chondrodermatitis, 7 on the antihelix and 27 on the helix, showed no discomfort or clinical recurrence 4 months after this procedure.

Chondrodermatitis nodularis chronica helix et antihelix. Munnoch DA, Herbert KJ, Morris AM. Br J Plast Surg 1996; 49: 473–6.

In total, 54 chondrodermatitis lesions (36 helix, 18 antihelix), including 23 recurrent after previous surgery, were treated by minimal skin excision combined with extensive cartilage resection. There were no recurrences and minimal postoperative deformity.

Narrow elliptical skin excision and cartilage shaving for chondrodermatitis nodularis. Rex J, Ribera M, Bielsa I, et al. Dermatol Surg 2006; 32: 400–4.

A narrow elliptical excision of the papule followed by a slice of the underlying cartilage was taken and trimmed carefully to remove any cartilage spikes. Good cosmetic results were obtained in all 74 patients retrospectively analyzed. The recurrence rate ranged from 10% for helical and 37% for antihelical lesions after a median follow-up of 54 and 50 months, respectively.

Modified surgical excision for the treatment of chondrodermatitis nodularis. Ormond P, Collins P. *Dermatol Surg* 2004; 30(2 Pt 1): 208–10.

Excision of the cartilage alone is therapeutically and cosmetically effective. To simplify the surgical procedure, a narrow ellipse of skin over the nodule was excised and cold steel dissection of the adjacent skin replaced by hydrodissection to create a plane of cleavage between the skin and cartilage. These two refinements maintained the clinical and cosmetic efficacy and simplified the surgical technique.

All these techniques are based on removal of damaged cartilage and avoidance of leaving irregular cartilaginous fragments, which act as a focus for recurrence. Treatment outcome is operator dependent. Skin excision is often included as it makes the procedure easier to perform but it is not a prerequisite for surgical success.

Third-Line Therapies

• Curettage	B
• Punch and graft	B
• Intralesional hyaluronic acid	B
• CO ₂ /argon laser ablation	C
• Collagen injections	D
• Photodynamic therapy	D
• Cryotherapy	E
• Incision and cartilage curettage	E

Chondrodermatitis nodularis chronica heliis treated with curettage and electrocauterization: follow-up of a 15-year material. Kromann N, Hoyer H, Reyman F. *Acta Derm Venerol* 1983; 63: 85–7.

In total, 142 cases of chondrodermatitis were principally treated by curettage followed by electrocauterization. Seventy-eight patients were reexamined after an average interval of 7.1 years. This simple surgical technique produced a relapse rate of 31%.

The surgical management of chondrodermatitis nodularis chronica heliis. Coldiron BM. *J Dermatol Surg Oncol* 1991; 17: 902–4.

An ellipse of skin is removed around the ulcerated area. The central necrotic or damaged cartilage is removed using a curette and the skin edges sutured. A series is not reported.

Chondrodermatitis nodularis chronica heliis. Successful treatment with the carbon dioxide laser. Taylor MB. *J Dermatol Surg Oncol* 1991; 17: 862–4.

The CO₂ laser was used to vaporize the cutaneous nodules and involved cartilage. The wounds were allowed to heal with only

minimal care using hydrogen peroxide cleansing and applications of topical antibiotic ointment. Twelve lesions have been treated with no recurrences after 2–15 months.

Argon laser therapy for chondrodermatitis nodularis chronica heliis. Hesse G, Schmoeckel C, Wichmann-Hesse A. *Hautarzt* 1994; 45: 222–4.

A small case series of nine patients in whom a 56% cure was seen.

The punch and graft technique: a novel method of surgical treatment for chondrodermatitis nodularis heliis. Rajan N, Langtry JA. *Br J Dermatol* 2007; 157: 744–7.

Twenty-three lesions (15 helix, 3 antihelix, 5 not recorded) were treated by punch removal of the nodule and underlying cartilage. The small defect was closed with a full-thickness skin graft taken from behind the ear using the same punch.

This 'punch and graft' technique contradicts the dogma about the necessity of leaving smooth cartilage margins after any surgical approach. Although the authors state a cure rate of 83%, the author's experience has been that of ultimate recurrence in the short- to medium-term with this technique.

Intralesional hyaluronic acid injection for chondrodermatitis nodularis heliis: a novel treatment for rapid relief of pain and healing of ulcerations. Carey W. *Dermatol Surg* 2021; 47: 373–376.

In this series, 24 patients were injected with 0.2 to 0.3mL of hyaluronic acid and followed up in 2 to 4 weeks intervals. Symptom benefit and improvement in clinical appearance was seen in 23 patients treated after 1 or 2 injections.

The treatment of chondrodermatitis nodularis chronica heliis with injectable collagen. Greenbaum SS. *Int J Dermatol* 1991; 30: 291–4.

Five patients treated with collagen to relieve pressure on the affected cartilage reportedly all gained benefit.

Chondrodermatitis nodularis heliis successfully treated with photodynamic therapy. Gilaberte Y, Frias MP, Perez-Lorenz JB. *Arch Dermatol* 2010; 146: 1080–2.

Retrospective review of five patients with an 80% reported success rate but confounded by prior use of curettage.

Chondrodermatitis nodularis chronica heliis and photodynamic therapy: a new therapeutic option? Pelligrino M, Taddeucci P, Mei S, et al. *Dermatologic Therapy* 2011; 24: 144–7.

A case report of two patients in whom photodynamic therapy was reportedly successful.

Cryotherapy has been advocated but, other than a single case report, no published outcome data exist.

Chromoblastomycosis

Wanda S. Robles, Mahreen Ameen



Chromoblastomycosis is a chronic fungal infection of cutaneous and subcutaneous tissues prevalent in tropical and subtropical climates including Central and South America, Africa, Asia (highest incidence in Japan), and Oceania (first described in Australia), with cases also reported from New Zealand and Solomon Islands. Most cases reported outside the tropical areas, particularly in Europe, are considered imported dermatoses. It is caused by the traumatic cutaneous implantation of dimorphic pigmented (dematiaceous) fungi, classified in the order *Chaetothyriales*. These produce characteristic thick-walled sclerotic bodies (also known as *muriform fumagoid* or *Medlar bodies*) in infected tissues. The most common etiologic agents are *Fonsecaea pedrosoi*, *Phialophora verrucosa* and *Cladophialophora carrionii*. Clinically, chromoblastomycosis presents as plaques, nodules, tumors, cicatricial or verrucous exophytic lesions, which are commonly located on the feet and lower legs. Lesions are indolent and slow growing; over years they extend centrifugally, leaving central areas of scarring. Disease is commonly localized but can spread through autoinoculation or lymphatic dissemination, producing metastatic lesions away from the primary site. Complications include ulceration, secondary bacterial infection, and lymphedema. Rarely, malignant transformation (squamous cell carcinoma) in chronic lesions and systemic involvement have been reported.

MANAGEMENT STRATEGY

Chromoblastomycosis is a difficult-to-treat mycosis characterized by low cure and high rates of relapse, particularly in chronic and extensive disease. There are no clinical trials that determine the best therapeutic approach. Studies report highly variable rates of clinical and mycological cure, ranging from 15% to 80%. The choice of treatment and outcome depend on the etiologic agent, severity and extent of the lesions, clinical topography, and the presence of complications (dermal fibrosis and edema may reduce tissue antifungal drug levels). *F. pedrosoi* is the most common etiologic agent but has the lowest sensitivity to the major systemic antifungal agents. *C. carrionii* and *P. verrucosa* are much more sensitive and have been found to respond more favorably to treatment.

Surgical excision may be successful for small and localized lesions. It is performed with wide surgical margins and is usually accompanied by chemotherapy in order to reduce the risk of recurrence. Curettage and electrodesiccation is not recommended because it may promote lymphatic spread. Other physical modalities include cryotherapy with liquid nitrogen, as well as thermotherapy (applying local heat to produce controlled temperatures ranging from 42°C to 45°C, which inhibit fungal growth) using a variety of methods, including benzene pocket warmers and pocket-handkerchief-type warmers. Cryosurgery and thermotherapy have the advantage that they are relatively inexpensive treatment options.

There are no comparative trials of antifungal chemotherapy for chromoblastomycosis. Itraconazole (100–400 mg daily) and terbinafine (250–500 mg daily) are considered first-line treatments, with both drugs having shown high in vitro activity against the causative agents of chromoblastomycosis. They are typically given for long periods at high doses. Dual therapy with itraconazole and terbinafine is recommended if it is affordable and tolerated. It is not uncommon for more than one treatment modality to be used, such as oral antifungals combined with surgery, cryotherapy, or thermotherapy. For example, itraconazole and/or terbinafine combined with cryosurgery is advocated for extensive disease. The antifungal is given first until there is a maximum reduction in lesion size, which usually requires 6–12 months of chemotherapy. The lesions then require several treatments with cryosurgery.

Of the other antifungal agents, ketoconazole is not recommended due to toxicity at high doses. Despite a few cases in the early literature reporting success with fluconazole, it too is not recommended as in vitro studies have shown that it has little activity against black fungi. Flucytosine (converted into 5-fluorouracil in fungal cells) was an early treatment that demonstrated some degree of efficacy. It is associated with a high risk of developing resistance, but this can be overcome if it is used in combination with another antifungal. It is also hepatotoxic and myelotoxic, requiring regular monitoring of serum levels. It is rarely used now except for resistant cases. Amphotericin B (AmB) monotherapy is ineffective, and even in combination with other antifungals, results are generally poor. However, AmB and flucytosine dual therapy has demonstrated efficacy, with in vitro studies having demonstrated synergistic activity between the two drugs. The new second-generation azoles, such as posaconazole and voriconazole, have shown acceptable results in case reports, but experience to date is limited mainly due to high costs in endemic areas.

Other modalities of treatment, including imiquimod, conventional photodynamic therapy, and carbon dioxide laser photocoagulation, are mainly anecdotal.

Specific Investigations

- Direct microscopy
- Culture
- Histopathology

A positive direct examination of scrapings in 10% potassium hydroxide will demonstrate thick-walled, brown sclerotic cells that are pathognomonic of chromoblastomycosis, irrespective of the causative species. Specimens are more likely to yield a positive result if they include the 'black dots' visible on the surface of the lesion. Culture enables the identification of the causative agent. It is a slow-growing fungus and culture may be inconclusive due to poor morphologic differentiation. Polymerase chain reaction (PCR) has been developed for the identification of *Fonsecaea* and *C. carrionii*. Serologic tests such as enzyme-linked

immunosorbent assay (ELISA) can be useful in evaluating therapy response, but like PCR they are not widely available in most endemic settings. A biopsy demonstrates the typical sclerotic bodies in a granulomatous lesion that may be accompanied by trans-epithelial elimination.

First-Line Therapies

• Itraconazole	B
• Terbinafine	B
• Combined	B

Treating chromoblastomycosis with systemic antifungals. Bonifaz A, Paredes-Solis V, Saul A. Expert Opin Pharmacother 2004; 5: 247–54.

A review article highlighting the difficulties in treating this condition. The authors state that the best results for therapy have been obtained with the combination and use of high-dose itraconazole and terbinafine for a minimum treatment period of 6–12 months.

Chromoblastomycosis. Lopez-Martinez R, Mendez Tovar LJ. Clin Dermatol 2007; 25: 188–94.

A comprehensive review article. Itraconazole is considered the treatment of choice in combination with surgery in some cases.

Chromoblastomycosis: an overview of clinical manifestations diagnosis and treatment. Queiroz-Telles F, Esterre P, Perez-Blanco M, et al. Med Mycol 2009; 47: 3–15.

The authors state that there is no treatment of choice but rather several treatment options: they suggest that physical therapies should enhance chemotherapy and that systemic combination therapies may increase cure rate but may be associated with a higher risk of adverse effects.

Pulse itraconazole 400 mg daily in the treatment of chromoblastomycosis. Ungpakorn R, Reangchainam S. Clin Exp Dermatol 2006; 31: 245–7.

In this small study, six cases of *F. pedrosoi* infection in Thailand were treated with pulse itraconazole 400 mg daily, for one week each month. All achieved clinical and mycological cure. Four patients were cured after 12 pulses of treatment, and one after 15 pulses of treatment. The remaining patient required 20 pulses of itraconazole as well as cryosurgery. Disease severity and duration did not appear to be predictive of treatment response. This study demonstrated that the monthly pulse regimen is well tolerated and as effective as the conventional continuous 200–400 mg daily regimen for the treatment of *F. pedrosoi*. The authors recommend that treatment is continued until absence of organisms is proven by histology and tissue culture. Given that the total drug dosage is reduced, there is a marked reduction in cost of therapy by 50% to 75%. They also claim that pulse therapy is associated with higher compliance, although therapy duration remains long.

The cost of long-term itraconazole therapy is expensive in endemic settings, making this an important and relevant study.

Treatment of chromoblastomycosis with itraconazole, cryosurgery and a combination of both. Bonifaz A, Martinez-Soto E, Carrasco-Gerard E, et al. Int J Dermatol 1997; 36: 542–7.

This study included 12 patients assigned to three different groups. Group 1, with small lesions, was treated with itraconazole 300 mg/day. Group 2, also with small lesions, was treated with one or more sessions of cryosurgery. Group 3, with large

lesions, started treatment with itraconazole 300 mg/day until reduction of lesions was achieved, followed by one or more sessions of cryosurgery. The results showed complete clinical and mycologic cure in two out of four patients in both groups 1 and 3. All four patients in group 2 achieved complete cure.

Although the case numbers were small, this study suggests that cryosurgery is a more suitable treatment option than antifungal therapy for small lesions.

Treatment of chromomycosis with terbinafine: preliminary reports of an open pilot study. Esterre P, Inzan CK, Ramarcel ER, et al. Br J Dermatol 1996; 134: 33–6.

A multicentre study from Madagascar. Of 43 patients treated, 36 (*F. pedrosoi*, *n*=29; *C. carrionii*, *n*=7) could be completely evaluated. Approximately one-third of the patients had been resistant to previous treatment with thiabendazole. Oral terbinafine 500 mg daily was given for 6–12 months. Within 2–4 months of commencement of treatment, there was a marked clinical improvement with resolution of secondary bacterial infection, edema, and elephantiasis. There was mycologic cure in 83% (24/29) of patients infected with *F. pedrosoi* at 12 months. Of those infected with *C. carrionii*, there was a cure in one and clinical improvement in a further three. Total cure was observed even in imidazole-refractory patients or those with chronic disease present for over 10 years. There was a mild transient rise in hepatic enzymes in some patients, but no serious adverse effects were reported.

Treatment of chromoblastomycosis with terbinafine: experience with four cases. Bonifaz A, Saul A, Paredes-Solis V, et al. J Dermatolog Treat 2005; 16: 47–51.

Four cases from Mexico (*F. pedrosoi*, *n*=3; *P. verrucosa*, *n*=1) were treated with oral terbinafine 500 mg daily. Three cases achieved clinical and mycologic cure after a mean treatment period of 7 months. Treatment was well tolerated with no abnormalities of liver enzymes.

Treatment of chromoblastomycosis with terbinafine: a report of four cases. Xibao Z, Changxing L, Yuqing H. J Dermatolog Treat 2005; 16: 121–4.

Four cases from China (*C. carrionii*, *n*=2; *F. pedrosoi*, *n*=2) treated with terbinafine 500 mg daily for the first month followed by 250 mg daily were cured after 4–8 months of therapy without evidence of relapse at follow-up 6 months later. The total dosage of terbinafine ranged from 37.5 g to 60 g.

Alternate week and combination itraconazole and terbinafine for chromoblastomycosis caused by *Fonsecaea pedrosoi* in Brazil. Gupta AK, Taborda PR, Sanzovo AD. Med Mycol 2002; 40: 529–34.

Four patients with longstanding disease refractory to standard therapies were treated with alternate week and combination therapy with itraconazole (200–400 mg daily) and terbinafine (250–1000 mg daily). Combination therapy proved to be more effective and was well tolerated.

The authors suggest that combination therapy with itraconazole and terbinafine may be synergistic, with in vitro studies having already demonstrated this against other fungi. Larger studies are required to evaluate combination therapy with itraconazole and terbinafine. However, it must be noted that both drugs are expensive in endemic settings.

Chromoblastomycosis: a neglected tropical disease. Queiroz-Telles F. Rev Inst Med Trop Sao Paulo 2015; 57 (Suppl 19): 46–50.

Itraconazole, either as monotherapy or associated with other drugs or with physical methods, is the mainstay of treatment. More recently, photodynamic therapy has been successfully used in combination with antifungals.

A case of chromoblastomycosis caused by *Fonsecaea pedrosoi* successfully treated with itraconazole together with terbinafine. Xu-Cheng S, Xiang-Nong D, Zhi-Min X, et al. *Dermatol Ther* 2020; 10(2): 321–7.

A case report of chromoblastomycosis diagnosed in a 56-year-old man by fungal culture and gene sequencing as caused by *Fonsecaea pedrosoi*. The treatment advocated is combination therapy with itraconazole and terbinafine.

Second-Line Therapies

• Amphotericin B	D
• Flucytosine	D
• Posaconazole	D
• Voriconazole	E

Extensive chromoblastomycosis caused by *Fonsecaea pedrosoi* successfully treated with a combination of amphotericin B and itraconazole. Paniz-Mondolfi AE, Colella MT, Negrin DC, et al. *Med Mycol* 2008; 46: 179–84.

This report describes a case of extensive disease affecting almost all of the right lower leg of 22 years' duration that had 15 years of previous failed therapy consisting of ketoconazole and fluconazole. The patient then achieved clinical and mycological cure with amphotericin B (cumulative dose of 2150 g) in combination with itraconazole 100 mg twice daily for approximately 3 months, followed by a further 1 year of itraconazole 100 mg daily.

Combination of amphotericin B and terbinafine against melanized fungi associated with chromoblastomycosis. Deng S, Lei W, de Hoog GS, et al. *Antimicrob Agents Chemother* 2018; 62(6): e00270–18.

This in vitro study showed that a combination of amphotericin B and terbinafine have a synergistic effect against several dematiaceous fungi responsible for chromoblastomycosis. This combination may be an alternative for treatment in refractory disease.

Posaconazole treatment of refractory eumycetoma and chromoblastomycosis. Negroni R, Tobón A, Bustamante B, et al. *Rev Inst Med Trop Sao Paulo* 2005; 47(6): 339–46.

Study of 12 patients with eumycetoma or chromoblastomycosis that had failed to respond to standard therapies. They were given posaconazole 800 mg/day in divided doses for a maximum of 34 months. Clinical good response was reported in five of six patients with eumycetoma and five of six patients with chromoblastomycosis. Two patients were reported as having stable disease. Posaconazole was well tolerated throughout the long-term administration of the drug. It should be considered in patients who fail to respond to standard therapies.

Extensive long-standing chromomycosis due to *Fonsecaea pedrosoi*: three cases with relevant improvement under voriconazole therapy. Criado PR, Careta ME, Valente MY, et al. *J Dermatol Treat* 2011; 22: 167–74.

Three patients with longstanding (10, 20, and 21 years) and extensive disease refractory to previous therapy with itraconazole and terbinafine were treated with voriconazole 200 mg twice daily for 12 months. Clinical response was evident after 30–50 days,

but at the end of treatment despite significant clinical improvement, none of the patients achieved cure. All patients showed elevation of serum gamma-glutamyl transpeptidase during the treatment without clinical relevance, and a single patient developed visual abnormalities and tremors requiring dose reduction.

This is the first report on the use of voriconazole for chromoblastomycosis. The partial response may be attributed to the severity of the disease. The report suggests that voriconazole represents an option for extensive disease refractory to conventional treatment.

Chromoblastomycosis. Quieroz-Telles F, de Hoog S, Santos DW, et al. *Clin Microbiol Rev* 2017; 30: 233–76.

The best review available on this condition to date. A group of experts, most of whom are contributors to the evidence and the publications available so far, review all literature available on the disease and ensure we understand all epidemiology, distribution, clinical presentations, diagnostic technologies, and controversies about management of this neglected skin disease. It is a delight to read.

Third-Line Therapies (May Also Be Used in Combination with First- and Second-Line Therapies; They May Also Be First-Line for Small Lesions or If Systemic Treatment Is Contraindicated)

• Cryotherapy	B
• Surgical excision	D
• Thermotherapy	D
• Laser therapy	D
• Photodynamic therapy	D
• Combined	D

Treatment of chromomycosis by cryosurgery with liquid nitrogen: 15 years' experience. Castro LG, Pimentel ER, Lacaz CS. *Int J Dermatol* 2003; 52: 408–12.

This retrospective study included 22 patients with *F. pedrosoi*. Small lesions were frozen in a single session, whereas larger lesions were frozen in small parts. The average number of cryosurgery treatments that each patient received was 6.7 (range 1–22 sessions). Nine patients (40.9%) were considered cured (clinically disease-free period of at least 3 years), and eight patients (36.4%) were under observation (clinically disease-free but fewer than 3 years of follow-up). The rest failed to clear with treatment.

This study suggests high efficacy for cryosurgery therapy, and also suggests, as do other studies, that cryosurgery is a useful and inexpensive therapeutic option for small lesions.

Successful treatment of chromoblastomycosis with topical heat therapy. Tagami H, Ginosa M, Imaizumi S, et al. *J Am Acad Dermatol* 1984; 10: 615–9.

Four cases (*F. pedrosoi* isolated from three) were treated with topical application of tolerable heat from hand warmers. Three patients responded after 2, 3, and 6 months of treatment. The fourth patient, who received treatment in an irregular manner, cleared only after a 12-month period.

Cutaneous chromoblastomycosis effectively treated with local heat monotherapy. Huang TH, Lan CE. *Clin Exp Dermatol* 2019; 44: 461–2.

A case report of a 61-year-old man with a 7-year history of a plaque on the right forearm. The diagnosis of chromoblastomycosis was made on culture of *Fonsecaea* spp. Difficulties for treatment arose when the patient showed abnormal levels of liver

enzymes. Therefore, the decision was made to treat the patient with a disposable chemical hand warmer. This was applied to the lesion and held in place with a bandage for 8 h/day. Clinically complete remission was achieved after 8 weeks.

Chromomycosis – successful CO₂ laser vaporization. Tsianakas A, Pappai D, Basoglu Y, et al. J Eur Acad Dermatol Venereol 2008; 22(11): 1385–6.

Case report of a 45-year-old man with a plaque on the left buttock for 12 years. This was diagnosed as chromomycosis after *F. pedrosoi* was identified in culture. Patient had 1-month treatment with itraconazole 100 mg/day, which he discontinued after 1 month. Patient was successfully treated with CO₂ laser vaporization (wavelength 10,600 nm) with no complications on wound healing and no recurrence after 2 years of follow-up.

This type of intervention may only be suitable for localized lesions.

5-aminolevulinic acid-based photodynamic therapy associated with itraconazole successfully treated a case of

chromoblastomycosis. Yan W, Zhang W, Luo J, et al. Photodiagnosis Photodyn Ther 2020; 29: 101589.

Refractory cases of chromoblastomycosis are not uncommon and there is no optimal treatment for them. This is the case of a 71-year-old male farmer, who responded to this combination treatment after 2 months.

Topical application of imiquimod as a treatment for chromoblastomycosis. Texeira de Sousa M, Belda W Jr, Spina R, et al. Clin Infect Dis 2014; 58(12): 1734–7.

First report of treatment of chromoblastomycosis with imiquimod, which shows benefits in four patients. All patients were treated with imiquimod in combination with oral itraconazole either together at the start of therapy, or after no improvement of the condition with oral antifungals, including terbinafine, or initiated as monotherapy followed by itraconazole.

This study only shows the benefit of accelerating response to conventional antifungal drugs.

Chronic actinic dermatitis

Sally H. Ibbotson, Robert S. Dawe



Chronic actinic dermatitis (CAD) is a chronic dermatitis mainly involving photoexposed sites, which is associated with objective evidence of abnormal photosensitivity. The photosensitivity is usually broadband although predominantly involving the ultraviolet B (UVB) waveband and often extending into the ultraviolet A (UVA) and even visible wavebands. The condition is considered to have an immunological basis, and no specific genetic susceptibility has been identified. Typically, CAD affects elderly males, although in younger patients it is reported particularly in association with atopic dermatitis. It is increasingly recognized in females and in patients of higher skin phototypes. Most cases arise on the background of a dermatitis, such as atopic, seborrheic, or contact allergic dermatitis. In more than 75% of cases of CAD, patch testing is positive, confirming the association with contact allergic dermatitis. Patient and clinician may not be aware of the link with sunlight because of perennial symptoms and covered site involvement, leading to delays in diagnosis.

MANAGEMENT STRATEGY

Thus the essential first step of management is accurate diagnosis and exclusion of other conditions, such as photoaggravated eczema or reversible causes, particularly drug-induced photosensitivity. Phototesting is essential and the gold standard investigation is monochromator phototesting, allowing accurate definition of wavelengths involved (action spectrum) and the degree of photosensitivity.

Photoprotection is essential, with emphasis on *environmental and behavioral measures* (including use of window film to prevent all ultraviolet (UV) transmission and double-envelope compact fluorescent lamps or light-emitting diodes (LEDs) for those with severe photosensitivity; seeking out the shade and avoiding sunlight in the middle of the day), *clothing choices* (tightly woven and dark colors if visible wavelengths are involved), and high SPF fragrance-free sunscreens. Patient education to reduce exposure to *contact allergens* is also essential, as contact allergy tends to persist indefinitely, whereas photosensitivity can resolve over time.

Active disease should be treated with *emollients* and *topical corticosteroids*. With severe flares or erythroderma, admission to hospital may be required to allow the patient to be nursed behind photoprotective screens. *Systemic corticosteroids* may be required for acute flares and then tapered over weeks. *Treatment with photo(chemo)therapy* may be possible, although patients are usually too UVB sensitive to be able to tolerate UVB phototherapy, and, thus, psoralen-UVA (PUVA) may be more effective and better tolerated. If these measures are inadequate for disease control, systemic immunosuppression may be needed.

Specific Investigations

- Phototesting (with UVB, UVA, and visible light from monochromator or broadband sources)
- Provocation testing (with solar simulator or other broadband source)
- Patch and, if not too severely photosensitive to allow this, photopatch tests
- Consider concomitant disease

Comparison of demographic and photobiological features of chronic actinic dermatitis in patients with lighter v darker skin types. Tan KW, Haylett AK, Ling TC, et al. *JAMA Dermatol* 2017; 153: 427–35.

Chronic actinic dermatitis: changing trends. Fityan A, Cho S-Y, Plant A, et al. *Br J Dermatol* 2019; 181(S1): 99.

These reports from UK centers indicate that CAD is now less frequently seen as a disease of elderly males, with Tan et al., reporting on 70 patients, with mean age of onset of 42.6 years and 41% (much higher than in their catchment area population) being of skin phototype V or VI. There was younger onset in the higher skin phototype patients and also a 2:1 male to female ratio in the lower skin phototypes and 1:2 in those of higher skin phototype. The authors also found that 23% had positive photopatch tests to sunscreens and/or non-steroidal antiinflammatories. Fityan et al. reported on 110 cases of CAD, with a mean age of onset of 42.3 years and males and females equally represented. Again, there was overrepresentation of skin phototypes V and VI and most were atopic, particularly in younger patients.

A preliminary investigation into the effect of exposure of photosensitive individuals to light from compact fluorescent lamps. Eadie E, Ferguson J, Moseley H. *Br J Dermatol* 2009; 160: 659–64.

Energy-saving lamps and their impact on photosensitive and normal individuals. Fenton L, Ferguson J, Ibbotson S, et al. *Br J Dermatol* 2013; 169: 910–5.

Tungsten lamp and chronic actinic dermatitis. Hu SC, Lan CE. *Australas J Dermatol* 2017; 58: e14–6.

Is photodynamic diagnostic flexible ureterorenoscopy suitable for a patient presenting with chronic actinic dermatitis? Valentine R, Kata S, Ibbotson S, et al. *Photodermatol Photoimmunol Photomed* 2015; 31: 279–81.

Patients with CAD may be at risk from exposure to UV radiation from compact fluorescent ('energy-saving') lamps. They also can have severe visible light sensitivity (such as through window glass and exposure to a bright 'ordinary' tungsten source used for ear cleaning), may be at risk from exposure to a wide range of artificial light sources, and this should be investigated and considered in management approaches.

Contact allergic sensitivity to plants and the photosensitivity dermatitis and actinic reticuloid syndrome. Frain-Bell W, Johnson BE. *Br J Dermatol* 1979; 101: 503–12.

Contact and photocontact sensitization in chronic actinic dermatitis: sesquiterpene lactone mix is an important allergen. Menagé H, Ross JS, Norris PG, et al. *Br J Dermatol* 1995; 132: 543–7.

Case report of chronic actinic dermatitis accompanied by UVA sensitivity in a chrysanthemum farmer. Fujii S, Washio K, Masaki T. *J Dermatol* 2019; 46: e229–30.

This case highlights the importance of considering CAD in any patient with Asteraceae (Compositae) contact allergy.

A European multicenter photopatch test study. European Multicenter Photopatch Test Study (EMCPPTS) Taskforce. *Br J Dermatol* 2012; 166: 1002–9.

Photopatch testing: recommendations for a European photopatch test baseline series. Goncalo M, Ferguson J, Boneville A, et al. *Contact Dermatitis* 2013; 68: 239–43.

Contact and/or photocontact allergy is common in CAD. Standard allergens, including fragrances, plants, and sunscreens, must be considered. Patch and photopatch testing, repeated at intervals as indicated by history, are essential investigations in order not to 'miss' new allergens or photoallergens. Because many CAD patients are abnormally sensitive to the UVA sources used for photopatch testing, this technique may be difficult to undertake and interpret. However, photopatch testing with suberythral UVA doses should be undertaken where possible.

Contact and photocontact sensitization in chronic actinic dermatitis: a changing picture. Chew AL, Bashir SJ, Hawk JLM, et al. *Contact Dermatitis* 2010; 62: 42–6.

Be aware of changing allergen patterns with alteration in exposure over time. Paraphenylenediamine reactions in CAD may have increased.

Chronic actinic dermatitis in Asian skin: a Singaporean experience. Tan AW, Lim KS, Chong WS. *Photodermatol Photoimmunol Photomed* 2011; 27: 172–5.

Three of 26 Singaporean patients with CAD were positive for HIV.

Other case series have found even greater proportions of CAD patients to have HIV. This does not prove a cause-and-effect relationship and may not be specific to HIV, but the possible association should be considered.

First-Line Therapies

• Photoprotective measures	C
• Avoidance of relevant contact allergens	C
• Topical corticosteroids	C
• Topical emollients	C

Photodermatoses: environmentally induced conditions with high psychological impact. Rizwan M, Reddick CL, Bundy C, et al. *Photochem Photobiol Sci* 2013; 12: 182–9.

Depression, anxiety, and dermatology life quality index scores were assessed in 185 of 260 adult patients with photosensitivity diseases who returned questionnaires. Twenty-three percent showed evidence of anxiety and 7.9% depression, and particular risk factors were facial involvement and duration of photosensitivity. This study showed high levels of psychological comorbidity in patients with photosensitivity diseases.

Chronic actinic dermatitis: a retrospective analysis of 44 cases referred to an Australian photobiology clinic. Yap LM, Foley P, Crouch R, et al. *Australas J Dermatol* 2003; 44: 256–62.

Restriction of sunshine and allergen exposure, along with sunscreens and topical corticosteroids, gave relief in 36% of CAD patients. The remainder also required oral immunosuppressants or phototherapy.

Photosensitivity dermatitis/actinic reticuloid syndrome in an Irish population: a review and some unusual features. Healy E, Rogers S. *Acta Derm Venereol* 1995; 75: 72–4.

Of nine CAD patients treated with sunscreens, emollients, topical corticosteroids, and antigen avoidance, six responded well, two achieved complete remission, and four were controlled on topical corticosteroids alone, although five also required oral corticosteroids initially.

Protection against ultraviolet radiation by commercial summer clothing: need for standardised testing and labelling. Gambichler T, Rotterdam S, Altmeyer P, et al. *BMC Dermatol* 2001; 1: 6.

Summer clothing textiles ($n=236$) were investigated spectrophotometrically for their ultraviolet protection factors (UPF). Over 70% of wool and polyester, but less than 30% of cotton, linen, and viscose fabrics, had UPFs over 30.

Second-Line Therapies

• Azathioprine	A
• Ciclosporin	E
• Mycophenolate	E
• Hydroxycarbamide	E
• PUVA	D
• UVB	D
• Topical calcineurin inhibitors	B

Chronic actinic dermatitis. Paek SY, Lim HW. *Dermatol Clin* 2014; 32: 355–61.

If conservative management of CAD with photoprotection and topical therapies is insufficient, systemic immunosuppressants,

such as glucocorticoids, azathioprine, ciclosporin, or mycophenolate mofetil, may be effective.

Azathioprine treatment in chronic actinic dermatitis: a double-blind controlled trial with monitoring of exposure to ultraviolet radiation. Murphy GM, Maurice PD, Norris PG, et al. *Br J Dermatol* 1989; 121: 639–46.

Five of eight patients with CAD treated in this randomized trial had complete clinical disease remission within 6 months of azathioprine (150 mg/day) commencement. No useful clinical response was seen in 10 patients treated with placebo. It is not known whether azathioprine causes objective improvement in photosensitivity.

Azathioprine in dermatology: a survey of current practice in the UK. Tan BB, Gawkrödger DJ, English JSC. *Br J Dermatol* 1997; 136: 351–5.

A questionnaire survey of 253 UK dermatologists demonstrated that 68% use azathioprine in CAD, 66% alone, and the others as a steroid-sparing agent. Most used 100 mg daily, with only 13% prescribing it by body weight. CAD had the highest proportion of perceived efficacy (62%) of all disorders treated with azathioprine.

Severe chronic actinic dermatitis treated with cyclosporine: 2 cases. Paquet P, Piérard GE. *Ann Dermatol Venereol* 2001; 128: 42–5.

Two patients with CAD unresponsive to high-dose oral steroids responded well to oral ciclosporin (at a maximum daily dose of 4 mg/kg for 3 months), without significant adverse effects. One relapsed in summer when ciclosporin was stopped but the other patient was in remission for 3 years after drug cessation.

Chronic actinic dermatitis treated with mycophenolate mofetil. Thomson MA, Stewart DG, Lewis HM. *Br J Dermatol* 2005; 152: 784–6.

Two patients with CAD who had failed to respond to topical steroids, prednisolone, PUVA, azathioprine, and ciclosporin were treated with mycophenolate mofetil, resulting in improvement within 6 weeks and subsequent clearance, without adverse effects. Remission was maintained with a continuous mycophenolate mofetil dose of 500 mg BD in one patient and 1 g BD in spring and summer only in the other patient.

Chronic actinic dermatitis (photosensitivity dermatitis/actinic reticuloid syndrome): beneficial effect from hydroxyurea. Gramvussakis S, George SA. *Br J Dermatol* 2000; 143: 1340.

Hydroxycarbamide (previously called hydroxyurea) at 500–1000 mg/day induced remission of CAD in one patient.

Chronic actinic dermatitis: successful treatment with psoralen-ultraviolet A photochemotherapy. Chee SN, Novakovic L, Fassihi H, et al. *Br J Dermatol* 2018; 178: e189–90.

A retrospective study of 16 patients with CAD treated with oral (one topical 8-methoxypsoralen) PUVA found 63% achieved patient-reported efficacy, with two confirmed to have reduced photosensitivity on phototesting. A low fixed dose (starting with a test UVA exposure at 0.05 J/cm² and UVA dose increments of 0.05 J/cm² at each treatment as tolerated for those receiving

oral PUVA [8-methoxypsoralen 25 mg/m² or 5-methoxypsoralen 50 mg/m²]) using a twice-weekly regimen over 10 weeks was used (one patient had a more intensive three times a week regimen at a starting UVA dose of 1 J/cm²). Typically, PUVA was commenced in February, with topical corticosteroids applied after each treatment and oral prednisolone taken on treatment days if there were flares. PUVA was most effective in younger male patients of higher skin phototype and in those only sensitive to UVB on phototesting. Two patients who failed previous immunosuppressants did not respond to PUVA and, likewise, positive patch tests to metals also seemed to be predictive of a poor response to PUVA.

Evaluation of narrow band ultraviolet B phototherapy in the treatment of chronic actinic dermatitis in Chinese patients. Ma L, Zhang Q, Hu Y, et al. *Dermatol Therapy* 2017; 30(6). doi: 10.1111/dth.12528.

A total of 19 patients were treated with NB-UVB (mean 27 treatments) along with a parenteral corticosteroid: there was clinical and phototest improvement and after the course only 1/19 rather than 12/19 still required systemic immunosuppressants.

Chronic actinic dermatitis with leonine facies and iatrogenic adrenal insufficiency successfully treated with topical tacrolimus. Busaracome P, Wattanakrai P, Rajaraman N. *Case Rep Dermatol* 2011; 3: 49–54.

A case report of one patient with CAD who had been treated with systemic corticosteroids for almost 20 years, which resulted in secondary adrenal insufficiency. The patient was subsequently well controlled with topical tacrolimus and photoprotection.

Successful treatment of chronic actinic dermatitis with topical pimecrolimus. Larangeira de Almeida H. *Int J Dermatol* 2005; 44: 343–4.

Pimecrolimus can be considered as an alternative therapy.

No comparative studies have been reported. Potent topical corticosteroids should generally be favored over topical calcineurin inhibitors, but these newer topical immunomodulators are appropriate to consider for those with inadequate responses to topical corticosteroids.

Third-Line Therapies

• Hydroxychloroquine	D
• Etretinate	E
• Danazol	E
• Thalidomide	E
• Interferon	E
• Infliximab	E
• Dupilumab	E
• Colostrum-macrophage-activating factor	E

Chronic actinic dermatitis. An analysis of 51 patients evaluated in the United States and Japan. Lim HW, Morison WL, Kamide R, et al. *Arch Dermatol* 1994; 130: 1284–9.

Photoprotection and topical corticosteroids were useful in 51 patients with CAD. Azathioprine (50–200 mg/day) was also commonly helpful. PUVA and oral corticosteroids were beneficial in

seven patients, ciclosporin in four, and etretinate in two. Hydroxychloroquine (200 mg once or twice daily) achieved partial/good responses in nine patients.

Chronic actinic dermatitis responding to danazol. Humbert P, Drobacheff C, Vigan M, et al. *Br J Dermatol* 1991; 124: 195–7.

A patient with CAD with low α_1 -antitrypsin levels responded dramatically to danazol (600 mg/day for 3 weeks), relapsed on stopping, improved on restarting, and remained controlled 18 months later while still on the drug. Danazol raises low serum α_1 -antitrypsin and protease inhibitor levels, and a protease–anti-protease imbalance has been said to cause abnormal inflammatory responses in several dermatoses.

Recalcitrant chronic actinic dermatitis treated with low-dose thalidomide. Safa G, Piéto-Le Corvaisier C, Hervagault B. *J Am Acad Dermatol* 2005; 52: E6.

A patient with CAD resistant to PUVA, azathioprine, ciclosporin, and hydroxychloroquine responded dramatically to thalidomide (100 mg/day reduced to 50 mg twice weekly) over 5 months without adverse effect.

Actinic reticuloid: treatment with recombinant interferon alpha-2b. Trevisi P, Farina P, Borda G, et al. *G Ital Dermatol Venereol* 1993; 128: 327–31.

Natural α -interferon in chronic actinic dermatitis. Report of a case. Parodi A, Gallo R, Guarrera M, et al. *Acta Derm Venereol* 1995; 75: 80.

In one patient with CAD in whom ciclosporin had to be discontinued because of hypertension, natural α -interferon (3 MU three times per week) was effective.

Successful therapy of chronic actinic dermatitis with infliximab. Schopf RE, Poblete-Gutiérrez P. *Exp Dermatol* 2009; 18:

302 (abstract at 36th Annual Meeting of Arbeitsgemeinschaft Dermatologische Forschung, Heidelberg, 2009).

Infliximab infusions were associated with marked improvement in one patient who had not shown useful response to previous therapies, including topical corticosteroids, PUVA, and ciclosporin.

A case report of therapeutically challenging chronic actinic dermatitis. Verma L, Pratt M. *JCMS Case Reports* 2019; 7: 1–3.

This was a report of a patient with CAD, who failed to respond to or tolerate methotrexate, hydroxychloroquine, apremilast, and ciclosporin, who went on to have only partial response to dupilumab. This mirrors our own unpublished experience in two patients, whose atopic eczema improved on dupilumab, but photosensitivity and phototesting did not notably improve. It appears the photosensitivity is perhaps mediated by different pathways to the underlying atopic dermatitis, but further experience of its use in CAD is warranted as these are very early observations in small numbers of patients.

Dupilumab for the treatment of chronic actinic dermatitis. Patel N, Konda S, Lim HW. *Photodermatol Photoimmunol Photomed* 2020; 36: 398–400.

Clinical improvement was found in five patients. Only two had repeat phototesting: greatest improvement was to longer wavelengths than to UVB.

A case of chronic actinic dermatitis that responded completely to treatment with oral colostrum-macrophage-activating factor (colostrum-MAF). Ichihashi M, Nakamura Y, Muto M, et al. *Photodermatol Photoimmunol Photomed* 2019; 35: 290–2.

In keeping with a possible therapeutic role of immunomodulation in CAD, this is a case report of a 41-year-old man with presumed CAD, based on clinical picture and UVA sensitivity.

Coccidioidomycosis

Mahreen Ameen, Wanda Sonia Robles



Courtesy Julio Salas-Alanís, Instituto Dermatológico de Jalisco, Mexico

Coccidioidomycosis is an endemic systemic mycosis caused by inhalation of dimorphic fungi of the genus *Coccidioides* (*C. immitis* and *C. posadasii*). It is endemic in desert regions of the Southwestern United States and Central and South America. Primary pulmonary disease is usually subacute and self-limiting. The immunocompromised are particularly susceptible to chronic pulmonary disease. One percent progress to disseminated disease, and again those with impaired cell-mediated immunity are at greater risk. Coccidioidomycosis is an opportunistic infection with advanced human immunodeficiency virus (HIV) infection and CD4 counts less than 250. Solid-organ transplant recipients, patients with hematologic malignancies, and those on long-term immunosuppressants, including corticosteroids and TNF- α antagonists, are also at risk. Extrapulmonary hematogenous dissemination can affect almost any organ but most frequently involves the skin, lymph nodes, skeletal system, and meninges. Dissemination to the skin can give rise to ulcerative and verrucous lesions with a predilection for the nasolabial area. Subcutaneous abscesses, sinus tracts, and fistulae can develop as a result of coccidioidal infection in neighboring lymph nodes, bones, or joints. Other dermatological manifestations include erythema nodosum and erythema multiforme associated with primary pulmonary infection. Primary infection of the skin is rare.

Dermatologists should consider this diagnosis in patients with atypical skin lesions, pulmonary infiltrates, and a history of travel to endemic areas.

MANAGEMENT STRATEGY

Treatment depends on disease extent and predisposing factors. Those with primary pulmonary infection and no risk factors require only periodic assessments up to 2 years to ensure that the infection is self-limiting. Some clinicians, however, prefer to treat with oral azoles to prevent any risk of progression, although there are no trial data supporting this. Antifungal therapy is indicated for severe or chronic pneumonia, progressive or disseminated infection. *Fluconazole* (400–800 mg daily) and *itraconazole* (200–600 mg daily) are the initial options for most chronic pulmonary and disseminated infections. *Ketoconazole* (400 mg daily) shows comparable efficacy to the other azoles, but is associated with a higher risk of adverse effects with long-term use. Parenteral *amphotericin B* (AmB deoxycholate 0.5–1.5 mg/kg/day or lipid formulations of AmB 2.0–5.0 mg/kg/day) is recommended for those with severely acute infection with respiratory failure, those with rapidly progressive and disseminated infection, women during pregnancy, and those who fail azole therapy. Published reports of its use, however, are still limited to small numbers of patients treated in open-label studies. There have been no clinical trials assessing the efficacy of lipid formulations of AmB. Newly available antifungals, which may be used for refractory infection, include the *triazoles*, *posaconazole* and *voriconazole*, in vitro studies having demonstrated their efficacy. However, there have been no comparative studies evaluating their efficacy against azoles used for treating coccidioidomycosis. There are early reports, too, of the successful use of *caspofungin*, an echinocandin, although results of in vitro susceptibility studies have varied widely.

In addition to drug therapy, *surgery* is sometimes indicated for the removal of focal infection such as pulmonary cavities, focal osseous infection, or the debridement of soft tissue. *Long-term prophylaxis with azoles* is indicated for the immunocompromised, and meningeal infection requires lifelong azole therapy to prevent recurrence. Recovery from infection confers lifelong immunity and provides the rationale for ongoing development of a vaccine.

Primary cutaneous coccidioidomycosis: an update. Reyna-Rodríguez IL, Ocampo-Candiani J, Chavez-Alvarez S. *Am J Clin Dermatol* 2020; 21: 681–96.

The authors state that although a rare entity, primary cutaneous coccidioidomycosis appears to be increasing. They describe 82 cases, the majority of which were treated with first-line azoles. They also note that it has an excellent prognosis even without treatment.

Treatment considerations in pulmonary coccidioidomycosis. Hartmann CA, Aye WT, Blair JE. *Expert Rev Respir Med* 2016; 10(10): 1079–91.

This review discusses current literature regarding medical treatment options, including the various triazoles and AmB products. In addition, it discusses uncomplicated and complicated pulmonary infections and their sequelae and the approach to managing coccidioidomycosis in certain patient populations, such as pregnant women, transplant recipients, HIV-infected individuals, and recipients of TNF- α inhibitors.

Coccidioidomycosis. Infectious Diseases Society of America Guidelines. Galgiani JN, Ampel NM, Blair JE, et al. *Clin Infect Dis* 2016.

Management of early coccidioidal infections, which are the commonest clinical presentation; coccidioidal meningitis;

management of coccidioidomycosis in specific at-risk groups such as those with HIV; solid-organ transplants; and pregnancy are specifically addressed.

Specific Investigations

- Direct microscopy
- Culture
- Serological tests
- Imaging studies (chest and bone radiography)
- Serology for HIV/acquired immunodeficiency syndrome infection (where relevant)

The characteristic globular spherules may be seen in potassium hydroxide mounts of infected material: sputum, cerebrospinal fluid, or pus. Culture is the definitive method of establishing the diagnosis. *Coccidioides* spp. grow rapidly on most media within 5 days. In the mycelial form, the fungus is highly infectious, so cultures should be handled with care. Serological tests are useful and can be used to assess response to therapy.

First-Line Therapies

• Fluconazole	A
• Itraconazole	A

Tolerability of long-term fluconazole therapy. Davis MR, Nguyen MH, Donnelly MA, et al. J Antimicrob Chemother 2019; 74(3): 768–71.

This was a single-center, retrospective study investigating the tolerability of long-term (> 28 days) fluconazole in 124 adult patients with coccidioidomycosis. They were treated with fluconazole 100–1600 mg daily (the most commonly prescribed dose was 400 mg daily). The median duration of treatment was 147 days (interquartile range [IQR] 59–399 days); 51.6% experienced adverse effects. The most common adverse effects were xerosis (16.9%), alopecia (16.1%), and fatigue (11.3%). Two-thirds experiencing adverse effects required a therapeutic intervention such as dose reduction, discontinuation, or switch to a new antifungal. Patients experiencing adverse effects were prescribed higher total daily fluconazole doses (6.7 vs. 5.7 mg/kg; $p < 0.01$).

The authors report a relatively high rate of adverse effects in a real-world setting as opposed to clinical trials.

Fluconazole therapy for coccidioid meningitis. The NIAID Mycoses Study Group. Galgiani JN, Catanzaro A, Cloud GA, et al. Ann Intern Med 1993; 119: 28–35.

Uncontrolled clinical trial, which included 50 patients with coccidioid meningitis. Of these, 47 were evaluated: 25 had received no previous treatment, and nine were HIV positive. Of the 47 patients, 37 (79%) responded to treatment. Response rates were similar in patients whether they had received previous therapy or not.

Fluconazole demonstrates efficacy in the treatment of coccidioid meningitis.

Comparison of oral fluconazole and itraconazole for progressive, nonmeningeal coccidioidomycosis. A randomized, double-blind trial. Galgiani JN, Catanzaro A, Cloud GA, et al. Ann Intern Med 2000; 133: 676–86.

In this randomized, double-blind, placebo-controlled trial, 198 patients with pulmonary and non-meningeal infection were treated with either fluconazole 400 mg daily or itraconazole 200 mg twice daily. Overall efficacy rates at 12 months were similar (itraconazole, 63%; fluconazole 50%; $p = 0.8$). However, the response rate was higher in patients with bone disease treated with itraconazole (52% vs. 26%; $p = 0.05$). The rates of relapse were comparable (itraconazole, 18%; fluconazole, 28%; $p > 0.2$). Both drugs were well tolerated.

This is the first prospective, randomized trial comparing two different azole drugs for the treatment of an endemic mycosis. The results demonstrate that both itraconazole and fluconazole are effective therapies for non-meningeal coccidioidomycosis.

Second-Line Therapies

• Amphotericin B	B
• Ketoconazole	B

Evaluation of amphotericin B lipid formulations for treatment of severe coccidioidomycosis. Sidhu R, Lash DB, Heidari A, et al. Antimicrob Agents Chemother 2018; 62(7): e02293–17.

69 patients with severe coccidioidomycosis. Infections were treated with a standard intravenous dose of 5 mg/kg daily of either amphotericin B lipid complex (ABLC) or liposomal amphotericin B (L-AmB). Treatment duration varied depending on clinical responses. The median treatment period was 16 weeks for ABLC (IQR 6–23) and 16.5 weeks for L-AmB (IQR 10–24.25). Both were equally efficacious. L-AmB may have less renal toxicity than ABLC and may be the preferred agent in baseline renal impairment.

The availability of effective azoles and triazoles mean that amphotericins are generally only used for severe and widely disseminated infection.

Ketoconazole therapy of progressive coccidioidomycosis. Comparison of 400- and 800-mg doses and observations at higher doses. Galgiani JN, Stevens DA, Graybill JR, et al. Am J Med 1988; 84: 603–10.

In this trial involving 112 patients with progressive pulmonary, skeletal, or soft tissue infections, patients were randomized to receive either 400 mg or 800 mg daily of oral ketoconazole. Success rate was similar for the two groups (23.2% vs. 32.1% for low- and high-dose therapy). Side effects were significantly higher with high-dose therapy (66% vs. 38%). Relapse rates were also higher with high-dose therapy (52% vs. 11%), although it depended also on the organs involved. Treatment duration depended on clinical responses. The study concluded little or no benefit with high-dose ketoconazole for non-meningeal infection.

Third-Line Therapies

• Posaconazole	B
• Voriconazole	C
• Caspofungin	D
• Isavuconazole	E
• Adjunctive corticosteroids	B
• Adjunctive interferon- γ immunotherapy	E

Safety, tolerance, and efficacy of posaconazole therapy in patients with nonmeningeal disseminated or chronic pulmonary coccidioidomycosis. Catanzaro A, Cloud GA, Stevens DA, et al. Clin Infect Dis 2007; 45(5): 562–8.

In this multicenter trial, 20 patients with chronic pulmonary or non-meningeal disseminated coccidioidomycosis were treated with posaconazole 400 mg daily for up to 6 months (median 173 days). Seventeen (85%) patients had a satisfactory response to treatment ($\geq 50\%$ reduction in the Mycoses Study Group score from baseline). No serious adverse effects were reported. Paired baseline and end-of-treatment culture results for *Coccidioides* species were available for four patients, all of whom converted from being positive to being negative for *Coccidioides* species. Relapse was experienced by three of nine patients who did not receive antifungal therapy during the follow-up period.

Posaconazole therapy for chronic refractory coccidioidomycosis. Stevens DA, Rendon A, Gaona-Flores V, et al. Chest 2007; 132(3): 952–8.

This was an open-label multinational study, which included 15 patients with pulmonary ($n=7$) and disseminated ($n=8$) disease that was refractory to previous therapy, which included AmB with and without an azole. They were treated with posaconazole 800 mg daily in divided doses for 34–365 days (median 306 days). Seventy-three percent of patients (11/15) responded to treatment with cure in four patients. Treatment was very well tolerated.

Treatment of refractory coccidioidomycosis with voriconazole or posaconazole. Kim MM, Vikram HR, Kusne S, et al. Clin Infect Dis 2011; 53(11): 1060–6.

This was a retrospective study of all cases treated with either voriconazole 200 mg twice daily ($n=21$) or posaconazole 400 mg twice daily ($n=16$) in a single center. There was a 67% and 75% improvement after a median duration of 6 and 17 months of treatment with voriconazole and posaconazole, respectively.

The authors concluded that voriconazole and posaconazole are reasonable but not infallible options for salvage treatment of refractory coccidioidomycosis.

Use of the echinocandins (caspofungin) in the treatment of disseminated coccidioidomycosis in a renal transplant recipient. Antony S. Clin Infect Dis 2004; 39: 879–80.

Oral caspofungin monotherapy at a dose of 50 mg daily for 4 weeks was successfully used to treat this case of disseminated infection without meningeal involvement.

Treatment of pediatric refractory coccidioidomycosis with combination voriconazole and caspofungin: a retrospective case series. Levy ER, McCarty JM, Shane AL, et al. Clin Infect Dis 2013; 56(11): 1573–8.

A retrospective review of nine pediatric patients treated with combination intravenous voriconazole (7.5 mg/kg daily) and caspofungin (0.7 mg/kg daily) salvage therapy for refractory coccidioidomycosis after failing conventional therapy consisting of a triazole, AmB, or a combination of both. Eight of the nine patients achieved remission. Caspofungin was only added when patients failed to respond to voriconazole monotherapy. The mean treatment period with voriconazole was 6 months (range 2–13 months).

The dramatic response of two cases of persistent and progressive respiratory coccidioidomycosis to adjunctive corticosteroid therapy is described. One case had been treated with combination fluconazole and liposomal amphotericin for over 6 weeks, with persistent fever and pneumonia. The other was treated with fluconazole and then amphotericin for 3 weeks, with progression to acute respiratory distress syndrome and shock. Both recovered after receiving short courses of intravenous methylprednisolone: one patient received a 12-day course starting at 40 mg daily and reducing by 10 mg every 3 days; the other received 60 mg 4 times daily for 4 days only.

The authors concluded that addition of systemic corticosteroids might hasten recovery in patients with severe coccidioidomycosis where it treated ongoing destructive inflammation as opposed to hypersensitivity.

Two cases illustrating successful adjunctive interferon- γ immunotherapy in refractory disseminated coccidioidomycosis. Duplessis CA, Tilley D, Bavaro M, et al. J Infect 2011; 63(3): 223–8.

The authors report two cases of refractory coccidioidomycosis, which demonstrated improved responses with adjunctive IFN- γ .

IFN- γ augments the antifungal activity of effector immune cells against a variety of fungi. Adjunctive immunotherapy given with chemotherapy has the potential to improve host immune responses and facilitate complete eradication of pathogens.

Isavuconazole in the treatment of coccidioidal meningitis. Heidari A, Quinlan M, Benjamin DJ, et al. Antimicrob Agents Chemother 2019; 63(3): e02232–318.

This was a retrospective review of nine patients with coccidioidal meningitis treated with isavuconazole 200 mg daily for a mean treatment period of 504 days (range 274–810 days). The authors report treatment success in three patients and stable disease in six patients.

Patients with coccidioidal meningitis require lifelong antifungal therapy. In the case of insufficient antifungal efficacy or if there is a risk of cumulative toxicity, salvage therapy may be required. Isavuconazole may represent a useful antifungal in these circumstances.

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Condyloma acuminata

Ismael Maatouk



Arising from infection with human papillomavirus (HPV), predominantly types 6 and 11, anogenital warts (AGWs) are the most commonly diagnosed viral sexually transmitted infection. Annual AGW incidence is 1%–2%. Out of over 200 types of HPV, at least 40 infect the anogenital tract. Condyloma acuminata (CA), the classic form of AGWs, are associated with 'benign' HPV types 6 and 11 (up to 90%) but may also be caused by oncogenic types such as 16 and 18 (70% of all cervical cancer), 31, 33, and 35.

MANAGEMENT STRATEGY

AGWs are contagious, associated with slow spontaneous clearance, significant impact on the quality of life and healthcare costs, and, potentially, progression to in situ squamous cell carcinoma (erythroplasia of Queyrat in penile mucosa) or to transformation into squamous cell carcinomas and other invasive cancers (cervical, vaginal, vulvar cancer, etc.). It is essential to identify effective treatment strategies and appraise evidence from controlled studies.

In the absence of an 'anti-HPV' drug per se, current treatments focus on stimulation of the host's immune response to enhance virus recognition. Treatments are categorized as either patient-administered (i.e., *podophyllotoxin*, *imiquimod*, *sinecatechins*, and *5-fluorouracil cream*) or provider-administered (bi- or trichloroacetic acid [TCA] application, *podophyllin resin*, CO_2 laser, cryotherapy, surgery, electrosurgery, intramuscular prophylactic or intralesional therapeutic HPV vaccine). In the latter, reduction or clearance was achieved by a cross-protection (HPV L1 capsids) or a non-specific upregulation (aluminum-containing adjuvant's immunity) in prophylactic vaccines and by a cytotoxic response against papilloma-transformed cells in therapeutic vaccines.

Podophyllotoxin treatment consists of twice daily application for 3 days, followed by 4 days' rest, for 4–5 cycles. Supervision is recommended if total area is $>4\text{ cm}^2$. Repeat cycles may be used if lesions are responding. Imiquimod 5% activates dendritic cells (adaptive T-cell response). It is applied overnight and washed off 6–10 hours later, 3 times a week, for 16 weeks. Longer courses have been used without clear evidence. Other concentrations

(3.75%) have been approved by the US Food and Drug Administration (FDA) in 2010 and showed similar cure rates, similar patient compliance, and fewer side effects compared with 5%. Sinecatechin 15% extract of green tea (*Camellia sinensis*) contains epigallocatechin gallate, exhibiting antiviral, anti-tumor, and immunostimulatory properties. It is applied 3 times a day for 16 weeks. Other green tea-based ointments are available. 5-Fluorouracil cream is not recommended for routine management.

Provider-administered therapies are either topical or surgical. Topical modalities include podophyllin resin, bi- or TCA, intralesional bleomycin, and ingenol mebutate. TCA 80–90% is not recommended for large volumes and requires a weekly application in a specialist clinic setting only. Podophyllin resin is applied for 1–6 hours and is less effective on dry areas (penile shaft, scrotum, and labia majora). Intralesional interferon- α and bleomycin are also effective therapies. Surgical treatments include cryotherapy, surgical removal by tangential shave (cold knife or scissors), curettage with or without electrosurgery, and lasers (CO_2 and pulsed dye laser [PDL]). Cryotherapy causes thermolysis and necrosis of keratinocytes hosting HPV. Liquid nitrogen usually requires one or two freeze–thaw cycles per session for two or three sessions. Recurrence rates are up to 40%. As this is the most used therapeutic intervention, a meta-analysis to compare the efficacy and safety of cryotherapy concluded, with low-level quality of evidence, that no evidence supports cryotherapy superiority or inferiority when compared with TCA, imiquimod, or podophyllin (see later). Surgery and CO_2 lasers are useful for treating extensive giant (i.e., Buschke–Löwenstein tumor) intraurethral and recalcitrant warts. Excision and electrosurgery require local anesthetic and are useful for large volume warts and difficult anatomic sites. Several case reports mentioned imiquimod as a successful treatment of Buschke–Löwenstein. All electrosurgical and laser techniques may generate a plume of smoke, which contains HPV DNA, potentially infectious to the respiratory tract in the operating personnel. Therefore, masks should be worn during these procedures.

Estimates of clearance and recurrence rates with various therapies are difficult due to differences in method of analysis, patient population, and duration of follow-up. No available therapy can be guaranteed to clear AGWs without any recurrence. Combination therapy using an immunomodulator after physical ablative therapy reduces recurrence rates with risky adverse events.

The development of the three FDA-approved multivalent HPV vaccines have shown high efficacy for HPV prevention. Cervarix and Gardasil were the first vaccines for cervical cancer prevention. Cervarix targets types 16 and 18 (responsible for 70% of all cervical cancer), while Gardasil also adds activity against types 6 and 11 (cause 90% of AGWs). In addition to these four types, the 9vHPV vaccine contains type 31, 33, 45, 52, and 58 antigens. Vaccines are safe with minor adverse effects. They also protect against precancerous lesions caused (types 16 and 18) in a naïve population. They are available for both males and females, preferably before they become sexually active, and are being successfully implemented in many developed countries with different inclusion criteria.

During pregnancy, podophyllotoxin and 5-fluorouracil should be avoided (teratogenic). Imiquimod is not approved for use (no data). Treatment is not always warranted but aims at preventing vertical transmission. Caesarean section is not indicated as it has not been shown to prevent the neonatal exposure to the virus. Caesarean section is only indicated in case of gross cervical warts. For the newborn, the only serious (rare) complication is recurrent respiratory papillomatosis. Cryotherapy, excision, and ablative methods are safe in pregnancy.

Treatments in children and adolescents follow the same principles as in adults. Anoscopy and/or speculum examination are used to evaluate the anal canal, vagina, or cervix. Biopsy is indicated for atypical-looking and recalcitrant lesions or in immunocompromised patients. Sexual abuse should be suspected but is not systematic.

Immunocompromised people (organ transplant recipients or living with HIV) experience lower response and increased relapse rates. Treatment recommendations are not modified but longer courses may be required.

Specific Investigations

- Papanicolaou (Pap) smear
- HPV typing (not standard of care)
- Biopsy
- Acetic acid 3%–5%

Cytology versus HPV testing for cervical cancer screening in the general population. Koliopoulos G, Nyaga VN, Santesso N, et al. *Cochrane Database Syst Rev* 2017; 8: CD008587.

In primary cervical cancer screening, HPV tests are less likely to miss cases of cervical intraepithelial neoplasia (CIN) grade 2 or worse and lead to more unnecessary referrals. However, a negative HPV test is more reassuring than a negative cytological test, as the latter has a greater chance of false negative, which could delay appropriate treatment.

First-Line Therapies

• Imiquimod (5%, 3.75%)	A
• Podofilox (podophyllotoxin)	A
• Sinecatechin extract of green tea	A
• Cryotherapy	A
• Podophyllin	B

Imiquimod versus podophyllotoxin, with and without human papillomavirus vaccine, for anogenital warts: the HIPvac factorial RCT. Gilson R, Nugent D, Bennett K, et al. Southampton (UK): NIHR Journals Library; 2020 Sep (Health Technology Assessment, No. 24.47). <https://www.ncbi.nlm.nih.gov/books/NBK562414/>. <https://doi.org/10.3310/hta24470>.

A 2020 randomized, controlled trial (RCT) did not support earlier evidence of a lower recurrence with use of imiquimod than with use of podophyllotoxin. Podophyllotoxin without quadrivalent human papillomavirus vaccine is the most cost-effective strategy at the current vaccine list price.

Cryotherapy to treat anogenital warts in non-immunocompromised adults: systematic review and meta-analysis. Bertolotti A, Dupin N, Bouscarat F, et al. *J Am Acad Dermatol* 2017; 77: 518–26.

In this systematic review, cryotherapy efficacy did not appear to differ from that of TCA, podophyllin, or imiquimod. Electro-surgery was weakly associated with better AGW clearance than cryotherapy (risk ratio [RR] 0.80). Cryotherapy was associated with immediate low-level adverse events and immediate pain but fewer erosions.

Imiquimod for anogenital warts in non-immunocompromised adults. Grillo-Ardila CF, Angel-Müller E, Salazar-Díaz LC, et al. *Cochrane Database Syst Rev* 2014; 12: CD010389.

The benefits and harms of imiquimod compared with placebo should be regarded with caution due to the risk of bias. The evidence that shows imiquimod and patient-applied treatment (podophyllotoxin or podophyllin) have similar benefits but fewer systematic reactions with the imiquimod is of low, or very low, quality.

Imiquimod cream 2.5% and 3.75% applied once daily to treat external genital warts in men. Rosen T, Nelson A, Ault K. *Cutis* 2015; 96: 277–82.

Evaluation of imiquimod cream 3.75% or 2.5% or placebo once daily until complete clearance or maximum of 8 weeks was reported in a placebo-controlled study ($n=447$). Complete clearance was 18.6% in the 3.75% imiquimod group and 14.3% in the 2.5% imiquimod group (compared with 4% in placebo; $p<0.03$ for both dosages). Both groups were significantly superior to placebo. The FDA approved 3.75% imiquimod cream.

Self-administered interventions for anogenital warts in immunocompetent patients: a systematic review and meta-analysis. Werner RN, Westfechtel L, Dressler C, et al. *Sex Transm Infect* 2017; 93: 155–61.

Complete clearance (CC) of imiquimod 3.75% and 5% cream, and podophyllotoxin 0.5% solution and gel, were superior to placebo. CC of podophyllotoxin 0.15% cream was inferior to podophyllotoxin 0.5% solution (active-controlled trial). No significant differences existed between imiquimod 5% and podophyllotoxin 0.5%. Due to the limited comparisons, conclusions on the efficacy of the different treatments are restricted.

Second-Line Therapies

• Surgical excision (with cold knife or scissors)	B
• Lasers (CO ₂ and PDL)	B
• Loop electrosurgical excisional procedure	B
• Electrodesiccation (see also earlier)	B
• Trichloroacetic acid (see also earlier)	B
• HPV vaccination:	
• 0–2–6-month (intramuscular prophylactic)	A
• or once per week every 5 weeks for men and 6 weeks for women (intralesional therapeutic vaccine)	C

Complete resolution of chronic multiple verruca vulgaris treated with quadrivalent human papillomavirus vaccine. Daniel BS, Murrell DF. *JAMA Dermatology* 2013; 149(3): 370.

Six patients of different ages received intramuscular HPV vaccine for their recalcitrant multiple warts. Improvement was noticed within weeks without adverse reactions. The mechanism of action could include cross-protection (HPV L1 capsids) or, alternatively, the aluminum-containing adjuvant through non-specific immune upregulation. This alternative can be useful for resistant warts, including AGWs.

Regression of human papillomavirus intraepithelial lesions is induced by MVA E2 therapeutic vaccine. Rosales R, López-Contreras M, Rosales C, et al. *Hum Gene Ther* 2014; 25: 1035–49.

Intraepithelial lesions (uterus, urethra, vulva, or anus) of 1176 females and 180 males were directly injected with a recombinant vaccinia virus Ankara containing the bovine papilloma virus E2 protein (MVA E2). All males (one injection per week for 5 weeks) and 1051 (89.3%) females (one injection per week for 6 weeks)

showed complete histological elimination. A specific cytotoxic response against papilloma-transformed cells (antibodies against MVA E2) was observed. No side effects were reported.

Pulsed dye laser therapy in the treatment of warts: a review of the literature. Veitch D, Kravvas G, Al-Niaimi F. *Dermatol Surg* 2017; 43: 485–93.

A literature review showed that facial and AGWs demonstrated excellent outcomes with pulsed dye laser (PDL). Recalcitrant warts displayed significant variability in their response (50%–100%). Recurrence rates at 4 months of follow-up were documented as 0%–15%. Cost and availability of this treatment remain a limitation; however, this modality can be used when other treatments have failed.

Human papilloma virus type and recurrence rate after surgical clearance of anal condylomata acuminata. D'Ambrogio A, Yerly S, Sahli R, et al. *Sex Transm Dis* 2009; 36: 536–40.

Patients ($n=140$) with anal canal condylomas had surgery followed by cauterization. Recurrence rate was 25% after day 120 of follow-up. HPV type 11 was statistically associated with higher recurrence rates.

CO₂ laser therapy versus cryotherapy in treatment of genital warts; a randomized controlled trial (RCT). Azizjalali M, Ghaffarpour G, Mousavifard B. *Iran J Microbiol* 2012; 4: 187–90.

Patients ($n=160$) with genital warts were treated with CO₂ laser or cryotherapy. CC was achieved in 95% treated by CO₂ laser and 46.2% treated with cryotherapy ($p<0.001$). Laser therapy was associated with less recurrence compared with cryotherapy (0.05% vs. 0.18%).

Treating vaginal and external anogenital condylomas with electrosurgery vs. CO₂ laser ablation. Ferenczy A, Behelak Y, Haber G, et al. *J Gynecol Surg* 1995; 148: 9–12.

In 208 patients, the efficacy and adverse effects of loop electrosurgical excision procedure (LEEP) were similar to those associated with laser ablation. LEEP adverse events included bleeding and scarring. Scarring of the penis can result in dysfunction; therefore, most physicians prefer CO₂ laser ablation or cryotherapy for penile warts.

Third-Line Therapies

• Intralesional interferon- α	A
• Interferon- β gel	A
• Oral isotretinoin	B
• Intralesional fluorouracil/epinephrine gel	A
• Cidofovir	B
• Aminolevulinic acid (ALA)-photodynamic therapy	B
• Intralesional bleomycin	C
• Ingenol mebutate	C

Natural interferon alfa for treatment of condyloma acuminata. Friedman-Kien AE, Eron LJ, Conant M, et al. *JAMA* 1988; 259: 533–8.

In this double-blind, placebo-controlled trial, CC was 62% (with intralesional interferon- α injections twice weekly for up to 8 weeks) versus 21% (placebo). Combinations of interferon with cryosurgery, podophyllin, or laser ablation have been promising.

Treatment of condylomata acuminata with oral isotretinoin. Tsambaos D, Georgiou S, Monastirli A, et al. *J Urol* 1997; 158: 1810–2.

Oral isotretinoin 1 mg/kg daily for 3 months achieved complete response in 39.6% of 56 male patients with history of refractory AGWs. It may be considered in immature and small AGWs.

Topical cidofovir (HPMPC) is an effective adjuvant to surgical treatment of anogenital condylomata acuminata. Coremans G, Margaritis V, Snoeck R, et al. *Dis Colon Rectum* 2003; 46: 1103–8.

Patients were treated with repetitive electrocoagulations ($n=27$) (control) or cidofovir ($n=20$) 1% cream applied daily for 5 hours for 5 consecutive days per week, repeated weekly for up to 18 weeks or until CC. Lesions refractory to cidofovir were cleared up with additional coagulations. Complete and partial responses with cidofovir were 32% and 60%, respectively. The relapse rate was significantly lower in the cidofovir group (3.7% versus 55%).

Combined surgery and cidofovir is an effective treatment for genital warts in HIV-infected patients. Orlando G, Fasolo MM, Beretta R, et al. *AIDS* 2002; 16: 447–50.

An open, randomized prospective pilot study included 74 HIV-positive patients. They received for AGWs: surgery (S); surgical-cidofovir (SC) (5 days per week for 2 weeks within 1 month of cautery), or cidofovir (C) 1% gel (5 days per week for up to 6 weeks). Complete response was 93.1% in S, 76.2% in C, and 100% in SC (*significant*). After 6 months, recurrences were significantly lower in SC.

Evaluation of photodynamic therapy using topical aminolevulinic acid hydrochloride in the treatment of condylomata acuminata: a comparative, randomized clinical trial. Liang J, Lu XN, Tang H, et al. *Photodermatol Photoimmunol Photomed* 2009; 25: 293–7.

In a trial, 91 patients received ALA-PDT or CO₂ laser. Complete response was 95.93% and 100%, respectively ($p>0.05$). At week 12 of follow-up, 9.38% and 17.39% had recurrent lesions ($p<0.05$). Adverse reactions were 8.82% and 100%, respectively ($p<0.05$). Pain and cost of the treatment are still a great challenge for the therapy.

Preliminary study of intralesional bleomycin injection for the treatment of genital warts. Lee JY, Kim CW, Kim SS. *Ann Dermatol* 2015; 27: 239–41.

Fifteen patients with a total of 164 refractory genital warts were treated with intralesional bleomycin 1.5 mg/mL every 2 weeks until clearance. Clearance was achieved in 73.3%.

Ingenol mebutate gel is effective against anogenital warts – a case series in 17 patients. Schopf RE. *J Eur Acad Dermatol Venereol* 2016; 30: 1041–3.

Seventeen patients were treated with one to three applications of ingenol mebutate gel (500 or 150 mcg/g). Curative effect was achieved very rapidly in 76% of the cases after 3–35 days with complete response in 16/17 patients. Remission was maintained after up to 240 days. The main challenge for this therapy is irritation and lack of clinical trials.

COVID-19 dermatoses

Justine Fenner



COVID-19 RELATED RASHES IN ADULTS

Coronavirus disease 2019 (COVID-19) is an acute respiratory viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease first appeared in China in December 2019 and has since spread throughout the globe, officially being called a pandemic by the World Health Organization (WHO) in March 2020.

Much is still being learned about this disease as it continues to affect millions of people worldwide. Typical symptoms of COVID-19 are fever, chills, dry cough, sore throat, nausea, headache, and myalgias. The incubation period is believed to be on average between 2 and 14 days, with some studies reporting incubation periods as long as 19–27 days. The main mode of transmission is believed to be by droplets but fecal transmission and direct contact are other possible modes of transmission. Some patients experience anosmia and ageusia without any other symptoms. More severe cases can present with shortness of breath or severe respiratory distress. Older patients with comorbidities are at higher risk for complications including respiratory failure and multiorgan dysfunction.

Initial studies coming out of China reported low frequencies of skin manifestations. Since then further studies with greater involvement of dermatologists have demonstrated rash in as high as 20.4% of patients with COVID-19. The most frequently reported cutaneous manifestations are: (1) maculopapular/morbilliform; (2) chilblain-like; (3) vesicular; (4) urticarial; (5) livedoid; and (6) purpuric. The differential diagnosis of these rashes

depends on the morphology. For example, morbilliform, vesicular, and urticarial rashes could be due to other viral infections or a drug reaction. The main differential for chilblain-like rashes is pernio or chilblain lupus.

Cutaneous manifestations related to coronavirus disease 2019 (COVID-19): a prospective study from China and Italy. De Giorgi V, Recalcati S, Jia Z, et al. *JAAD* 2020 May 19 [Epub ahead of print].

In this multicenter, prospective study of 678 patients with COVID-19, 53 patients had new inflammatory skin findings, and 13 patients had new vascular skin manifestations. Diffuse petechiae, multiple/generalized purpura, and acroischemia were seen in more severe cases, whereas erythematous, vesicular, and urticarial rashes could not be correlated with disease severity.

Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Galván Casas C, Català A, Carretero Hernández G, et al. *Br J Dermatol* 2020; 183(1): 71–7.

Patients with a pseudo-chilblain presentation of COVID-19 tended to be younger with less severe disease while patients with livedoid/necrotic lesions were older with more severe disease.

MANAGEMENT STRATEGY

The best way to mitigate the effects of SARS-CoV-2 is to prevent its spread. In the setting of a pandemic, this means maintaining excellent hand hygiene, keeping 6 feet (2 m) apart from others when in public, and wearing a mask when this is not possible, as well as self-isolating/quarantining when appropriate. With the introduction of safe and effective vaccines, individuals who can be vaccinated against COVID-19 should receive the vaccine.

Often fever and respiratory symptoms in the setting of an epidemic allow for the clinical diagnosis of COVID-19 infection. If there is any question, reverse-transcription polymerase chain reaction (RT-PCR) of samples, such as nasal swabs, often establishes the diagnosis. Unfortunately, more needs to be learned about the sensitivity of this test as several studies using chest computed tomography (CT) scans have found the sensitivity of RT-PCR to be as low as 71%. In diagnosing COVID-19, CT scan can identify viral pneumonia, but cannot distinguish what specific virus is implicated. The presence of SARS-CoV-2 antibodies suggests prior infection, however more studies are needed to determine the sensitivity and utility of this test.

For mild cases of COVID-19 the therapy is *supportive care*. Supportive care includes *anti-pyretics* for fever in addition to *hydration*. More severe disease requires hospitalization and *supplemental oxygen* as needed. Skin findings are generally mild and resolve without specific therapy.

The cutaneous manifestations of COVID-19 infection are typically self-limited and resolve without intervention. *Antihistamines* are helpful for urticarial presentations; *systemic corticosteroids* are seldom needed for the maculopapular rash; topical steroids may be tried, especially if the eruption is pruritic; and anticoagulation with agents like *enoxaparin* may help the ischemic manifestations. For the chilblain-like changes called “COVID toes”, *topical nitroglycerin* preparations may be helpful.

Treatments for systemic complications of COVID-19 are still evolving or controversial and will not be covered in detail.

Laboratory abnormalities seen in COVID-19 include leukopenia, leukocytosis, and elevated CRP. While leukopenia is seen more

commonly, leukocytosis has been associated with a worse prognosis. Other laboratory abnormalities reported include elevated aspartate aminotransferase (AST) and elevated ESR. More severe cases have been associated with elevated levels of alanine transaminase, creatinine, lactate dehydrogenase (LDH), and prothrombin time. Additionally, the cytokine storm seen in severely ill patients results in elevated proinflammatory cytokines including interleukin (IL)-2, IL-6, IL-8, IL-10, interferon- γ , IL-1 β , tumor necrosis factor-alpha (TNF- α), and granulocyte colony stimulating factor.

Specific Investigations

- Reverse-transcription polymerase chain reaction
- CT scan when diagnosis is unclear or patient is ill
- Immunoassay to detect SARS-CoV-2 antibodies
- Chest X-ray when patient requires hospitalization
- Skin biopsy may be needed to rule out other diagnostic possibilities
- CBC, comprehensive metabolic panel, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), prothrombin time, D-dimer when patients are ill

What do we need to know to improve diagnostic testing methods for the 2019 novel coronavirus? Mustafa Z, Ghaffari M. *Cureus* 2020; 12: e8263.

This review discusses the various modes of testing for COVID-19, highlighting their value and limitations.

Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Ai T, Yang Z, Hou H, et al. *Radiology* 2020; 296: E32–E4 [Epub ahead of print].

In this study using RT-PCR as a reference, sensitivity of CT of the chest for COVID-19 was 97%. In the subgroup of patients who initially tested negative but went on to test positive by RT-PCR for COVID-19, 67% had positive chest CT findings before initial negative RT-PCR testing. This study highlights the high sensitivity of CT imaging in diagnosing COVID-19, especially in the early stages of disease.

Value of leukocytosis and elevated C-reactive protein in predicting severe coronavirus 2019 (COVID-19): a systematic review and meta-analysis. Yamada T, Wakabayashi M, Yamaji T, et al. *Clinica Chimica Acta* 2020; 509: 235–43.

In this study compiling data from 3278 patients with COVID-19, elevated white blood cell count (WBC) and CRP were associated with poor outcomes, while leukopenia was associated with a better prognosis.

Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Qin C, Zhou L, Hu Z, et al. *Clin Infect Dis* 2020 [Epub ahead of print].

This retrospective, single center study demonstrated that patients with severe COVID-19 had significantly elevated inflammatory cytokines including TNF- α , IL-2R, IL-6, IL-8, and IL-10 compared with non-severe cases.

First-Line Therapies

- Antipyretics (e.g. acetaminophen) **D**
- Supportive care/hydration **D**

Second-Line Therapies

- Enoxaparin and topical nitroglycerin 2% for COVID toes **E**
- Experimental therapies for COVID-19 infection continue to be developed and studied

Treatment of COVID-19 induced chilblains with topical nitroglycerin. Weingarten M, Abittan B, Rivera-Oyola R, et al. *Int J Dermatol* 2020; 59: 1522–4.

In this case series a patient with COVID-19 associated chilblains experienced rapid improvement of cutaneous symptoms after initiation of topical nitroglycerin 0.2% twice daily along with systemic enoxaparin therapy.

IDSA Guidelines on the treatment and management of patients with COVID-19. Bhimraj A, Morgan RL, Shumaker AH et al. *IDSA* 2021; Version 4.2.0.

This living guideline created by an expert panel of infectious diseases specialists, experts in public health and front-line physicians summarizes the therapeutic options for mild and severe COVID-19 infections.

PEDIATRIC MULTISYSTEM INFLAMMATORY SYNDROME

Preliminary evidence suggests that while children are as likely as adults to contract SARS-CoV-2, they are less likely to become symptomatic or develop severe disease. While there is less pediatric literature describing cutaneous findings in association with COVID-19 compared with the adult literature, there are case reports describing erythema multiforme, chilblain-like lesions, maculopapular, varioliform, and roseoliform eruptions in COVID-19 pediatric patients. More recently pediatric patients have been reported to present with an inflammatory syndrome similar to Kawasaki disease, macrophage activation syndrome, and toxic shock syndrome. While this multisystem inflammatory syndrome in children (MIS-C) is rare, its presentation is severe with end organ damage. Most patients present with fever, gastrointestinal symptoms, and mucocutaneous features including rash, conjunctivitis, and lip redness/swelling.

Mucocutaneous manifestations of multisystem inflammatory syndrome in children during the COVID-19 pandemic. Young TK, Shaw KS, Shah JK, et al. *JAMA Dermatol* 2021; 157: 207–12.

In this retrospective case series of 35 pediatric patients suspected of having MIS-C the most common cutaneous findings were conjunctival injection (n = 21), palmoplantar erythema (n = 18), lip hyperemia (n = 17), lip cracking (n = 13), periorbital erythema and edema (n = 7), strawberry tongue (n = 8), and malar erythema (n = 6). Less common findings were scarlatiniform eruptions (n = 5), morbilliform eruptions (n = 3), urticarial eruptions (n = 3), and reticulated eruptions (n = 3). Mucocutaneous findings were not associated with disease severity.

Multisystem inflammatory syndrome in children in New York State. Dufort EM, Koumans EH, Chow EJ, et al. *N Engl J Med* 2020; 383: 347–58.

Through descriptive analysis this group summarized the clinical findings of 99 suspected or confirmed MIS-C cases in New

York between March 1 and May 10, 2020. They found that 100% of patients presented with subjective fever or chills, 80% had gastrointestinal symptoms, 60% had rash, 56% had conjunctival injection, and 27% had mucosal changes.

MANAGEMENT STRATEGY

The WHO and Centers for Disease Control and Prevention (CDC) have each created their own recommended diagnostic criteria requiring fever, laboratory evidence of inflammation, and evidence of COVID-19. The main difference between the two criteria is that the WHO is more specific in the features required for diagnosis, requiring two of the following: (1) rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation; (2) hypotension or shock; (3) features of cardiac dysfunction; (4) evidence of coagulopathy; or (5) acute gastrointestinal problems, while the CDC requires evidence of dysfunction of any two organ systems.

A range of immunomodulatory medications have been used to treat pediatric multisystem inflammatory syndrome associated with COVID-19 including intravenous immunoglobulin (IVIG), aspirin, steroids, anakinra, infliximab, and tocilizumab. Remdesivir has also been used. Additionally, some patients have recovered with supportive care alone. The American College of Rheumatology recommends first line treatment of hospitalized patients with MIS-C with IVIG. Methylprednisolone should be added in patients with shock or organ threatening disease.

Specific Investigations

- CBC, ESR, CRP, ferritin, comprehensive metabolic profile, lipid profile
- Procalcitonin levels, urinalysis
- Fibrinogen, D-dimer, IL-1, IL-6, IL-8, TNF- α levels
- Troponin 1, creatinine kinase-MB, N-terminal pro-B-type natriuretic peptide
- Echocardiogram at 0, 2, and 6 weeks

Pediatric COVID-19: systematic review of the literature. Patel N. Am J Otolaryngol 2020; 41: 102573.

In this systematic review of pediatric patients with COVID-19, without multisystem inflammatory syndrome, median lab values for WBC, lymphocyte count, and CRP were within reference range. Procalcitonin levels were slightly elevated. These findings are notably different from adults with COVID-19.

Multisystem inflammatory syndrome in children (MIS-C) related to COVID-19: a New York City experience. Riollano-Cruz M, Akkoyun E, Briceno-Brito E, et al. J Med Virol 2020 June 25 [Epub ahead of print].

Retrospective chart review in which all patients had elevation of CRP, D-dimer, IL-6, and IL-8. Lymphopenia was found in 87%

of patients and thrombocytopenia was found in 40% of patients. Interestingly, TNF- α was only minimally elevated in 73% of patients and no patients had elevated IL-1.

Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. Whittaker E, Bamford A, Kenny J, et al. JAMA 2020 June 8 [Epub ahead of print].

This case series of 58 children from eight hospitals in England divided the patients into three groups in order to make comparisons: (1) patients with persistent fever and elevated inflammatory markers without features of Kawasaki disease, shock, or organ failure; (2) patients who fulfilled diagnostic criteria for Kawasaki disease; and (3) patients with shock or evidence of myocardial injury. Patients who developed shock had higher CRP, neutrophil count, troponin, and N-terminal pro-B-type natriuretic peptide as well as lower albumin and lymphocyte count. Laboratory findings between children who developed coronary artery dilatation or aneurysms were not significantly different from those without coronary artery abnormalities.

First-Line Therapies

- IVIG and low-dose aspirin
- Methylprednisone in patients with shock or organ threatening disease

Second-Line Therapy

- Anakinra or methylprednisolone

Kawasaki-like multisystem inflammatory syndrome in children during the COVID-19 pandemic in Paris, France: prospective observational study. Toubiana J, Poirault C, Corsia A, et al. BMJ 2020; 369: 2094.

In this case series all 21 children met criteria for either Kawasaki disease or incomplete Kawasaki disease. All 21 patients received IVIG and low-dose aspirin. Seven patients also received steroids. Five patients were resistant to the first IVIG dose, with four of those patients also receiving a second dose of steroids. All patients were discharged home with no deaths.

American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: Version 2. Henderson LA, Canna SW, Friedman KG, et al. Arthritis Rheumatol 2021; 73: e13-e29.

These guidelines, designed by experts in rheumatology, infectious diseases, cardiology and cytokine storm-related syndromes, offer a diagnostic pathway for MIS-C as well as an algorithm for immunomodulatory treatment of MIS-C.

Cryopyrin-associated periodic syndrome (CAPS)

Margaret A. MacGibeny, Edward W. Cowen



Cryopyrin-associated periodic syndrome (CAPS) is a rare autosomal dominantly-inherited autoinflammatory disease characterized by urticarial rashes, conjunctivitis, fever, fatigue, articular involvement, and inflammation, which may be triggered by cold exposure in some patients. It encompasses a spectrum of mild-to-severe conditions including familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID). Left untreated, patients with severe involvement may develop sensorineural hearing loss, visual loss, chronic meningitis, and amyloidosis. CAPS is caused by gain-of-function mutations in the *NLRP3* gene, which lead to inappropriate *NLRP3* inflammasome activation and overproduction of interleukin-1 β (IL-1 β). New nomenclature for CAPS was recently proposed to incorporate FCAS, MWS, and NOMID under one name, *NLRP3*-associated autoinflammatory disease (*NLRP3*-AID), with mild, moderate, and severe phenotypic subtypes.

MANAGEMENT STRATEGY

Early diagnosis and aggressive treatment of CAPS are essential to prevent organ damage, and early symptoms may be reversible if treatment is commenced expediently. Symptoms may be present from birth or may not become apparent until childhood or early adulthood. Diagnosis is complicated by the fact that, even if molecular genetic analysis of *NLRP3* is performed, mutations cannot always be demonstrated. However, high-throughput sequencing has identified somatic mosaic *NLRP3* mutations in some 'mutation-negative' patients, including adults with late-onset CAPS symptoms. Evidence-based criteria were proposed in 2019 for the classification of CAPS based on clinical symptoms with or without genetic analysis (Table 48.1).

Table 48.1 Criteria for CAPS classification

With genetic analysis

Confirmatory *NLRP3* mutation plus at least one symptom:^{*}
or Non-confirmatory *NLRP3* mutation plus at least two symptoms:^{*}

- Urticarial rash
- Red eye (conjunctivitis, episcleritis, uveitis)
- Sensorineural hearing loss

With unknown genetics

At least two of five symptoms:^{*}

- Urticarial rash
- Cold/stress-triggered episodes
- Sensorineural hearing loss
- Chronic aseptic meningitis
- Skeletal abnormalities (epiphyseal overgrowth/frontal bossing)

^{*}Must have recurrent disease symptoms (≥ 6 months), elevated acute phase reactants (C-reactive protein [CRP]/serum amyloid A [SAA]) during at least one flare, and exclusion of confounding disease (i.e., infection, neoplasm, autoimmune condition, inborn errors of immunity).

CAPS is ideally managed by a multidisciplinary team with expertise in autoinflammatory disease. Patients should have access to genetic counseling, psychosocial support, hearing aids, orthotic aids, and physiotherapy. The mainstay of medical management is pharmacologic blockade of IL-1.

Three IL-1 blockers are currently used to treat CAPS: *anakinra*, *canakinumab*, and *rilonacept*. All are administered as subcutaneous injections. Anakinra is a recombinant IL-1 receptor antagonist; canakinumab is a human monoclonal antibody targeting IL-1 β and has a much longer half-life than anakinra; and rilonacept is a fusion protein consisting of the binding domains of the IL-1 receptor and its accessory protein linked to the Fc portion of human IgG1. All three drugs currently have US Food and Drug Administration (FDA) approval for use in CAPS, whereas only anakinra and canakinumab are approved by the European Medicines Agency (EMA).

Side effects associated with IL-1 blockers include injection-site reactions and increased risk of infection. Most injection-site reactions occur within the first 6 months of treatment and are generally mild and resolve over a period of weeks without requiring discontinuation of treatment. Headaches and arthralgia may also occur. Live vaccines are not recommended during IL-1 blockade.

The primary treatment target is complete remission, and the dosing of IL-1 blockers should be individually adjusted using a treat-to-target strategy. Anakinra is given at a starting dose of 1–2 mg/kg/day in adults and children but can be escalated based on phenotypic severity and clinical response. Doses as high as 5–8 mg/kg/day have been required in some children. Anakinra is currently FDA approved for patients of all ages with NOMID.

Canakinumab dosing is also weight-based but given every 8 weeks, starting at 150 mg (> 40 kg) or 2 mg/kg (15–40 kg); some patients require dose escalation up to 8 mg/kg every 8 weeks. Canakinumab is currently FDA approved for patients 4 years and older with MWS and FCAS.

Rilonacept is initiated with a loading dose of 320 mg (adults) or 4.4 mg/kg (children), followed by weekly injections of 160 mg (adults) or 2.2 mg/kg (children). It is FDA approved for patients 12 years and older with MWS and FCAS.

During symptomatic flares, short courses of non-steroidal anti-inflammatory drugs (NSAIDs) or oral corticosteroids may be used as adjunct therapy in association with IL-1 blockers. However, monotherapy with NSAIDs or oral corticosteroids is not recommended due to the potential disease-modifying effect of IL-1 blockers. Treatment with tocilizumab, a monoclonal antibody targeting the IL-6 receptor, has led to symptomatic improvement in isolated CAPS patients as monotherapy (initiated prior to CAPS diagnosis) or when used as adjunct therapy with IL-1 blockers. Evidence supporting the efficacy of tocilizumab for CAPS is currently lacking.

Specific Investigations

- Skin biopsy of urticarial rash will show characteristic scattered dermal neutrophilic infiltrate without vasculitis
- C-reactive protein (CRP) and serum amyloid A (SAA) to determine systemic inflammatory activity
- Genetic testing for *NLRP3* mutation to confirm diagnosis (mutation may not be apparent by Sanger sequencing in some patients due to mosaicism)
Autoinflammatory disease panels are available from multiple genetic testing labs

Monitoring

- Full physical examination, urine testing for proteinuria, audiogram, and ophthalmologic examination

In severe disease consider:

- Cognitive testing
- Radiologic imaging (brain, inner ear, skeletal)
- Lumbar puncture

Consensus proposal for taxonomy and definition of the autoinflammatory diseases (AIDs): a Delphi study. Ben-Chetrit, E, Gattorno M, Gul A, et al. *Ann Rheum Dis* 2018; 77: 1558–65.

Revision of autoinflammatory diseases nomenclature by an international expert committee after systematic literature review. The proposed name for CAPS is *NLRP3*-associated autoinflammatory disease.

Classification criteria for autoinflammatory recurrent fevers. Gattorno M, Hofer M, Federici S, et al. *Ann Rheum Dis* 2019; 78: 1025–32.

Consensus report of evidence-based criteria for classifying hereditary recurrent fever syndromes, including CAPS. Criteria were developed by an international consensus committee after systematic literature review, statistical analyses, and cross-sectional validation on 1018 patients randomly selected from the Eurofever Registry.

Consensus protocols for the diagnosis and management of the hereditary autoinflammatory syndromes CAPS, TRAPS, and MKD/HIDS: a German PRO-KIND initiative. Hansmann S, Lainka E, Horneff G, et al. *Pediatr Rheumatol* 2020; 18: 17.

Consensus evidence-based treat-to-target therapeutic guidelines for autoinflammatory diseases, including CAPS, developed by an expert committee.

Late-onset cryopyrin-associated periodic syndromes caused by somatic *NLRP3* mosaicism – UK single center experience. Rowczenio DM, Gomes SM, Aróstegui JI, et al. *Front Immunol* 2017; 8: 1410.

Retrospective cohort study of eight patients with CAPS onset at median age of 50 years, who were *NLRP3* mutation-negative by Sanger sequencing but found to have somatic *NLRP3* mutations by amplicon-based deep sequencing. All patients responded to anakinra therapy with improvement of end organ function in four patients.

First-Line Therapies

• Anakinra	B
• Canakinumab	A
• Rilonacept	A

Sustained response and prevention of damage progression in patients with neonatal-onset multisystem inflammatory disease treated with anakinra: a cohort study to determine 3- and 5-year outcomes. Sibley CH, Plass N, Snow J, et al. *Arthritis Rheum* 2012; 64: 2375–86.

Observational open-label study of 26 patients (22 children and 4 adults) with NOMID receiving anakinra over 3–5 years. Dose escalation was described in some patients. Damage progression in the eye, ear, and CNS was prevented, but bony lesions progressed.

Long-term safety profile of anakinra in patients with severe cryopyrin-associated periodic syndromes. Kullenberg T, Löfqvist M, Leinonen M, et al. *Rheumatology* 2016; 55: 1499–506.

Prospective open-label study of 43 patients (36 children, 7 adults) with severe CAPS treated for up to 5 years, in which 14 patients experienced 24 serious adverse events, such as pneumonia and gastroenteritis, all of which resolved during the study period and did not result in discontinuation of the drug. Continued anakinra treatment during infective episodes did not appear to complicate their course and prevented complications of CAPS.

Use of canakinumab in the cryopyrin-associated periodic syndrome. Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, et al. *N Engl J Med* 2009; 360: 2416–25.

Randomized, double-blind, placebo-controlled withdrawal study after an open run-in period demonstrated 34 of 35 patients aged 4–75 years with CAPS associated with an *NLRP3* mutation had complete response to treatment. Disease flares occurred in 13 of 16 patients receiving placebo, whereas all 15 patients who received canakinumab remained in remission during the withdrawal phase of the study.

Rapid and sustained long-term efficacy and safety of canakinumab in patients with cryopyrin-associated periodic syndrome ages five years and younger. Brogan PA, Hofer M, Kuemmerle-Deschner JB, et al. *Arthritis Rheumatol* 2019; 71: 1955–63.

Prospective open-label, extension study of 17 patients ages 5 years and younger (6 patients under 2 years) with all types of CAPS who received canakinumab for up to 152 weeks. A complete response was achieved in 94% of patients within 56 weeks and in 100% of the patients within 72 weeks. Dose titration was required in patients with more severe phenotypes. Severe adverse events, such as pneumonia and bronchitis, were experienced by 47% of patients during the extension study, none of which resulted in discontinuation of treatment.

Efficacy and safety of rilonacept (interleukin-1 trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. Hoffman HM, Throne ML, Amar NJ, et al. *Arthritis Rheum* 2008; 58: 2443–52.

In the first study, 47 patients with *NLRP3* mutations and symptoms of CAPS underwent a 6-week trial of weekly 160-mg rilonacept injections versus placebo in a randomized, double-blinded trial. A second study followed, which consisted of 9 weeks of single-blind treatment plus a 9-week double-blind, randomized withdrawal. Of the patients who received rilonacept, 87% achieved at least 50% reduction in key symptom score versus 8% who received placebo.

Long-term efficacy and safety profile of rilonacept in the treatment of cryopyrin-associated periodic syndromes: results of a 72-week open-label extension study. Hoffman HM, Throne ML, Amar NJ, et al. Clin Ther 2012; 34: 2091–103.

A total of 101 patients were studied, including 44 of the 47 patients who were involved in the phase III studies described earlier. All had *NLRP3* gene mutations. The improvements seen after 6 weeks of treatment with rilonacept were sustained for up to 96 weeks after treatment, with persistence of biomarker normalization for up to 48 weeks after treatment.

Second-Line Therapies	
• NSAIDs	D
• Oral corticosteroids	D

Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review. Ter Haar N, Lachmann H, Özen S, et al. Ann Rheum Dis 2013; 72: 678–85.

Analysis of 94 patients with CAPS on the Eurofever Registry found that NSAIDs and corticosteroids were beneficial in 19/24 and 25/36 patients already receiving IL-1 blockers. Four patients receiving NSAIDs alone showed partial response, and one was reported to have complete response. One patient had partial response to corticosteroids alone. Two patients had partial response to NSAIDs and corticosteroids.

Third-Line Therapy	
• Tocilizumab	E

The first case series of cryopyrin-associated periodic syndrome in Korea. Han JH, Je YJ, Yoon HJ, et al. Allergy Asthma Immunol Res 2019; 11: 583–8.

Case series of three Korean patients with CAPS. Tocilizumab monotherapy, initiated prior to genetic testing, led to symptomatic improvement and CRP normalization in a 4-year-old male.

Cryptococcosis

Wanda S. Robles, Mahreen Ameen



Cryptococcosis is a systemic mycosis acquired most commonly by the respiratory route with the primary focus of infection in the lungs. It is caused by yeasts associated with avian excreta of which there are two species: *Cryptococcus neoformans* and *Cryptococcus gattii*. These two species can further be classified into three varieties and five serotypes. *C. neoformans* is classified into serotype A and D and the hybrid strain AD. *C. gattii* is classified into serotype B and C. It was considered that *C. neoformans* was distributed worldwide, whereas *C. gattii* was restricted to tropical and subtropical areas. More recently it has been recognized that the latter has been responsible for outbreaks in new geographical environments including temperate climates. In the past it was a relatively uncommon disease. However, it has become more common over the past decades with the increase of the immunocompromised population, though it may also affect the immunocompetent host. Susceptible individuals include HIV/AIDS patients, organ transplant recipients, cancer patients, and other immunosuppressed patients for other conditions, including those on biologic interventions. Pulmonary and central nervous system infections are by far the most common. Pulmonary disease can be asymptomatic and self-limiting. Hematogenous dissemination is responsible for involvement of other organs including the central nervous system, causing meningitis. Skin lesions are seen in 10%–15% of cases and produce a variety of them, including flesh-colored or erythematous papules and nodules as well as subcutaneous abscesses. In the immunocompromised, molluscum contagiosum-like and acneiform lesions occur, particularly on the face. Cryptococcal cellulitis with necrotizing vasculitis can mimic bacterial cellulitis and is more common in the immunocompromised patient.

With the global emergence of AIDS the incidence of cryptococcosis increased and it is considered the most common invasive mycosis in advanced HIV infection. In this cohort of patients, the infection is characteristically widespread, affecting the lungs, meninges, skin, bone marrow, and genitourinary tract, including the prostate. Certainly, the use of highly active antiretroviral therapy (HAART) has dramatically improved the outcome of cryptococcosis in HIV-infected patients. Immune restoration and low serum cryptococcal antigen titers are associated with lower cryptococcosis relapse rates. However, a subset of HIV-infected

individuals started on HAART is at risk of immune reconstitution inflammatory syndrome (IRIS)-associated cryptococcosis that can be severe. In developing countries with limited access to HAART, the morbidity and mortality associated with cryptococcosis remains very high. Both *C. neoformans* and *C. gattii* can cause cryptococcosis in the immunocompetent host. However, the percentage of *C. gattii* infections is significantly higher in this population than *C. neoformans*. Other predisposing factors in addition to HIV/AIDS infection include malignancies, autoimmune diseases, biologic therapies, use of systemic steroids and/or immunosuppressive therapies, solid organ transplantation recipients, chronic pulmonary or liver disease, diabetes mellitus, renal failure, and/or peritoneal dialysis.

MANAGEMENT STRATEGY

Cryptococcal infection left untreated is fatal. Treatment depends on disease extent and predisposing factors, particularly AIDS or any other immunosuppressive state. The recommended treatment in the immunocompetent individual with symptomatic non-meningeal infection is fluconazole 200–400 mg daily for 3–6 months. An alternative is itraconazole 200–400 mg daily for 6–12 months. More severe non-meningeal infection is treated with amphotericin B (AmB), either lipid formulation or deoxycholate, for 6–10 weeks. Meningeal infection in the immunocompetent or non-HIV immunocompromised is treated with AmB 0.7–1.0 mg/kg daily plus 5-flucytosine (5-FC) 100 mg/kg daily for 2 weeks followed by fluconazole 400 mg daily for a minimum of 10 weeks (up to 6–12 months depending on the clinical status of the patient).

Cryptococcal disease with HIV always requires treatment. For non-disseminated infection, fluconazole 400 mg daily is given. Itraconazole 20–400 mg daily, voriconazole 200–400 or posaconazole 400–800 mg daily are good alternatives in the immunocompetent. More severe infection is treated with a combination of fluconazole 400 mg daily and 5-FC 100–150 mg/kg daily for 10 weeks followed by fluconazole maintenance therapy 200 mg daily. Cryptococcal meningitis with HIV is treated with AmB 0.7–1.0 mg/kg daily and 5-FC 100 mg/kg daily for a 2- to 10-week induction period followed by itraconazole maintenance therapy or alternatively with fluconazole 400–800 mg daily and 5-FC 100–150 mg/kg daily for 6 weeks. The lipid formulation of AmB can be used instead in those with impaired renal function.

Dexamethasone as adjunctive therapy did not reduce mortality in HIV-associated cryptococcal meningitis.

Specific Investigations

- Direct microscopy
- Culture
- Cytology and histopathology
- Serology
- Pulmonary and brain imaging studies
- Serology for HIV

India ink examination of cerebrospinal fluid (CSF), pus, skin scrapings, and other fluids may demonstrate the yeast. Culture of skin, CSF, blood, sputum, urine, or bone marrow enables confirmation. *C. neoformans* is difficult to visualize with routine hematoxylin and eosin stains, requiring the use of special stains. Histopathological staining of centrifuged CSF sediment allows a sensitive and rapid diagnosis of cryptococcal meningitis. The gold standard diagnostic test for serological diagnosis of cryptococcosis is the detection of cryptococcal capsular polysaccharide

antigen in serum or body fluids by a latex agglutination technique. It is considered both sensitive and specific. The detection of cryptococcal antibodies has not been adopted for the diagnosis of cryptococcosis.

Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Perfect JR, Dismukes WE, Dromer F, et al. Clin Infect Dis 2010; 50: 291–322.

These are the latest updated guidelines available. They emphasize that control of host immunity, the site of infection, antifungal drug toxicity, and underlying disease are still the most critical factors for the successful treatment of cryptococcosis. The management strategy for cryptococcal disease is organized under four major headings with additional subdivisions: treatment of meningoencephalitis (in HIV-infected individuals, transplant recipients, and others); treatment of non-meningeal cryptococcosis (pulmonary and extrapulmonary sites); complications during treatment (including IRIS and relapse); and cryptococcosis in special clinical situations (pregnancy, children, resource-limited regions, and *C. gattii* infections).

The recommended treatment for immunosuppressed and immunocompetent patients with mild-to-moderate non-meningeal cryptococcosis is fluconazole 400 mg daily for 6–12 months. The treatment of choice for patients with HIV infection and cryptococcal meningitis is induction therapy with parenteral AmB 0.7–1.0 mg/kg daily plus oral flucytosine 100 mg/kg daily for 2 weeks followed by fluconazole 400 mg daily for a minimum period of 8 weeks. Amphotericin B in lipid formulation can be used for patients with renal impairment. It is recommended that all HIV-infected individuals receive prophylaxis against cryptococcosis and that this is continued for life. Fluconazole 200 mg daily is given or itraconazole 200 mg twice daily in those unable to tolerate fluconazole.

First-Line Therapies

• Amphotericin B (AmB)	B
• AmB plus 5-flucytosine	B
• Fluconazole	B

Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomized trial. Brouwer AE, Rajanuwong A, Chierakul W, et al. Lancet 2004; 363: 1764–7.

This controlled trial assessed the fungicidal activity of the combination of AmB, 5-FC, and fluconazole for the treatment of cryptococcal meningitis. Sixty-four patients with a first episode of HIV-associated cryptococcal meningitis were randomized to initial treatment with AmB (0.7 mg/kg daily); AmB plus 5-FC (100 mg/kg daily); AmB plus fluconazole (400 mg daily); or triple therapy with AmB, flucytosine, and fluconazole. Results demonstrated that clearance of cryptococci from the CSF was exponential and significantly faster with AmB and flucytosine dual therapy than with any other drug combination.

Successful use of amphotericin B lipid complex in the treatment of cryptococcosis. Baddour LM, Perfect JR, Ostrosky-Zeichner L. Clin Infect Dis 2005; 40: S409–13.

The efficacy and renal safety of AmB lipid complex (ABLC) were assessed in 106 patients, 83 (78%) of whom had CNS infection. Twenty-seven received concomitant azole therapy. Sixty-six percent of evaluable patients (67/101) achieved clinical response (cured or improved). Response rates with and without

CNS infection were 65% (51/78) and 70% (16/23), respectively, and for patients with HIV infection it was 58% (30/52). A mean serum creatinine level decrease of 0.02 mg/dL occurred. ABLC was an effective treatment for cryptococcal infection in immunocompromised patients.

Treatment of cryptococcosis in the setting of HIV coinfection. Khawcharoenporn T, Apisarnthanarak A, Mundy LM. Expert Rev Anti Infect Ther 2007; 5: 1019–30.

This review discusses evidence-based treatment algorithms that exist for the use of antifungal drugs, as well as the importance of maintaining normal intracranial pressure in HIV-infected hosts with cryptococcal meningitis. It suggests that further studies are required for the management of refractory infection, cryptococcosis-related immune reconstitution syndrome, and the role of adjuvant therapies. Primary and secondary prevention strategies remain at the crux of global control strategies for cryptococcal disease.

High-dose amphotericin B with flucytosine for the treatment of cryptococcal meningitis in HIV-infected patients: a randomized trial. Bicanic T, Wood R, Meintjes G, et al. Clin Infect Dis 2008; 47: 123–30.

In this study from South Africa, 64 HIV-seropositive, antiretroviral therapy-naïve patients with a first episode of cryptococcal meningitis were randomized to receive either AmB 0.7 mg/kg/day plus flucytosine 25 mg/kg four times daily ($n=30$) or AmB 1 mg/kg daily plus flucytosine 25 mg/kg four times daily ($n=34$). Both regimens were given for 2 weeks followed by oral fluconazole. The primary outcome measure was early fungicidal activity determined by CSF cryptococcal cultures. Early fungicidal activity was significantly greater for the first regimen. The 10-week mortality rate was 24% with no difference between groups.

Cutaneous cryptococcosis in solid organ transplant recipients. Sun HY, Alexander BD, Lortholary O, et al. Med Mycology 2010; 48: 785–91.

Fluconazole and lipid formulation AmB were used to treat localized and disseminated disease, respectively. The outcomes in both groups were comparable.

This study described cutaneous cryptococcosis representing disseminated infection in transplant recipients with preferential involvement of the extremities.

Cryptococcosis. Marziarz EK, Perfect JR. Diag Treat Fungal Inf 2015:175–93.

A highly comprehensive review of cryptococcosis that highlights the fact that infection may occur in the immunocompetent host as well the immunocompromised, a population that is expanding and will continue to expand with availability of new therapies with direct impact on the immune system. Therefore, they argue that cryptococcosis will remain a very important opportunistic fungal infection, particularly of the immunocompromised population.

Cryptococcal infections in non-HIV-infected patients. Pappas PG. Trans Am Clin Climatol Assoc 2013; 124: 61–79.

This is a very good review that stresses the differences in the epidemiology, clinical features, treatment, and outcome between HIV-infected patients (knowledge acquired over the last 3 decades) and non-HIV-infected hosts with cryptococcosis. It includes a review of an outbreak of *C. gattii* reported in the Pacific Northwest of the USA and Canada affecting mainly immunocompetent individuals.

Cryptococcosis. Zavala S, Baddley JW. *Semin Respir Crit Care Med* 2020; 41: 69–79.

This comprehensive review article highlights the importance of early diagnosis as it is now well recognized that cryptococcal infection occurs not only in the immunocompromised, but also in the immunocompetent host. It also reviews the mainstay of treatment, which continues to be amphotericin B preparations plus 5-flucytosine for cryptococcal meningitis, moderate-to-severe lung disease, and disseminated infection, followed by fluconazole as consolidation therapy.

Integrated therapy for HIV and cryptococcosis. Srichatrapimuk S, Sungkanuparph S. *AIDS Res Ther* 2016; 13: 42.

This study highlights the three aspects of treatment of cryptococcosis aiming to decrease mortality caused by the disease in HIV-infected patients. These include antifungal therapy, management of intracranial pressure in cryptococcal meningitis, and antiretroviral therapy to restore immune function. In terms of antifungal treatment, it advocates the use of a combination of two drugs, either amphotericin B plus flucytosine or fluconazole for the induction phase, and fluconazole monotherapy for consolidation and maintenance phases. It also stresses the importance of delaying the start of antiretroviral therapy until 5 weeks after starting antifungal drugs in HIV patients with cryptococcal meningitis and the safety of the combination of the two treatments, as drug interactions between antiretroviral drugs and AmB, flucytosine, and fluconazole are minimal.

Second-Line Therapies

- Itraconazole **C**
- Voriconazole **C**

The efficacy of fluconazole 600mg/day versus itraconazole 600mg/day as consolidation. Mootsikapun P, Chetchotisakd P, Anunnatsiri S, et al. *J Med Assoc Thai* 2003; 86: 293–8.

In this trial, HIV-infected patients with primary cryptococcal meningitis who had been treated with AmB preparations for 2 weeks were randomized to receive either fluconazole 600mg daily or itraconazole 600mg daily for 10 weeks. The results demonstrated equal efficacy of both regimens. In addition, the results suggested that the higher dose regimen may be superior to treatment regimens using lower doses of these medications.

Voriconazole treatment for less-common, emerging, or refractory fungal infections. Perfect JR, Marr KA, Walsh TJ, et al. *Clin Infect Dis* 2003; 36: 1122–31.

A multicenter, controlled clinical trial to assess the efficacy, tolerability, and safety of voriconazole as salvage treatment for patients with refractory and intolerant-to-treatment fungal infections, as well as primary treatment for patients with infections for which there is no approved treatment. The efficacy rate for voriconazole in the treatment of cryptococcosis was 38.9%. Voriconazole was reported to be well tolerated, and discontinuation of treatment was observed in less than 10% of patients.

Third-Line Therapies

- Dexamethasone **A**
- Recombinant interferon-gamma 1b **A**

Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. Beardsley J, Wolbers M, Kibengo FM, et al. *N Engl J Med* 2016; 374: 542–54.

A double-blind, randomized, placebo-controlled trial. This trial was stopped for safety reasons and after enrollment of 451 patients. Mortality was reported as 47% in the dexamethasone group and 41% in the placebo group by 10 weeks. The study concluded that dexamethasone did not reduce mortality among patients with HIV-associated cryptococcal meningitis. It was indeed associated with more adverse events and disability than placebo.

Recombinant interferon-gamma 1b as adjunctive therapy for AIDS-related acute cryptococcal meningitis. Pappas PG, Bustamante B, Ticona E, et al. *J Infect Dis* 2004; 189: 2185–91.

This was a phase II, double-blind, placebo-controlled study to evaluate the safety and antifungal activity of adjuvant recombinant interferon (rIFN)-gamma (γ) 1b in patients with AIDS and acute cryptococcal meningitis. Patients received 100 or 200 mcg of rIFN-γ 1b or placebo thrice daily for 10 weeks, plus standard therapy with AmB, with or without flucytosine, followed by fluconazole. Among 75 patients, 2-week culture conversion occurred in 13% of placebo recipients, 36% of rIFN-γ 1b (100 mcg) recipients, and 32% of rIFN-γ (200 mcg) recipients. There was evidence of improved combined mycologic and clinical success in rIFN-γ 1b recipients (26% vs. 8%; $p = 0.078$), and therapy was well tolerated.

Cutaneous candidiasis and chronic mucocutaneous candidiasis

Caroline Halverstam, Steven R. Cohen



Courtesy of Christos Zouzias.

CUTANEOUS CANDIDIASIS

Cutaneous candidiasis is typically caused by *Candida albicans*, which exists as normal flora of human skin as well as in the gastrointestinal and genitourinary systems. Overgrowth of *Candida* species is suppressed by normal bacterial flora. Other *Candida* species occasionally cause mucocutaneous infections, the second most common being *Candida tropicalis*. Under certain conditions, these *Candida* species overgrow and become pathogens. Warmth and moisture of the intertriginous skin (axilla, inguinal folds, abdominal creases, inframammary creases, finger or toe webs), an increased skin pH, and the administration of antibiotics can disrupt the normal bacterial flora, allowing *Candida* to proliferate. Clinically, candidiasis presents as scaly, erythematous patches with satellite papules and pustules. The diagnosis is made either microscopically, with a potassium hydroxide (KOH) preparation revealing spores and pseudohyphae, or by culture.

MANAGEMENT STRATEGY

Topical antifungal agents include, but are not limited to, polyenes, azoles, allylamines, and ciclopirox olamines. Most studies

required therapy twice daily for 4 weeks to ensure complete clearance in all patients. Notably, microscopic cure was often present before complete clinical clearance.

Topical corticosteroids are a source of controversy. Although the addition of corticosteroids to local antifungal therapy may reduce local inflammation in acute candidiasis, their use should be limited because of their immunosuppressant properties.

Systemic therapy may be appropriate for cutaneous infections in immunosuppressed patients, in the setting of extensive disease not responding to topical therapy, or in patients who are non-adherent to topical therapy. Fluconazole 150mg weekly appears to be as efficacious as fluconazole 50mg daily. As in topical therapy, microscopic cure often precedes complete clinical clearance. Since 2013, the Food and Drug Administration (FDA) has removed the indication for oral ketoconazole to be used in *Candida* and dermatophyte infections due to the risk of severe hepatotoxicity and adrenal insufficiency.

Specific Investigations

- KOH
- Culture

First-Line Therapies

• Topical antifungal	A
• Topical antifungal combined with topical corticosteroids	A

The efficacy and safety of sertaconazole cream in diaper dermatitis. Bonifaz A, Tiredo-Sánchez A, Graniel MJ, et al. Mycopathologia 2013; 175: 249–54.

Twenty-seven patients with a clinical and mycologic diagnosis of *Candida* diaper dermatitis were treated twice daily for 2 weeks with sertaconazole. Eighty-nine percent of patients showed a clinical and mycologic cure by the end of 4 weeks (2 weeks after treatment ended).

A multicenter, open-label study to assess the safety and efficacy of ciclopirox topical suspension 0.77% in the treatment of diaper dermatitis due to *Candida albicans*. Gallup E, Plott T. J Drugs Dermatol 2005; 4: 29–34.

A multicenter, open-label study that included 44 male and female subjects aged 6–29 months with diaper dermatitis due to *C. albicans*. The study medication was applied topically to the affected area twice daily for 1 week. The results showed a statistically significant improvement in both the rate of mycologic cure and the reduction of severity score.

Naftifine cream in the treatment of cutaneous candidiasis. Zaia N, Astorga E, Cordero CN, et al. Cutis 1988; 42: 238–40.

In a double-blind, parallel-group clinical trial, 60 patients with cutaneous candidiasis were randomly assigned to receive naftifine cream 1% or its vehicle twice a day for 3 weeks. Two weeks after the end of therapy, 77% of the naftifine-treated patients were mycologically cured (negative results on KOH preparations and culture) and had no clinically apparent disease, compared with only 3% of patients treated with vehicle alone.

A comparison of nystatin cream with nystatin/triamcinolone acetone combination cream in the treatment of candidal inflammation of the flexures. Beveridge GW, Fairburn E, Finn OA, et al. Curr Med Res Opin 1977; 4: 584–7.

In a multicenter, double-blind trial, 31 patients with bilateral candidal lesions of the flexures were treated for 14 days with nystatin cream on one side and with a combination of nystatin and triamcinolone acetonide cream on the other side. Both treatments proved equally effective in terms of mycologic cure rate and clinical improvement. There was a weak trend by both patients and physicians to favor the combination preparation because symptoms resolved more rapidly.

Second-Line Therapy

- Systemic azoles

B

Prospective aetiological study of diaper dermatitis in the elderly. Foureur N, Vanzo B, Meaume S, et al. *Br J Dermatol* 2006; 155: 941–6.

Of 46 patients, all over 85 years of age with dermatitis of the diaper area, 24 were identified as candidiasis. Of these, eight (33%) were cured after 1 month of topical bifonazole therapy, three (12.5%) improved, and 13 (54%) were cured after the addition of oral fluconazole 100 mg once daily for 1 month. Although topical antifungal drugs represent the first line of treatment for diaper dermatitis in the elderly, more than half the patients in this study required an oral antifungal to achieve a complete cure.

A comparison of the efficacy of oral fluconazole, 150 mg/week versus 50 mg/day, in the treatment of tinea corporis, tinea cruris, tinea pedis, and cutaneous candidosis. Nozickova M, Koudelkova V, Kulikova Z, et al. *Int J Dermatol* 1998; 37: 703–5.

Patients received either fluconazole 150 mg/week or 50 mg/day until clinically cured or for a maximum of 4 weeks. Of the patients in this study with candidiasis, 10 of 11 patients receiving fluconazole 150 mg weekly had a positive response (microscopic cure with marked clinical improvement) and 12 of 13 taking fluconazole 50 mg daily had a positive response. Thus weekly treatment was determined to be equivalent to daily dosing.

Clinical trials and double-blind studies of oral antifungals for cutaneous candidiasis are sparse.

Third-Line Therapies

- Lavender oil
- Topical mupirocin

E

C

Antifungal activity of *Lavandula angustifolia* essential oil against *Candida albicans* yeast and mycelial form. D'Auria FD, Tecca M, Strippoli V, et al. *Med Mycol* 2005; 43: 391–6.

The antifungal activity of the essential oil of *Lavandula angustifolia* (lavender oil) and its main components, linalool and linalyl acetate, was studied. Lavender oil showed both fungistatic and fungicidal activity against *C. albicans* strains.

Perianal candidosis: a comparative study with mupirocin and nystatin. De Wet PM, Rode H, Van Dyk A, et al. *Int J Dermatol* 1999; 38: 618–22.

This clinical trial compared the efficacy and clinical outcome of 2% mupirocin in a polyethylene glycol base and nystatin cream for the treatment of diaper candidiasis. Eradication of all *Candida* organisms was achieved within 2–6 days (mean 2.6 days) in 10 patients receiving topical mupirocin therapy (three to four times

daily or with each diaper change). The 10 patients who received topical nystatin cream successfully cleared within 5 days (mean 2.8 days). Although both agents eradicated *Candida*, a major difference was the marked response of the diaper dermatitis to mupirocin, presumably due to its well-documented bactericidal effects. The authors conclude that mupirocin is an excellent antifungal agent and a superior therapy for diaper dermatitis because of its polymicrobial toxicity.

CHRONIC MUCOCUTANEOUS CANDIDIASIS

Chronic mucocutaneous candidiasis (CMC) is a heterogeneous group of disorders with progressive and recurrent infections of the skin, nails, and mucosal surfaces caused by *C. albicans*. The clinical presentation in patients with CMC can range from recurrent or recalcitrant thrush with a mild rash and dystrophic nails to severe, generalized, crusted plaques. It usually presents in childhood unless it is caused by an underlying disorder such as human immunodeficiency virus (HIV) or diabetes mellitus.

About half of those affected are identified as having autoimmune polyendocrinopathy, candidiasis, and ectodermal dysplasia (APECED), an autosomal recessive disorder. APECED is caused by mutations in the *AIRE* gene, which plays a key role in immunotolerance. It is characterized by multiorgan autoimmunity, including hypoparathyroidism, hypothyroidism, and adrenal or gonadal failure. Malabsorption, gastric cell atrophy, or autoimmune hepatitis occurs in about a third of patients. Alopecia, vitiligo, dental enamel dysplasia, and keratitis are frequent associations. *Candida* susceptibility in APECED is most likely due to autoantibodies directed against IL-17 and IL-22.

Autosomal dominant CMC has been associated with mutations in the *STAT1* gene that lead to defective Th1 and Th17 responses. Thymoma has been also associated with rare cases of IL-17 and IL-22 autoantibody-positive CMC.

MANAGEMENT STRATEGY

Once the symptom complex etiology is confirmed with a positive culture for *C. albicans*, a workup should test for immunodeficiency. Patients should also be tested for endocrine dysfunction characteristic of APECED. If clinical suspicion for APECED is high, genetic analysis for the *AIRE* gene can be performed. An association of CMC with abnormalities in iron metabolism or thymoma has also been reported in adult patients, so iron and radiologic studies may be warranted in HIV-negative patients with adult-onset CMC.

Treatment usually begins with an oral azole, most commonly fluconazole 100–200 mg/day. Intermittent use is sometimes advocated to prevent resistance. However, resistance in CMC patients to first-line drugs is frequent, and alternative options include second-generation azoles such as voriconazole and posaconazole, as well as echinocandins such as caspofungin and micafungin. Oral ketoconazole should be avoided because of the risk of hepatotoxicity and adrenal insufficiency. Amphotericin B can be administered orally with variable response but minimal side effects. Due to toxicity, intravenous amphotericin B should generally be limited to short treatment courses with a transition to alternative therapies. Relapse after withdrawal of these agents is the rule because the inherent immune defect remains.

There have been anecdotal reports of patients improving with Janus kinase (JAK) inhibitors (both reports have been in patients with *STAT1* mutations) and cimetidine in combination with zinc.

Specific Investigations

- Complete blood count with differential
- HIV-antibody test
- Thyroid-stimulating hormone
- Fasting blood glucose
- Plasma cortisol level
- Parathyroid hormone
- Serum calcium
- Serum iron and ferritin
- Chest X-ray or computed tomography (CT) scan if thymoma suspected
- Genetic testing for *AIRE* gene if suspicion of APECED

Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. Kisand K, Boe Wolff AS, et al. *J Exp Med* 2010; 207: 299–308.

Patients with APECED were found to have severely reduced IL-17F and IL-22 responses to *C. albicans* antigens.

STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. van der Veerdonk FL, Plantinga TS, Hoischen A, et al. *N Engl J Med* 2011; 365: 54–61.

DNA sequencing identified missense mutations in *STAT1*.

First-Line Therapy

- Systemic azole antimycotics **D**

Fluconazole in the management of patients with chronic mucocutaneous candidiasis. Hay RJ, Clayton YM. *Br J Dermatol* 1988; 119: 683–4.

Eight patients with CMC (five idiopathic cases, three APECED cases) and oral candidiasis were treated with 50 mg of fluconazole daily for up to 4 weeks. Clinical and mycologic remissions were achieved in all patients after a mean of 10 days. Three patients relapsed within 4 months (mean 56 days), but all responded to fluconazole 50 mg daily for 3 days. The authors suggest intermittent oral antifungal therapy as the most appropriate method to manage patients with oral candidiasis in CMC after induction of remission.

Itraconazole in the treatment of two young brothers with chronic mucocutaneous candidiasis. Tosti A, Piraccini BM, Vincenzi C. *Pediatr Dermatol* 1997; 14: 146–8.

Two children with CMC involving the mouth and nails were successfully treated with itraconazole 200 mg/day for 2 months. A rapid cure rate of both infections was observed. No relapses of oral or nail candidiasis were identified at a follow-up examination more than a year later. The drug was very well tolerated.

Voriconazole: a broad spectrum triazole for the treatment of serious and invasive fungal infections. Maschmeyer G, Haas A. *Future Microbiol* 2006; 1: 365–85.

This is an excellent review of voriconazole (a second-generation triazole) for treating life-threatening fungal infections. Voriconazole can be given intravenously (6 mg/kg every 12 hours for two doses and then 4 mg/kg every 12 hours for maintenance dosing) or orally (200 mg every 12 hours for individuals over 40 kg and 100 mg every 12 hours for individuals less than 40 kg). It is

effective for fluconazole-susceptible and fluconazole-resistant candidiasis.

Although transient visual disturbances, liver enzyme abnormalities, skin cancers, and skin rashes are reported, these rarely lead to discontinuation of treatment.

Successful treatment of chronic mucocutaneous candidiasis caused by azole-resistant *Candida albicans* with posaconazole. Firinu D, Massidda O, Lorrain MM, et al. *Clin Dev Immunol* 2011; 4: Article ID 283239.

A 39-year-old female patient with familial CMC who developed candidiasis that was resistant to multiple antifungal drugs was successfully treated with amphotericin B 50 mg/day intravenously for 2 weeks followed by posaconazole 400 mg twice daily. After 2 months, the dose was reduced to 200 mg/day without a relapse. When posaconazole was discontinued, oral candidiasis recurred after 2 weeks. Thereafter, the patient was maintained successfully on cycles of posaconazole 200 mg, three times per day, for a month alternating with 15 days off-drug.

Second-Line Therapies

• Echinocandins	E
• Oral amphotericin B	D
• Intravenous amphotericin B	E

Activity of amphotericin B, anidulafungin, caspofungin, micafungin, posaconazole, and voriconazole against *Candida albicans* with decreased susceptibility to fluconazole from APECED patients on long-term azole treatment of chronic mucocutaneous candidiasis. Rautemaa R, Richardson M, Pfaller MA, et al. *Diagn Microbiol Infect Dis* 2008; 62: 182–5.

A total of 43 isolates of *C. albicans* were taken from 23 patients with APECED and tested for resistance to various antifungals. Isolates were divided into two groups: fluconazole-susceptible dose-dependent and fluconazole-susceptible groups. All isolates were highly susceptible to amphotericin B and echinocandins. Posaconazole and voriconazole were active against all isolates, but more active in the fluconazole-susceptible group, suggesting a possibility that patients may develop some cross-resistance to these drugs when they take fluconazole.

Successful treatment of azole-resistant chronic mucocutaneous candidiasis with caspofungin. Jayasinghe M, Schmidt S, Walker B, et al. *Acta Derm Venereol* 2006; 86: 563–4.

An 18-year-old woman with CMC developed severe symptoms from an azole-resistant strain of *C. albicans* after 3 years of treatment with fluconazole. After a 70-mg loading dose of intravenous caspofungin on the first day, the regimen was adjusted to 50-mg infusions four to seven times per week for almost 12 months. Clinical improvement of oral and cutaneous candidiasis was sustained during a follow-up period of 12 months. The treatment was well tolerated; the only side effect was a temporary elevation of hepatic enzyme levels that did not necessitate discontinuation of therapy.

Prolonged oral treatment of chronic mucocutaneous candidiasis with amphotericin B. Montes LF, Cooper MD, Bradford LG, et al. *Arch Dermatol* 1971; 104: 45–56.

Amphotericin B was given orally to four patients with CMC in doses of 1000–1800 mg/day. One patient had complete clearance of extensive candidal granulomas after 6 months of treatment; one patient had a slower but excellent response. Two other

patients had minimal or no response; of these, one was hypothyroid and the other had a thymoma. Of note, the serum levels were significantly higher in the first two patients than in the latter two. In all four patients the oral amphotericin B was free of side effects both clinically and in laboratory studies.

Chronic mucocutaneous candidiasis treated with amphotericin B. Case report. Waweru HW, Owili DM. *East Afr Med J* 1983; 60: 588–91.

A 5-year-old girl with CMC was treated with intravenous amphotericin B at a dose of 1 mg/kg every other day for a cumulative dose of 200 mg. The crusts and plaques completely cleared, but with residual atrophy, hypopigmentation, and scarring alopecia. She remained free of recurrence for 2 years.

Third-Line Therapies	
• JAK 1/2 inhibitors	C
• Cimetidine and zinc sulfate	E

Use of ruxolitinib to successfully treat chronic mucocutaneous candidiasis caused by gain-of-function signal transducer and activator of transcription 1 (STAT1) mutation. Higgins E, Al Shehri T, McAleer MA, et al. *J Allergy Clin Immunol* 2015; 135: 551–3.

A 28-year-old woman with CMC associated with a *STAT1* mutation had a 2-year history of severe alopecia areata and was treated with ruxolitinib. In addition to hair regrowth, the patient experienced resolution of oral candidiasis. It recurred within 2 weeks of discontinuing ruxolitinib, despite concomitant oral fluconazole.

Case report: successful treatment with cimetidine and zinc sulphate in chronic mucocutaneous candidiasis. Polizzi B, Origgi L, Zuccaro G, et al. *Am J Med Sci* 1996; 311: 189–90.

The clinical efficacy of high-dose cimetidine, 400 mg three times daily, and zinc sulfate, 200 mg daily (subsequently adjusted to maintain blood zinc levels at the upper normal range), was evaluated in a patient with CMC for 16 months. An impressive reduction in infectious events was correlated with an increased CD4 (helper/inducer) cell count.

Cutaneous larva migrans

Huda Al-Kutubi, Anthony Abdullah



Hookworm-related cutaneous larva migrans (Hr-CLM) is a disease caused by percutaneous penetration and migration of animal hookworm larvae in the human skin, most commonly *Ancylostoma braziliense*, *Ancylostoma caninum*, *Uncinaria stenocephala*, and *Bunostomum phlebotomum*. People at risk are the inhabitants and returning travelers from tropical/subtropical countries and children playing in sandpits. The incubation period can vary between a few days and 7 months after exposure to contaminated soil or sand. The clinical picture is that of a characteristic 'creeping eruption' with serpiginous, papular, vesicobullous, and erythematous lesions due to the presence of moving parasites. The common sites involved are the feet, buttocks, and thighs. Rare complications include pulmonary eosinophilic infiltrates, hookworm folliculitis, and oral mucosal lesions.

MANAGEMENT STRATEGY

Hr-CLM is self-limiting: most lesions resolve within 2–8 weeks because the human is a 'dead-end host.' However, the lesions can be extremely pruritic and extensive, significantly reducing quality of life, thus necessitating treatment.

The systemic treatment normally used by the authors for patients over the age of 2 years is oral *albendazole* 400 mg daily for 3 days. An alternative is *ivermectin* given as a single dose of 12 mg orally (or 200 mcg/kg) for adults and children older than 5 years or more than 15 kg in weight. Topical treatment usually takes the form of *thiabendazole* in a suitable lipophilic vehicle.

Specific Investigations

Clinical appearance is characteristic. Peripheral eosinophilia and raised serum IgE may be seen.

First-Line Therapies

• Systemic albendazole	B
• Systemic ivermectin	B

One-week therapy with oral albendazole in hookworm-related cutaneous larva migrans: a retrospective study on 78 patients. Veraldi S, Bottini S, Rizzitelli G, et al. *J Dermatolog Treat* 2012; 23: 189–91.

Seventy-eight patients with multiple and/or extensive lesions of Hr-CLM were treated with albendazole 400 mg/day for 1 week. Cure rate was 100% at 3-months' follow-up. The disappearance of pruritus was reported after 2–3 days and skin lesions after 5–7 days of therapy. The authors concluded the regime was very effective with no severe side effects reported.

Management of imported cutaneous larva migrans: a case series and mini review. Kincaid L, Klowak M, Klowak S, et al. *Travel Med Infect Dis* 2015; 13(5): 382–7.

Twenty-five patients were identified, 16 of whom had localized lesions to the feet. Twenty-three responded appropriately to a 3-day course of 400 mg albendazole. Two patients required a repeat course of treatment.

A randomized trial of ivermectin versus albendazole for the treatment of cutaneous larva migrans. Caumes E, Carriere J, Datry A, et al. *Am J Trop Med Hyg* 1993; 49: 641–4.

A comparison of efficacy between oral ivermectin (12 mg) and oral albendazole (400 mg). Twenty-one patients were randomly assigned to receive ivermectin ($n=10$) or albendazole ($n=11$). All patients who received ivermectin responded and none relapsed (cure rate 100%). All except one patient in the group receiving albendazole responded, but five relapsed after a mean of 11 days (cure rate 46%; p ts} = ts}0.017). No major adverse effects were observed. The authors suggest that a single dose of ivermectin is more effective than a single dose of albendazole.

Hookworm-related cutaneous larva migrans in Northern Brazil: resolution of clinical pathology after a single dose of ivermectin. Schuster A, Lesshaft H, Reichert F, et al. *Clin Infect Dis* 2013; 57: 1155–7.

Ninety-two patients, median age 9.5 years, were treated with a single dose of 200 mcg/kg ivermectin. Two weeks after treatment there was a significant reduction in complex tracts, and at 4 weeks all complex tracts had disappeared with marked symptomatic improvement.

The efficacy of single dose ivermectin in the treatment of hookworm related cutaneous larva migrans varies depending on the clinical presentation. Vanhaecke C, Perignon A, Monsel G, et al. *J Eur Acad Dermatol Venereol* 2014; 28: 655–7.

Sixty-two travelers with Hr-CLM and creeping dermatitis were treated with a single dose of ivermectin (200 mcg/kg). Six patients (10%) also had associated hookworm folliculitis. The authors concluded that efficacy of a single dose of oral ivermectin is higher in patients with only creeping dermatitis than in those with associated hookworm folliculitis ($p=0.02$).

Treatment of 18 children with scabies or cutaneous larva migrans using ivermectin. Del Mar Saéz-De-Ocariz M, McKinster CD, Orozco-Covarrubias L, et al. Clin Exp Dermatol 2002; 27: 264–7.

A report of 18 children aged 14 months to 17 years, of whom seven had Hr-CLM. All seven were cured with a single dose of 150–200 mcg/kg ivermectin, with no significant adverse effects. In the authors' experience, ivermectin is a safe and effective alternative treatment for cutaneous parasitosis in children.

Second-Line Therapies

• Topical thiabendazole in a lipophilic vehicle	D
• Carbon dioxide laser	D

Efficacy and tolerability of thiabendazole in a lipophilic vehicle for cutaneous larva migrans. Chatel G, Scolari C, Gulletta M, et al. Arch Dermatol 2000; 136: 1174–5.

Six patients were treated twice daily for 5 days with topical applications of 15% thiabendazole ointment in a lipophilic vehicle of base fat cream (24 g) and dimethyl sulfoxide gel (35 g). The ointment was prepared by crushing the tablets of thiabendazole in the lipophilic base. All patients experienced a clinical resolution within a median of 48 hours. No adverse effects and no recurrence had occurred in any patient at 3-months' follow-up.

Treatment with topical thiabendazole ointment at 10%–15% concentration in a hydrophilic vehicle has shown 98% efficacy within a median of 10 days of treatment.

Treatment of cutaneous larva migrans with a single session of carbon dioxide laser: a study of ten cases in the Philippines. Soriano LE, Piansay-Soriano ME. J Cosmet Dermatol 2017; 16(1): 91–4.

Ten cases (8 patients) were treated with a single session of carbon dioxide laser. The first three cases underwent 1–2 passes and experienced further larval migration. The subsequent cases

received 3–4 passes, with no further progression noted. There was no recurrence at 1-month follow-up. The authors concluded that this represented an effective physical modality for treatment.

Third-Line Therapies

• Topical albendazole	E
• Topical ivermectin	E
• Cryotherapy	E

Efficacy of albendazole ointment on cutaneous larva migrans in 2 young children. Caumes E. Clin Infect Dis 2004; 38: 1647–8.

Two patients, both 2 years old, were treated with a 10% albendazole ointment, prepared by crushing three 400-mg tablets of albendazole in 12 g of petroleum jelly. Treatment was applied three times daily for 10 days. The cutaneous lesions disappeared within a week. One patient had recurrence at 3 months, lesions disappearing within a week of re-treating. The author suggests that albendazole ointment is a safe and effective treatment for Hr-CLM in children.

Hookworm-related cutaneous larva migrans of the penis successfully treated with topical ivermectin. Gelmetti C, Brena M, Veraldi S. Pediatric Dermatology 2019; 36: 391–2.

A 4-year-old boy with Hr-CLM of the penis treated with topical ivermectin 1% cream BD for 2 weeks, with almost complete remission observed on day 2 and no recurrence at 6-weeks' follow-up. The authors concluded that this is an effective treatment in select patients.

A case of cutaneous larva migrans presenting in a pregnant patient. Kudrewicz K, Crittenden KN, Himes A. Dermatol Online J 2014; 20(10): 25526012.

Cryotherapy with liquid nitrogen resulted in complete resolution of the patient's lesion and symptoms. Oral anthelmintic agents are contraindicated in pregnancy.

Cutaneous polyarteritis nodosa

Cindy E. Owen, Jeffrey P. Callen



Polyarteritis nodosa (PAN) is a necrotizing vasculitis that predominantly involves medium-sized arteries. Small arteries may also be targeted, but small vessels (arterioles, capillaries, and venules) are not. Classic PAN is characterized by fever, weight loss, cutaneous ulcers, livedo reticularis, myalgias and weakness, arthralgias or arthritis, neuropathy, abdominal pain, ischemic bowel, testicular pain, hypertension, and renal failure. By contrast, cutaneous PAN (cPAN), sometimes termed *benign cutaneous polyarteritis*, is a localized necrotizing arteritis that does not affect internal organs and runs a chronic but benign course. It is characterized by livedo reticularis, retiform purpura, tender nodules, digital infarction, and ulceration. cPAN most often affects the legs but can appear on the arms and trunk. Extracutaneous manifestations can include fever, malaise, myalgias, arthralgias, and neuropathy. Many reports have linked cPAN to infections including group A streptococcus (most common), hepatitis B and C, parvovirus B19, *Mycobacterium tuberculosis*, and urinary tract pathogens. Inflammatory bowel disease, hairy cell leukemia, and minocycline exposure are also associated with cPAN. Occasional reports have linked cPAN to antiphospholipid antibodies, cryoglobulins, or antineutrophil cytoplasmic antibodies (pANCA or atypical ANCA more commonly than cANCA), but these are typically negative/normal in cPAN. One recent report has demonstrated that interleukin-6 is elevated in roughly 40% of patients. A mutation in the *CERC1* gene leading to deficiency in the ADA2 protein has been identified in some patients with early cPAN and early-onset vasculopathy. cPAN is seen more commonly in women than men (ratio of 1.7:1 in one study) in contrast to PAN, which is more common in men. Age of onset is typically between ages 30 and 50 but children can also be affected.

MANAGEMENT STRATEGY

cPAN causes pain and discomfort and may ulcerate, thereby causing disability. Therapy may include local measures, for example,

gradient pressure stockings, or systemic therapies, including colchicine, dapsone, pentoxifylline, hydroxychloroquine, systemic corticosteroids, methotrexate, azathioprine, cyclophosphamide, infliximab, etanercept, rituximab, and intravenous immunoglobulin (IVIG). Most of the reports are anecdotes or small case series.

Treatment is often indicated for underlying and associated conditions.

Specific Investigations

- Skin biopsy
- Serology for hepatitis B and C, assessment for tuberculosis, streptozyme titers, antineutrophil cytoplasmic antibodies, antinuclear antibodies, antiphospholipid antibodies, complement components (C3 and C4), rheumatoid factor, and cryoglobulins
- Assessment for systemic involvement (CBC, CMP, urinalysis with microscopic evaluation, blood pressure evaluation)
- Assessment for inflammatory bowel disease (history and possibly anti-*Saccharomyces cerevisiae* antibodies [ASCA])
- Assessment for drugs that have been linked to cPAN
- In cases with early onset, measurement of ADA2 levels

Cutaneous periarteritis nodosa: a clinicopathological study of 79 cases. Daoud MS, Hutton KP, Gibson LE. *Br J Dermatol* 1997; 136: 706–13.

In this analysis, ulceration was associated with neuropathy and a prolonged course. Most patients (60%) had no associated medical condition. Systemic PAN did not develop in any patient. Corticosteroids, azathioprine, pentoxifylline, and hydroxychloroquine appeared effective in individual patients, and patients with non-ulcerative disease responded better than those with ulcers.

Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. Navon Elkan P, Pierce SB, Segel R, et al. *N Engl J Med* 2014; 370(10): 92.

This study identified recessive loss of function mutations in *CECR1*, the gene encoding adenosine deaminase 2 (ADA2), in six families with multiple cases of systemic or cutaneous PAN.

Clinical and laboratory markers associated with relapse in cutaneous polyarteritis nodosa. Kato A, Hamada T, Miyake T, et al. *JAMA Dermatol* 2018; 154(8): 922.

In this retrospective case series of cPAN, pretreatment cutaneous ulcer, and high C-reactive protein levels, absolute neutrophil count, neutrophil-to-lymphocyte ratio, and systemic immune-inflammation indices were associated with relapse; arthropathy and neuropathy were not.

High titer of phosphatidylserine–prothrombin complex antibodies in patients with cutaneous polyarteritis nodosa. Kawakami T, Yamazaki M, Mizoguchi M, et al. *Arthritis Rheum* 2007; 57: 1507–13.

Antiphosphatidylserine–prothrombin complex and/or anticardiolipin antibodies were positive in all 16 cPAN patients tested compared with none in the control group.

Epidemiological, clinical and laboratory profiles of cutaneous polyarteritis nodosa patients: report of 22 cases and literature review. Criado PR, Marques GF, Morita TC, et al. *Autoimmun Rev* 2016; 15: 558–63.

cPAN was more prevalent in women (77%) with a mean age at time of diagnosis of 39.4 years (9–61 years). Clinical manifestations in decreasing order of frequency were ulcers, livedo racemosa, subcutaneous nodules, atrophie blanche, and purpura. Lower limbs were affected in all cases, but trunk and upper limbs were affected at equal frequency of 27%. No cases of cPAN progressed to systemic PAN. Symptoms reported were pain (64%) and paresthesias (30%). Twenty-three percent were diagnosed with mononeuritis multiplex. The most common infectious agent in this study was *Mycobacterium tuberculosis*.

Polyarteritis-like vasculitis in association with minocycline use: a single center case series. Kermani T, Ham E, Camilleri M, et al. *Semin Arthritis Rheum* 2012; 42: 213–21.

Nine cases occurring in the context of minocycline use – four with cutaneous-only disease. All had positive pANCA. Minocycline was discontinued, and six patients required immunosuppressive therapy.

Vasculitic conditions mimicking cPAN have also been reported with isotretinoin and amphetamines.

Manifestations, clinical course and prognostic markers in cutaneous polyarteritis nodosa. Munera-Campos M, Bielsa I, Martínez-Morillo M, et al. *J Dtsch Dermatol Ges* 2020; 18(11):1250-1259.

In a series of 31 patients, cPAN manifestations were nodules (90.3%), livedo reticularis (45.2%), ulceration (35.5 %), livedo racemosa (12.9%) and purpura (3.2%). At least one extracutaneous manifestation was reported in 67.7% of patients—myalgia (58.1%), paresthesia (45.2%) and arthralgia without arthritis (19.4%). Mononeuritis multiplex was noted in 9 of 21 patients (29%) who had electroneuromyography. The most common comorbid conditions were hypertension (22.6%), Type 2 diabetes mellitus (16.1%) and autoimmune hypothyroidism (9.68%). Relapse was seen in 17 (54.8%) of patients. Ulceration at presentation was the strongest predictor of relapse.

First-Line Therapies

• Local measures (i.e., support stockings, rest, leg elevation, local wound care)	E
• Non-steroidal antiinflammatory drugs, penicillin (if antecedent streptococcal infection), systemic corticosteroids	E
• Immunosuppressants: azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide	E

Low-dose weekly methotrexate for unusual neutrophilic vascular reactions: cutaneous polyarteritis nodosa and Behçet's disease. Jorizzo JL, White WL, Wise CM, et al. *J Am Acad Dermatol* 1991; 24: 973–8.

Three patients responded dramatically.

Ulcerative cutaneous polyarteritis nodosa treated with mycophenolate mofetil and pentoxifylline. Kluger N, Guillot B, Bessis D. *J Dermatolog Treat* 2011; 22: 175–7.

This single case report combines a second-line and a third-line therapy.

Complete resolution of refractory cutaneous arteritis by intravenous cyclophosphamide pulse therapy. Kawakami T, Okano T, Takeuchi S, et al. *Int J Dermatol* 2015 Aug; 54(8): e323–5.

In two patients with steroid-dependent cPAN, the addition of pulsed IV cyclophosphamide resulted in remission, allowing discontinuation of systemic steroids.

Gangrenous digital infarcts in a severe case of cutaneous polyarteritis nodosa. Mahmood-Rao H, Gandhi N, Ding T. *BMJ Case Rep* 2017; 2017: bcr-2017-220300.

A patient with severe cPAN and gangrenous infarcts failed initial immunosuppressive treatment with high-dose steroids and azathioprine. Escalation of therapy to intravenous cyclophosphamide resulted in disease remission.

Second-Line Therapies

• Intravenous immunoglobulin	E
• Pentoxifylline	E
• Hydroxychloroquine	E

Intravenous immunoglobulins as treatment of severe cutaneous polyarteritis nodosa. Marie I, Miranda S, Girszyn N, et al. *Intern Med J* 2012; 42: 459–62.

Three patients with refractory cPAN resulting in painful leg ulcers and toe necrosis were treated with IVIG 1 g/kg/day for 2 days monthly. Skin signs dramatically improved after two infusions and completely healed after the third.

Intravenous immunoglobulins for cutaneous polyarteritis nodosa resistant to conventional treatment. Breda L, Franchini S, Marzetti V, et al. *Scand J Rheumatol* 2016; 45(2): 169–70.

cPAN in an 8-year-old associated with streptococcal pharyngitis responded to IVIG after failing systemic steroids, ibuprofen, azathioprine, and indomethacin. Review of the literature revealed two cases of pediatric streptococcal-associated cPAN responding to IVIG.

Successful treatment of cutaneous PAN with pentoxifylline. Calderon MJ, Landa N, Aguirre A, et al. *Br J Dermatol* 1993; 12: 706–8.

A patient who failed to respond to aspirin and penicillin was treated with pentoxifylline. Withdrawal of the pentoxifylline resulted in a relapse that again responded to therapy.

New use for an old treatment: hydroxychloroquine as a potential treatment for systemic vasculitis. Casian A, Sangle SR, D'Cruz DP, et al. *Autoimmun Rev* 2018; 17(7): 660–4.

The authors report two cases of cPAN responding to hydroxychloroquine.

Third-Line Therapies

• Tamoxifen	E
• Infliximab	E
• Etanercept	D
• Rituximab	E
• Tonsillectomy	D
• Warfarin	E
• Tocilizumab	E

Estrogen-sensitive cutaneous polyarteritis nodosa: response to tamoxifen. Cvancara JL, Meffert JJ, Elston DM. *J Am Acad Dermatol* 1998; 39: 643–6.

Tamoxifen at a dose of 10–20 mg daily led to control of disease in a patient who seemed to worsen with conjugated estrogen therapy. Relapse occurred within 5 days of interruption of the therapy and rapidly responded with reinitiation of the tamoxifen.

Successful response to infliximab in a patient with undifferentiated spondyloarthropathy coexisting with polyarteritis nodosa-like cutaneous vasculitis. Garcia-Porrúa C, Gonzalez-Gay MA. Clin Exp Rheumatol 2003; 21: S138.

Remission induced by infliximab in a childhood polyarteritis nodosa refractory to convention immunosuppression and rituximab. Campanilho-Marques R, Ramos F. Joint Bone Spine 2014; 81: 267.

A 13-year-old boy responded to infliximab after failing prednisolone, methotrexate, cyclophosphamide, and rituximab.

Cutaneous polyarteritis nodosa in pediatric patients successfully treated with TNF- α inhibitor and methotrexate: case series and literature review. Do N, Ringold S, Brandling-Bennett H. Pediatr Dermatol 2019; 36(6): 932–5.

The authors report successful treatment of pediatric cPAN with infliximab in combination with methotrexate. They also review four cases from the literature treated successfully with either etanercept or infliximab without concomitant methotrexate.

A case of refractory cutaneous polyarteritis nodosa in a patient with hepatitis B carrier status successfully treated with tumor necrosis alpha blockade. Zoshima T, Matsumura M, Suzuki Y, et al. Mod Rheumatol. 2013; 23: 1029–33.

Report of a case, and literature review of five similar cases, successfully treated with etanercept.

Rituximab in refractory cutaneous polyarteritis. Krishnan S, Bhakuni DS, Kartik S. Int J Rheum Dis 2012; 15: e127.

A 34-year-old woman with cPAN refractory to prednisolone and cyclophosphamide developed digital gangrene of two fingers. Rituximab (two courses) resulted in complete healing of ulcers within 4 weeks. Six-month follow-up showed no recurrence on prednisolone and azathioprine.

Cutaneous polyarteritis nodosa: therapy and clinical course in four cases. Misago N, Mochizuki Y, Sekiyama-Kodera H, et al. J Dermatol 2001; 28: 719–27.

Two cases resolved after tonsillectomy. The authors proposed that chronic streptococcal disease might be responsible for cPAN.

Use of warfarin therapy at a target international normalized ratio of 3.0 for cutaneous polyarteritis nodosa. Kawakami T, Soma Y. J Am Acad Dermatol 2010; 63: 602–6.

Three patients with antiphosphatidylserine–prothrombin complex antibodies resolved on sustained warfarin therapy.

Successful treatment of tumor necrosis factor inhibitor-resistant cutaneous polyarteritis nodosa with tocilizumab. Inoue N, Shimizu M, Mizuta M, Yachie A. Pediatr Int 2020; 62: 753–755.

An 8-year old girl with TNF inhibitor-resistant cPAN responded to tocilizumab, a humanized monoclonal anti-IL-6 receptor antibody, given intravenously every 2 weeks at a dose of 8 mg/kg.

Darier disease

Benjamin S. Daniel, Genevieve A. Casey, Dedee F. Murrell



Darier disease (DD) is inherited in an autosomal dominant manner with an incidence of 1:25,000–1:100,000. Patients begin to develop malodorous, greasy, and crusted hyperkeratotic papules in seborrheic and flexural areas around puberty. DD is caused by mutations in the *ATP2A2* gene, which encodes sarcoplasmic/endoplasmic reticulum calcium-ATPase type 2 (SERCA2). There is no validated scoring system for DD to enable proper RCTs. An increased risk of cardiac failure has been demonstrated by a case-control study related to the role of this enzyme in the cardiac muscle.

MANAGEMENT STRATEGY

General measures include antiseptic washes, liquid soap-free washes, and loose, cotton clothing. Some patients flare with ultraviolet (UV) exposure and need photoprotection.

In mild disease or linear disease reflecting genetic mosaicism, *topical retinoids* may be sufficient. These include topical isotretinoin (0.05%), tretinoin cream (0.05%), adapalene gel (0.1%), and tazarotene gel (0.1% short contact for 15 minutes). Treatment is applied on alternate days to begin with, increasing to once daily if possible, as irritation is common. The addition of a topical corticosteroid (alternating with the retinoid) may alleviate some of the side effects. Superinfection with viruses and bacteria is frequent, so combined corticosteroid/antibiotic preparations are logical. Sweating may be reduced by a trial of oral naltrexone.

In more extensive disease, an *oral retinoid* is required. Isotretinoin (0.5–1.0 mg/kg daily) and alitretinoin (30 mg daily) are preferred over acitretin because teratogenicity is a problem, and

pregnancy is contraindicated for 2 years after stopping treatment with acitretin and 1 month after isotretinoin or alitretinoin. In males acitretin is an alternative but, bearing in mind that 50% of genetic relatives may have the same condition, such drugs could be dangerous if shared among females in the family. Compliance with contraceptive measures in females is very important as the treatment is usually long term.

The rare vesiculobullous form of the disease may respond to *prednisolone*. Hypertrophic flexural disease unresponsive to retinoids may require a surgical approach with *laser*, *electrosurgery*, *debridement*, or *excision*. Recurrence is a problem.

Oral lithium exacerbates the disease and should be avoided if possible.

Specific Investigations

- Skin biopsy. The characteristic finding is focal, suprabasal, acantholytic dyskeratosis
- Skin swab/scraping for bacterial, viral, and fungal culture
- Genetic testing for the mutation (counseling for prenatal diagnosis if desired)

Darier-White disease: a review of the clinical features in 163 patients. Burge SM, Wilkinson JD. *J Am Acad Dermatol* 1992; 27: 40–50.

Fourteen percent of patients in this series had herpes simplex complicating their disease.

Painful blisters arising in a patient with DD are usually due to secondary infection with *Staphylococcus aureus* or herpes simplex.

First-Line Therapies

• Cool cotton clothing	E
• Emollients	D
• Topical corticosteroids	D
• Topical retinoids	D

Darier's disease. Cooper SM, Burge SM. *Am J Clin Dermatol* 2003; 4: 97–105.

A detailed review of the management of DD.

Genetic counseling can be helpful, and written information is often appreciated.

Topical isotretinoin in Darier's disease. Burge SM, Buxton PK. *Br J Dermatol* 1995; 133: 924–8.

Six of 11 patients improved with 0.05% isotretinoin gel applied to a test patch. Patients were treated up to twice/day for 3 months if tolerated. Erythema, burning, and irritation were common. All patients relapsed after 1 month of stopping the treatment.

Successful treatment of Darier's disease with adapalene gel. Abe M, Inoue C, Yokoyama Y, et al. *Pediatr Dermatol* 2011; 28: 197–8.

Adapalene gel 0.1% applied daily for 2 months to the right side of the abdomen of a 12-year-old boy resulted in dramatic improvement in the area that was treated.

Tazarotene gel for Darier's disease. C G Burkhart CG, Burkhart CN. *J Am Acad Dermatol* 1998; 38: 1001–2.

Short-contact therapy with topical tazarotene in Darier disease. Sanz-Sánchez T, Díaz-Díaz RM, López-Barrantes O, et al. *Actas Dermosifiliogr* 2012; 103: 255–6.

Tazarotene has been used effectively as short contact or with topical steroids with improvement within 3 months.

Second-Line Therapies

• Oral isotretinoin	B
• Oral alitretinoin	C
• Oral acitretin	B
• Topical 5-fluorouracil 5%	E
• Topical tacrolimus 0.03%, 0.1%	E
• Topical pimecrolimus 0.05%	E
• Topical diclofenac sodium 3%	E

Clinical and ultrastructural effects of acitretin in Darier's disease. Lauharanta J, Kanerva L, Turjanmaa K, et al. *Acta Dermatol Venereol* 1988; 68: 492–8.

Thirteen patients treated with acitretin starting at 30 mg daily for 16 weeks showed some improvement, but side effects included itching (5 patients) and hair loss (2 patients).

Acitretin monotherapy in Darier's disease. Van Dooren-Greebe RJ, van de Kerkhof PC, Happle R. *Br J Dermatol* 1989; 121: 375–9.

Acitretin monotherapy at initial dose of 35 mg/day in five patients showed marked improvement with up to total clearance in four out of the five.

Isotretinoin treatment of Darier's disease. Dicken CH, Bauer EA, Hazen PG, et al. *J Am Acad Dermatol* 1982; 6: 721–6.

This multicenter open study assessed the effect of short and longer courses of treatment. The starting dose was 0.5 mg/kg, but longer courses were adjusted according to symptoms. Isotretinoin was effective but did not give long-term remission. Some patients were maintained on alternate-day or alternate-week regimens.

Successful treatment with oral alitretinoin in women of childbearing potential with Darier's disease. Zamiri M, Munro CS. *Br J Dermatol* 2013; 169: 709–10.

Two women were treated with 30 mg daily, with improvement after 4–6 weeks. Relapse occurred upon stopping, and treatment was continued in one patient for 18 months.

A case of Darier's disease successfully treated with topical tacrolimus. Rubegni P, Poggiali S, Sbrano P, et al. *J Eur Acad Dermatol Venereol* 2006; 20: 84–7.

Topical tacrolimus 0.1% ointment to the face and neck resulted in complete remission after 6 weeks, with no relapse 1 year later using maintenance therapy of 0.03%.

Improvement of Darier disease with diclofenac sodium 3% gel. Millan-Parrilla F, Rodrigo-Nicolas B, Moles-Poveda P, et al. *J Am Acad Dermatol* 2014; 70: e89–90.

Third-Line Therapies

• Ciclosporin	E
• Oral prednisolone (vesiculobullous)	E
• Laser (CO ₂ , erbium:YAG, pulse-dye)	E
• Photodynamic therapy	D
• Botulinum toxin	E
• Electron beam radiation	E
• Dermabrasion	E
• Debridement	E
• Excision	E

Darier's disease: severe eczematization successfully treated with cyclosporine. Shahidullah H, Humphreys F, Beveridge GW. *Br J Dermatol* 1994; 131: 713–6.

Ciclosporin may be helpful in widespread eczematized DD but had no effect on the underlying disease.

Vulvar Darier's disease treated successfully with cyclosporine. Stewart LC, Yell J. *J Obstet Gynaecol* 2008; 28: 108–9.

A previously therapy-resistant case was treated with ciclosporin (initial dose 5 mg/kg) for 6 months with good response and was subsequently maintained on acitretin.

Vesiculobullous Darier's disease responsive to oral prednisolone. Speight EL. *Br J Dermatol* 1998; 139: 934–5.

A patient with the vesiculobullous form of the disease responded to a short course of oral prednisolone.

Prednisolone may also be useful in the eczematized form.

Extensive recalcitrant Darier disease successfully treated with laser ablation. Brown VL, Kelly SE, Burge SM, et al. *Br J Dermatol* 2010; 162: 227–8.

Trunk, limbs, and scalp were treated under general anesthetic every 2 months with CO₂ laser. Wounds healed within 33 weeks, and the patient remained disease free in some areas for 9 years.

Darier-White disease treated with fractional CO₂ laser in two cases. Raszewska-Famielec M, Dudra-Jastrzebska M, Borzecki A, et al. *Dermatol Ther* 2015; 24: 254–7.

Three sessions of fractional CO₂ laser resurfacing with 0.8- to 1-mm density every 6 weeks resulted in removal of papular lesions. Topical anesthetic (5% EMLA) cream was used. Some recurrence was observed after 6 months.

Efficacy of erbium:YAG laser ablation in Darier disease and Hailey-Hailey disease. Beier C, Kaufmann R. *Arch Dermatol* 1999; 135: 423–7.

Disease cleared in two patients, but follow-up was less than 2 years.

Successful treatment of Darier disease with the flashlamp-pumped pulse-dye laser. Roos S, Karsai S, Ockenfel HM, et al. *Arch Dermatol* 2008; 144: 1073–5.

Submammary disease improved at 8 weeks post treatment, with no progression at 15 months.

Treatment of Darier's disease with photodynamic therapy. Exadaktylou D, Kurwa HA, Calonje E, et al. *Br J Dermatol* 2003; 149: 606–10.

Six patients received photodynamic therapy with topical 5-aminolevulinic acid as a photosensitizer. One patient could not tolerate the treatment, but five experienced sustained improvement, with initial inflammatory response lasting 2–3 weeks.

Botulinum toxin type A: an alternative symptomatic management of Darier's disease. Kontochristopoulos G, Katsavou AN, Kalogirou O, et al. *Dermatol Surg* 2007; 33: 882–3.

Submammary disease was treated with botulinum toxin as adjuvant therapy: 100 U were injected, with improvement sustained for 4 months. Reduced sweating may alleviate maceration and reduce bacterial colonization.

Treatment of recalcitrant Darier's disease with electron beam therapy. Kittridge A, Wahlgren C, Fuhrer R, et al. *Dermatol Ther* 2010; 23: 302–4.

Electron beam radiation therapy to the inframammary folds resulted in initial severe local dermatitis, followed by complete resolution sustained for 18 months.

Recalcitrant hypertrophic lesions were debrided under local anesthesia. Symptomatic and cosmetic improvement was maintained for 2 years.

The surgical treatment of hypertrophic Darier's disease. Wheeland RG, Gilmore WA. J Dermatol Surg Oncol 1985; 11: 420-3.

Decubitus (pressure) ulcers

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From Istanbul Medeniyet University Department of Dermatology archive.

Pressure ulcers (decubitus ulcers, bed sores, pressure sores, to torsion stress) represent damage within the skin and soft tissue that can extend through the subcutaneous tissue and muscle layer onto the underlying bone. They generally occur over bony prominences, the most common being the sacrum, ischial tuberosities, greater trochanters, calcaneus, and lateral malleoli.

MANAGEMENT STRATEGY

Prevention

Repositioning is a significant part of prevention. A patient in an ordinary bed who is at risk for developing a pressure ulcer should be repositioned at frequent intervals; however, the correct timing for turning has never been established. The National Pressure Ulcer Advisory Panel (NPUAP) has admitted that evidence on repositioning every 2 hours is arbitrary and varies from country to country, even from facility to facility, and that repositioning at 2–4-hour intervals may be more appropriate.

Pillows and foam wedges are used to maintain an appropriate position and to keep bony prominences apart. Completely immobile patients should have their heels raised from the bed by a pillow or boot and not be placed on their trochanters, unless a specialized bed is used. To avoid the latter, use a 30-degree position from the horizontal lying on the side. The head of the bed should not be raised more than 30 degrees from the horizontal for an extended period. Knees should be flexed at 5–10 degrees to minimize the risk of deep-vein thrombosis.

Where possible, use lifting devices or draw sheets to reposition or to transfer patients. Minimize pressure from medical devices, such as catheters, oxygen tubing, and restraints. Finally, when appropriate, the patient should be placed on a *pressure-reducing*

device such as *alternating air, gel, or water mattress*. Foam rings, foam cut-outs, or donut-style devices should not be used, as these devices distribute pressure inappropriately.

A patient sitting in a wheelchair should be repositioned frequently, perhaps every hour, and be taught to shift weight every 15 minutes. A pressure-reducing device made of foam, gel, air, or a combination of each is indicated. Unfortunately, even in paraplegics, the exact time interval for repositioning has never been accurately determined.

Barrier creams are useful for conserving the intact skin of incontinent patients and of those at risk for skin breakdown.

Theoretically, pressure ulcers should be preventable, but despite these measures, many simply are not. If they are associated with immobility, sustained pressure, and the loss of pain sensibility, these problems can and should be addressed. In practice, successful prevention is often foiled by our limited understanding of the pathogenesis, as well as by complicating comorbidities. There is also some evidence that many deep ulcers are initiated by multiple microthromboses of deep tissues. This indicates that dehydration, along with any factor that might increase blood coagulability, should be addressed.

Management

The management of skin lesions caused by pressure is based on these principles:

- Elimination of relative/sustained pressure
- Reposition of the patient regularly and frequently
- Removal of necrotic debris
- Maintenance of a moist wound environment
- Correction of the underlying contributing factors
- Nutritional supplements and screening for nutritional deficiencies
- Wound care with topical products and/or dressing

The patient should not lie on the ulcer. A patient who is at risk for developing additional ulcers and can assume a variety of positions without lying on the ulcer should be placed on a *static support surface* (i.e., *air, foam, or water*). If the patient cannot assume various positions without lying on the ulcer or bottoms out while on a static surface, or if the ulcer does not heal after 2–4 weeks of optimal care, place the patient on a *dynamic support surface* when possible. These supporting surfaces can be categorized as constant low-pressure (CLP) devices conforming to body shaper or replacing pressure devices that alter pressure mechanically. CLP devices, such as high-specification foam mattresses with overlays, and bead-filled and water-filled mattresses, may lessen the development of pressure ulcers and tend to be more successful than standard foam hospital mattresses. Alternating-pressure (AP) mattresses and overlays include a variety of compartments filled with air inflating and deflating in a coordinated way to alter pressure continually across the body. Unfortunately, there is no proof to show exactly which type is better for protection and treatment; however, both CLP and AP devices are more successful than standard hospital mattresses for prevention and treatment.

Removal of Necrotic Debris

Debridement is required to expose granulation tissue, decrease infection risk, and improve healing, especially when there is an extensive eschar or necrotic tissue. Debridement can be conducted through surgical (sharp) and nonsurgical (enzymatic, autolytic, mechanical, and biologic). The debridement method is dependent on several factors, including the characteristics of the patient, the wound, the risk of infection risk, and even the cost.

Surgical debridement is indicated for infected ulcers with necrotic debris, if the patient has advancing cellulitis and systemic infection, devitalized tissue, and eschars other than those on the heel; however, the extent of tissue needing to be removed is highly variable. An eschar on the heel should be excised only if it is fluctuant, draining, or surrounded by cellulitis, and if the patient is septic. If there is a high index of suspicion that a biofilm is present (i.e., wound failing to heal despite proper wound care and antimicrobial therapy), then surgical debridement is required.

Major debridement is performed in the operating room, but serial sharp debridement can be performed at the bedside. The use of *systemic antimicrobials* should be considered to prevent bacteremia during significant debridement. A *bone biopsy* is recommended while debriding ulcers, when bone is exposed, and for non-healing deep ulcers (stage 3 or 4) after 2–4 weeks of optimal therapy.

Mechanical debridement methods, such as hydrotherapy, whirlpool baths, and wound irrigation are among other measures that have benefits, such as improving local circulation, reducing pain and fever, relieving debris and bacteria, helping with wound removal, and accelerating wound healing. Saline wet-to-dry gauze is an additional alternative.

Autolytic debridement provides a moist wound area that allows the body enzymes to digest necrotic tissue. Similarly, enzymatic debridement uses enzymes for the liquefaction of dead tissue in the wound and clears them with dressings like collagenase to remove necrotic tissue, and moist wounds are the best place for them to work. Autolytic and enzymatic debridement is indicated for non-infected ulcers that are unlikely to get infected.

Biologic debridement utilizes non-infectious larvae and maggots, which has been observed to have increased complete debridement over conventional therapy (80% versus 48%, respectively).

Maintenance of a Moist Wound Environment

The choice of a synthetic dressing depends on the presence of infection, amount of exudate, status of the periwound skin, and amount of pain experienced by the patient. *Saline dressings* and *alginates* are indicated for infected ulcers. *Synthetic dressings* (i.e., *films*) are used on ulcers with minimal exudate, *hydrocolloid wafers* for moderate exudate, and *foam wafers* and *alginates* for ulcers with a large amount of exudate. Ulcers with fragile or dermatitic periwound skin should be covered with *hydrogel wafers* or *non-adherent foam wafers*. All occlusive dressings relieve pain, when present, but the hydrogel wafers are best for this purpose.

Correction of the Underlying Contributing Factors

Attention to the medical status is important; diabetes mellitus, nutritional conditions (malnutrition, hypoproteinemia, anemia), peripheral vascular disease, deep venous thrombosis, congestive heart failure, lower extremity edema, cardiac disease, malignancy, mental health problems, and even Alzheimer disease may prevent any ulcer healing. Unfortunately, even the best medical care may not permit healing.

General Measures

Treatment of the pressure ulcer can be simplified and made more effective if the following recommendations are considered:

- It is essential that the heels are inspected at least daily and any changes are recorded
- Saline should be used to clean most pressure lesions; soap and disinfectants are too irritating for more than occasional use. Scrubbing may prove too irritating, so gentle washing is indicated

- When ulcers are not infected, synthetic dressings should be changed only if they become dislodged or wound fluid escapes from under the dressing
- Periwound skin must be kept dry not only to avoid maceration but also to permit the dressing to adhere to the skin
- To obliterate dead space, *fill deep ulcers loosely with a hydrocolloid, a hydrogel wound filler, or an alginate rope* before applying a synthetic dressing. This same material should be placed under the edge of the ulcer when undermining is present. Bleeding after serial surgical debridement can often be controlled with an alginate dressing. Moistening with saline can loosen an alginate dressing that adheres to granulation tissue
- A clean ulcer failing to show signs of healing and revealing inflammatory signs of erythema, edema, and warmth, purulent discharge and persistent excessive exudate, discoloring or darkening of granulation tissue, giving off a foul odor, and presenting with heightened local pain should be treated with antibacterial agents, such as *1% silver sulfadiazine, cadexomer iodine, triple antibiotic, or retapamulin*, for 2 weeks to reduce the bacterial burden; however, topical antimicrobials may create the risk of resistant bacterial strains emerging. *Metronidazole gel* would be the exception, as the odor of an infected ulcer can often be eliminated by applying it to the ulcer bed. Increased bacterial burden may impede healing before clinical signs of infection become apparent. Cytotoxic agents, such as hydrogen peroxide and povidone-iodine, should be avoided
- Clinical observation is the key to making the diagnosis. Cutaneous biopsies will not be helpful, although biopsies for aerobic and anaerobic bacteriology cultures could be useful if infection is suspected
- *Systemic antibiotics* are recommended only in the presence of bacteremia, sepsis, advancing cellulitis, or osteomyelitis. Bacterial testing and analysis with comprehensive swabbing cannot provide all the information required. Infection that is described as a variety of bacteria bigger than 10^5 CFU/g of tissue is partially relevant. It is recommended the wound is controlled for signs of infections: pain, warmth, erythema, drainage, bad odor, and/or systemic manifestations. Osteomyelitis usually accompanies stage 4 pressure ulcers and deep ulcers. X-rays, MRI, and bone biopsy should be used to check for osteomyelitis
- Although most synthetic dressings relieve pain, treatment for moderate-to-severe pain can include topical anesthetics (lidocaine), non-steroidal antiinflammatory drugs, opiates, antidepressants, and sedatives

Dermatologic Observation

Observe for:

- Blanchable erythema
- Non-blanchable erythema
- Superficial ulcer
- Deep ulcer
- Eschar
- Necrosis
- Gangrene
- Decubitus dermatitis

Blanchable Erythema and Non-blanchable Erythema

Blanchable and non-blanchable erythema represent the initial development of the pressure ulcer. The early lesions of non-blanchable erythema are bright red; later, they become dark red to purple. Both can be treated with *adherent synthetic dressings* to protect the lesion from friction and shear, *topical corticosteroids*, or *zinc oxide paste*. The bright red lesion can also be treated with 2%

nitroglycerin ointment; 0.5–1 cm of the ointment is applied over the lesion and covered with an impermeable plastic wrap (such as Saran Wrap) for 12 hours daily.

Superficial and Deep Ulcers

Superficial and deep ulcers without necrotic debris are treated with *saline wet-to-dry gauze* or an *adherent synthetic dressing*. Deep ulcers should be loosely filled with a *synthetic wound filler* before applying a synthetic dressing.

Eschar and Necrosis

The deep ulcer with necrotic debris requires debridement and is then treated as a clean ulcer. Covering the lesion with an adhesive occlusive dressing for several days after scarification will often soften the eschar before excision is undertaken. The firmly adherent dry eschar that is not attached to underlying bone can often be separated from the surrounding skin with 5% 5-fluorouracil cream. After scarification and application of zinc oxide paste to protect the surrounding skin, 5-fluorouracil is applied to the eschar, including its margin, and then covered with an impermeable plastic wrap. Application is repeated every 8 hours. When separation occurs, it can be excised.

Decubitus Dermatitis

Decubitus dermatitis is treated with topical corticosteroids, vaseline gauze, or a hydrogel wafer. Large bullae may be debrided before applying the dressing.

Specific Investigations

- Categorize patient
- Stage the degree of ulceration
- Total protein, serum albumin, liver, and kidney function
- Daily calorie intake
- Complete blood count
- Physical examination for dehydration and malnutrition
- Care for comorbid disorders

Categories of Patients

Patients at risk need to be considered in terms of the underlying disease process:

- Spinal cord injury in an otherwise healthy person
- Neurologic disease with no medical disease but a devastating condition, such as multiple sclerosis or a cerebral vascular accident compromising the body integrity
- Debilitation with a multitude of medical diseases affecting the patient (e.g., arteriosclerosis, diabetes mellitus, Parkinson disease, Alzheimer disease, malignancy, malnutrition, and peripheral vascular disease)
- Surgical procedures requiring lengthy positioning on the operating table for cardiovascular or orthopedic procedures

Grading or Evaluation

Grading or evaluation can be accomplished by dermatologic observation and staging. Bear in mind that ulcer staging is arbitrary and does not reflect the dynamics of ulcer formation.

Staging

Stages are as follows:

- Stage 1: Non-blanchable erythema of intact skin

- Stage 2: Partial-thickness skin loss with exposed dermis. Adipose or deeper tissues are not exposed
- Stage 3: Full-thickness skin loss. Adipose tissue is visible in the ulcer bed, which may have undermining and tunneling (see figure)
- Stage 4: Full-thickness skin and tissue loss. Fascia, muscle, tendon, ligament, cartilage, or bone is exposed; undermining, tunneling, and epibole may be present
- Unstageable: Obscured full-thickness skin and tissue loss. Extent of tissue damage within the ulcer is obscured by slough or eschar and cannot be determined; removal of slough or eschar reveals a stage 3 or 4 pressure injury
- Deep tissue pressure injury: Persistent non-blanchable deep red, maroon, or purple discoloration (may be seen with intact or non-intact skin)

NPUAP recently have added two further pressure injury types to their definitions, both of which are caused by medical devices. Medical devices can lead to pressure injury and injury to mucosal membranes; staging is not possible for these types of pressure injury.

Most superficial ulcers do not progress to stage 2 or even 3 or 4 ulcers. The concept of staging need not be thought of as a progression.

Accumulating evidence suggests that a number of ulcers (most stages 3 and 4) may initially originate in the deep tissue compartment and progress outward to the dermis and epidermis (inside-out theory).

Pathophysiology

The relationship between common risk factors and the pathophysiology of pressure ulcer development: a systematic review. Blackburn J, Ousey K, Taylor L, et al. *J Wound Care* 2020; 29: 4–12.

The most important risk factors in pressure ulcer etiology are ischemia, recovery of blood flow, and the pathologic effect of pressure and shear. Among other risk factors are force and pressure (shear force, type of force, the relative position of external forces compared to bony prominences), agedness, spinal cord injury, and type 1 diabetes with cardiac autonomic neuropathy.

Dilemmas about the pressure ulcer: skin-fold ulcerations and apposition lesions. Parish LC, Lowthian PT. *Exp Rev Dermatol* 2008; 3: 287–91.

Pressure ulcers continue to have an uncertain etiology.

Risk Assessment Tools

Predictive validity of pressure ulcer risk assessment tools for elderly: a meta-analysis. Park SH, Lee YS, Kwon YM. *West J Nurs Res* 2016; 38: 459–83.

Typical screening tools (Braden, Norton, and Waterloo scales) utilized for pressure ulcer risk are limited as to their validity and accuracy among older adults due to heterogeneity throughout studies.

Risk assessment tools for the prevention of pressure ulcers. Moore ZE, Patton D. *Cochrane Database Syst Rev* 2019; 1: CD006471.

No proof suggesting the reduction of the incidence or the severity of pressure ulcers is available on the use of structured and systematic pressure ulcer risk assessment tools.

Predictive validity of Braden for pressure ulcers in critical care: a meta-analysis. Wei M, Wu L, Chen Y, et al. *Nurs Crit Care*. 2020; 25: 165–70.

Braden scale provided a moderately predictive validity and had a fair sensitivity and low specificity in critically ill adult patients.

Predictive efficacy of the Braden Q Scale for pediatric pressure ulcer risk assessment in the PICU: a meta-analysis. Chun X, Lin Y, Ma J, et al. *Pediatr Res* 2019; 86: 436–43.

The Braden Q scale anticipated the risk in the pediatric intensive care unit moderately accurate.

25 years of pressure ulcers. Parish LC, Sibbald RG. *Adv Skin Wound Care* 2012; 25: 57–8.

Role of staging may provide more confusion than merit.

Staging system: revised Pressure Injury Staging System. Edsberg LE, Black JM, Goldberg M, et al. Revised National Pressure Ulcer Advisory Panel. *J Wound Ostomy Continence Nurs* 2016; 43: 585–97.

The European Pressure Ulcer Advisory Panel developed a staging system in 1998 that is composed of four stages: Grade 1 to Grade 4. The classification system most popularly adopted and used is the one presented in 1989 by the NPUAP. This classification system has been updated and revised. A new stage, suspected deep tissue injury, was incorporated in 2016. The extent of the tissue loss present and the presence and absence of anatomical features in the stage of the injury is described in each definition. The revised description of a stage 2 pressure injury aims to demonstrate the difference between moisture-associated skin damage and injury led by pressure and/or shear. The suspected definition has been eliminated from the Deep Tissue Pressure Injury diagnostic label.

Noninvasive staging of pressure ulcers using photoacoustic imaging. Hariri A, Chen F, Moore C, et al. *Wound Repair Regen* 2019; 27: 488–96.

Q-switched Nd:YAG laser and light-emitting diode (LED)-based photoacoustic imaging systems analyze photoacoustic intensity and photoacoustic depth. The average and standard deviation of ulcer depths from 10 different A-lines are measured with this new technology.

Developing a mobile app for prevention and treatment of pressure injuries. Salomé GM, Ferreira LM. *Adv Skin Wound Care* 2018; 31: 1–6.

The current study defines the planning and development of a mobile application to prevent and treat pressure injuries for use by providers. The application outlines the risk factors for pressure injury development, supplies an assessment of the wound, suggests wound clearing procedures, maintains pressure injury staging, and suggests treatment interventions.

Factors Predicting Pressure Ulcers

Risk factors for pressure ulcer development in Intensive Care Units: a systematic review. Lima Serrano M, González Méndez MI, Carrasco Cebollero FM, et al. *Med Intensiva* 2017; 41: 339–46.

The occurrence of pressure ulcers cannot be explained by a single factor. Risk factors predictive of pressure ulcer development are usually age, length of ICU stay, diabetes, time of MAP <60–70 mmHg, length of mechanical ventilation, intermittent hemodialysis or continuous veno-venous hemofiltration therapy, vasopressor support, sedation, and turning.

A prediction tool for hospital-acquired pressure ulcers among surgical patients: surgical pressure ulcer risk score. Aloweni F, Ang SY, Fook-Chong S, et al. *Int Wound J* 2019; 16: 164–75.

Important risk factors for the likelihood of developing hospital-acquired pressure ulcers are age (≥ 75 years), female gender, low body mass index (< 23), preoperative Braden score ≤ 14 , anemia, respiratory disease, and hypertension.

Nutritional parameters predicting pressure ulcers and short-term mortality. Montalcini T, Moraca M, Ferro Y, et al. *J Transl Med* 2015; 13: 305.

Lower hemoglobin and albumin were inversely related to pressure ulcers, where patients with lower albumin showed notably higher short-term mortality than patients with higher serum albumin.

Factors predicting the development of pressure ulcers in an at-risk population who receive standardized preventive care. Demarre L, Verhaeghe S, Van Hecke A, et al. *J Adv Nurs* 2015; 71: 391–403.

Pressure ulcers in categories 2–4 were significantly related to non-blanchable erythema, urogenital disorders, and higher body temperature. Predictive factors relating to superficial pressure ulcers were: admittance to an internal medicine ward; incontinence-associated dermatitis; non-blanchable erythema; and a lower Braden score. Incontinence-associated dermatitis was greatly related to superficial sacral pressure ulcers.

Risk factors associated with pressure ulcer development in critically ill traumatic spinal cord injury patients. Wilczweski P, Grimm D, Gianakis A, et al. *J Trauma Nurs* 2012; 19: 5–10.

Clinical variables associated with pressure ulcers were fecal management systems, incontinence, acidosis, support surfaces, steroids, and additional equipment, with hypotension as the strongest predictor of pressure ulcers in 94 spinal cord injury patients.

Treatment

Wound, pressure ulcer and burn guidelines – 2: guidelines for the diagnosis and treatment of pressure ulcers, second edition. Fujiwara H, Isogai Z, Irisawa R, et al. *J Dermatol* 2020; 47: 929–78.

A comprehensive guide that is used to stage the wound according to color, acuteness, and chronicity in a pressure ulcer, with recommendations of care and treatment.

WOCN 2016 Guideline for Prevention and Management of Pressure Injuries (Ulcers): An Executive Summary. Wound, Ostomy and Continence Nurses Society–Wound Guidelines Task Force. *J Wound Ostomy Continence Nurs* 2017; 44: 241–6.

It offers an outline of the process that is exploited to update and improve the guideline, and lists the specific suggestions for evaluation, prevention, and treatment of pressure injuries.

Pressure ulcers: prevention and management. Mervis JS, Phillips TJ. *J Am Acad Dermatol* 2019; 81: 893–902.

This review article focuses on pressure ulcer prevention and management, with an emphasis on the evidence for commonly accepted practices.

First-Line Therapies

• Elimination of pressure	B
• Repositioning	B
• Pressure-reducing and -relieving devices	A
• Palliative care	B
• Removal of necrotic debris	B
• Maintenance of a moist environment	C
• Moisturizing	C
• Fatty acid cream	A
• Silicone foam	A
• Topical	B
• Cleansing	C
• Nutrition	C
• Dietary	C
• Maggot therapy	A

Eliminating Pressure and Relieving Devices

Support surfaces for pressure ulcer prevention: a network meta-analysis. Shi C, Dumville JC, Cullum N. *PLoS One* 2018; 13: e0192707.

The evidence that powered active air surfaces and powered hybrid air surfaces are likely to decrease pressure ulcer incidence was moderately certain; yet, standard hospital surfaces are possibly more comfortable than powered active air surfaces.

Support surfaces for the treatment and prevention of pressure ulcers: a systematic literature review. Rae KE, Isbel S, Upton D. *J Wound Care* 2018; 27: 467–74.

A useful tool to aid pressure ulcer prevention and wound healing is pressure mattresses and are accepted to be more suitable than standard foam mattresses. Medical grade sheepskins are agreed to be useful for those who have low-medium risk of developing pressure ulcers compared with standard foams. Higher specification mattresses are similar to each other (i.e., active and reactive surfaces) and it is hard to make a descriptive conclusion in terms of mattress superiority since the outcomes of the research are controversial.

Support surfaces for pressure ulcer prevention. McInnes E, Jammali-Blasi A, Bell-Syer SE, et al. *Cochrane Database Syst Rev* 2015; (9): CD001735.

Foam mattresses that are alternative to standard hospital foam mattresses decrease the occurrence of pressure ulcers for risk groups. Higher specification foam mattresses are recommended for people with a high risk of pressure ulcer development. The benefits of higher-specification CLP and AP support surfaces to prevent pressure ulcers are not clear but AP mattresses might be more affordable.

Support surfaces for treating pressure ulcers. McInnes E, Jammali-Blasi A, Bell-Syer SE, et al. *Cochrane Database Syst Rev* 2018; 10: CD009490.

The contribution of high-tech pressure support surfaces (such as low-air-loss beds, air suspension beds, and AP surfaces) or low-tech support surfaces to the improvement of the healing process of pressure ulcers.

Prevention of pressure ulcers with a static air support surface: a systematic review. Serraes B, van Leen M, Schols J, et al. *Int Wound J* 2018; 15: 333–43.

Static air mattress overlays are more efficient for the prevention of pressure ulcers when compared with standard mattresses in nursing homes and intensive care environments.

Comparing the effects of 3 different pressure ulcer prevention support surfaces on the structure and function of heel and sacral skin: an exploratory cross-over trial. Tomova-Simitchieva T, Lichterfeld-Kottner A, Blume-Peytavi U, et al. *Int Wound J* 2018; 15: 429–37.

Skin structure and function are affected by the type of support surface during loading. When gel and air mattresses are compared with foam mattresses, they were found to be more protective; however, the difference was insignificant.

An investigation of geriatric nursing problems in hospital. Norton D, McClaren R, Exton-Smith AN. London: Churchill Livingstone, 1975; 238.

Patients who developed fewer pressure sores were those who were turned every 2–3 hours.

This is based on a book published in 1916!

Shearing force as a factor in decubitus ulcers in paraplegics. Reichel SM. *JAMA* 1958; 166: 762–3.

As a result of shear, blood vessels in the sacral area become twisted and distorted, and the tissue may become ischemic and necrotic.

Drawsheets for prevention of decubitus ulcer. Witkowski JA, Parish LC. *N Engl J Med* 1981; 305: 1594.

Use of draw sheets reduces the incidence of friction burns.

Repositioning for pressure ulcer prevention in adults. Gillespie BM, Chaboyer WP, McInnes E, et al. *Cochrane Database Syst Rev* 2014; (4): CD009958.

Present evidence is not adequate and might be biased; and the evidence whether there is a decrease in pressure ulcers with the 30-degree tilt is not strong compared with the standard 90-degree position, nor is the evidence on the effect of repositioning.

The data collected from an economic assessment are not clear about the cost efficiency of nursing time of repositioning every 3 hours using the 30-degree tilt and whether or not it is more efficient than standard care including repositioning every 6 hours using a 90-degree tilt.

Palliative Care

Pressure ulcers in patients receiving palliative care: a systematic review. Ferris A, Price A, Harding K. *Palliat Med* 2019; 33: 770–82.

Patients who receive palliative care have 12.4% prevalence of pressure ulcers, and this is higher than the average population. Decreased mobility, older age, increased Waterlow score, and long duration of stay are among the most commonly identified risk factors.

Effectiveness of pressure ulcer prevention strategies for adult patients in intensive care units: a systematic review. Tayyib N, Coyer F. *Worldviews Evid Based Nurs* 2016; 13: 432–44.

The silicon foam dressing positively influences the reduction of sacrum and heel pressure ulcers' occurrence in patients who are critically ill. There is limited evidence on the efficiency of nutrition, skin-care regimen, positioning and repositioning program, support surfaces, and the role of education in preventing hospital-acquired pressure ulcers development in the ICU.

Moisturizing

Wound, pressure ulcer and burn guidelines – 2: guidelines for the diagnosis and treatment of pressure ulcers, second edition. Fujiwara H, Isogai Z, Irisawa R, et al. *J Dermatol* 2020; 47: 929–78.

Moisture creams should be applied to protect the skin and to avoid pressure ulcers. Should topical agents be necessary, oil-based ointments like white petrolatum, zinc oxide, and dimethyl isopropyl azulene should be used to protect the wound surface, and silver sulfadiazine to prevent infection.

Debridement

Debridement of cutaneous ulcer: medical and surgical aspects. Witkowski JA, Parish LC. *Clin Dermatol* 1991; 9: 585–93.

Debridement can be accomplished by cold steel cutting, by chemical application, or by autohemolytic destruction under an occlusive dressing.

Changing attitudes toward maggot debridement therapy in wound treatment: a review and discussion. King C. *J Wound Care* 2020; 29: 28–34.

Maggot debridement therapy induces healing and disinfects wounds. It may also be used for full debridement of a necrotic wound and clearing a methicillin-resistant *Staphylococcus aureus* infection. Irrigation of the wound by exudates formed by the host responding to the maggots, killing and ingestion of bacteria by the maggots, secretion of proteolytic enzymes by the maggots leading to breakdown and ingestion of necrotic tissue into liquid, and quick formation of granulation tissue by constant larval movement in the wound are included in the maggot-aided wound healing. The discussion about the engagement of health-care employees and the reduction of anxiety on the use of maggots as a treatment on hard-to-heal wounds is ongoing.

The role of surgical debridement in healing of diabetic foot ulcers. Gordon KA, Lebrun EA, Tomic-Canic M, et al. *Skinmed* 2012; 10: 24–6.

Evidence to support debridement in enhancing healing is scarce, and there are insufficient data to support debridement for venous ulcers and pressure ulcers.

Cleansing

Cleansing the traumatic wound by high pressure syringe irrigation. Stevenson TR, Thacker JG, Rodeheaver GT, et al. *J Am Coll Emerg Phys* 1976; 5: 17–21.

Cleansing provides enough force to remove bacteria and other debris and loosen eschar.

Wound cleansing for pressure ulcers. Moore ZE, Cowman S. *Cochrane Database Syst Rev* 2013; 3: CD004983.

Studies that used saline spray containing aloe vera, silver chloride, and decyl glucoside; isotonic saline solution; and pulsatile lavage, water, and sham (the lavage flow was directed into a wash basin positioned adjacent to the wound and not visible to the participants).

There currently is no promising trial evidence to advocate for the use of a specific wound cleansing solution or technique for pressure ulcers.

Wound cleansing, topical antiseptics and wound healing. Atiyeh BS, Dibo SA, Hayek SN. *Int Wound J* 2009; 6: 420–30.

Wound cleansers, povidone-iodine, chlorhexidine, alcohol, acetate, hydrogen peroxide, boric acid, silver nitrate, silver sulfadiazine, and sodium hypochlorite may affect normal human cells and may be antimetabolic, adversely affecting normal tissue repair. Negative outcomes may occur with repeated and excessive wound treatment with antiseptics without proper indications; however, when applied at the appropriate times and concentrations, some classes of antiseptics may function as a tool for the clinician to steer the wound bed in specific directions.

Beyond skin deep: managing pressure injuries. Podd D. *JAAPA* 2018; 31: 10–17.

Clearing the wounds should be done first, preferably with 0.9% sodium chloride solution at each dressing change. The use of cytotoxic antiseptic agents such as 5% mafenide acetate, 0.25% sodium hypochlorite solution, povidone-iodine, 3% hydrogen peroxide, and 0.25% acetic acid, killing granulation tissue and impairing wound healing, should be avoided on clean wounds. Sodium hypochlorite, which is antiseptic, is suitable on infected and malodorous wounds that have large slough, and debrides necrotic tissue.

Antimicrobial Agents

Topical metronidazole for odor control in pressure ulcers. Lyvers E, Elliott DP. *Consult Pharm* 2015; 30: 523–6.

When metronidazole was applied to the wound two or three times daily (0.75% and 1% creams, gels, lotions, and intravenous solutions of metronidazole) it was effective with nearly complete odor resolution in 2 to 7 days. Although there was the risk for systemic absorption, almost no systemic adverse events were reported in the literature. Monitoring is still required, as nausea, gastrointestinal distress, and neural toxicities from long-term use are still possible but unlikely.

Dressings and topical agents for preventing pressure ulcers. Moore ZEH, Webster J. *Cochrane Database Syst Rev* 2018; 12: CD009362.

No harm or benefit was displayed on many trials that explore the effect of topical applications on pressure ulcer occurrence. Dimethyl sulfoxide (DMSO) cream might raise the pressure ulcer risk. The incidence of pressure ulcers can be decreased by the use of fatty acid versus a control compound (a cream not including fatty acid). Pressure ulcer incidence at any stage may be reduced with silicone dressings.

Bacteriology of pressure ulcers in individuals with spinal cord injury: what we know and what we should know. Dana AN, Bauman WA. *J Spinal Cord Med* 2015; 38: 147–60.

Staphylococcus aureus, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis* were the organisms most frequently identified in pressure ulcers.

Nutrition

Efficacy of a disease-specific nutritional support for pressure ulcer healing: a systematic review and meta-analysis. Cereda E, Neyens JCL, Caccialanza R, et al. *JMGA. J Nutr Health Aging* 2017; 21: 655–61.

The improvement of PU healing in comparison to standard formulas is linked with the use of high-calorie, high-protein, disease-specific formulas enhanced with arginine, zinc, and antioxidants as oral supplements and tube feeds for at least 8 weeks.

Pressure ulcer and nutrition. Saghaleini SH, Dehghan K, Shadvar K, et al. *Indian J Crit Care Med* 2018; 22: 283–9.

The main risk factors for the development of pressure ulcers and impaired wound healing are dietary deprivation and deficient nutritional intake. How much nutrient intake is ideal for wound healing is not clear, but increased need for energy, protein, zinc, vitamins A, C, E, and amino acids have been reported. Sufficient fluid intake is required for the support of the blood flow toward wound tissue and the prevention of additional breakdown of the skin.

The role of nutrition for pressure injury prevention and healing: The 2019 International Clinical Practice Guideline Recommendations. Munoz N, Posthauer ME, Cereda E, et al. *Adv Skin Wound Care* 2020; 33: 123–36.

Adults experiencing noticeable weight loss and those underweight might need extra energy intake. If dietary needs are insufficient, fortified foods and/or high-calorie, high-protein oral nutritional supplements between meals should be provided.

The EPUAP/NPIAP/PPPIACPG recommends 30–35 kcal/kg of body weight per day for malnourished adults with a pressure injury (PI) or those at risk of malnutrition. The recommended protein intake is 1.25–1.5 g/kg of body weight per day. The EPUAP/NPIAP/PPPIA CPG suggests providers encourage adequate fluids, which is an intake of 1 mL fluid/kcal.

Synthetic Dressing

Second-Line Therapies

• Hydrocolloid wafer dressing	C
• Hydrogel	C
• Synthetic dressing	C

Wound, pressure ulcer and burn guidelines – 2: guidelines for the diagnosis and treatment of pressure ulcers, second edition. Fujiwara H, Isogai Z, Irisawa R, et al. *J Dermatol* 2020; 47: 929–78.

When dressing materials are used in the acute phase, those allowing observation of the wound surface (such as polyurethane film and hydrocolloids) are preferable. To prevent pressure ulcers, polyurethane film application, polyurethane foam, polyurethane foam/soft silicone, bone protrusions should be used.

Successful treatment of unstageable pressure ulcers by using advanced wound dressing. Sunarti S. *Med Indones* 2015; 47: 251–2.

The stages of healing are cleaning, granulation, and epithelialization. Alginate dressing, dextranomer dressing, hydrofiber dressing, flax dressing, silver-supplemented dressing, or enzyme-supplemented dressing are the proposed dressings for the cleaning phase, whereas for the granulation phase, alginate dressing, hydrocolloid dressing, flax dressing, polyurethane foam dressing, or tender wet dressing should be utilized. For the epithelialization phase, hydrofiber dressing, hydrocolloid dressing, hydrogel dressing, flax dressing, and semipermeable dressing may be used.

Using transparent polyurethane film and hydrocolloid dressings to prevent pressure ulcers. Dutra RA, Salomé GM, Alves JR, et al. *Wound Care* 2015; 24: 268, 270–1, 273–5.

The transparent polyurethane film (8.7%) performed better and was more effective than the hydrocolloid dressing (15%) in preventing pressure ulcer development, as evidenced in 160 patients.

Hydrogel dressing for treating pressure ulcers. Dumville JC, Stubbs N, Keogh SJ, et al. *Cochrane Database Syst Rev* 2015; 2: CD011226.

It is not explicit if hydrogel dressings are more or less effective than other treatments in healing pressure ulcers or if different hydrogels have contrasting effects. Most trials that have been performed in this area are very small and poorly reported, so the risk of bias is uncertain.

Dressings and topical agents for preventing pressure ulcers. Moore ZE, Webster J. *Cochrane Database Syst Rev* 2018; 12(12): CD009362.

Although the occurrence of pressure ulcers was reduced when dressings were employed to protect the skin, results were compromised by the low quality of the included trials.

No harm or benefit was displayed on many trials that explore the effect of topical applications on pressure ulcer occurrence. The incidence of pressure ulcers can be decreased by the use of fatty acid versus a control compound (a cream not including fatty acid). Pressure ulcer incidence at any stage may be reduced with silicone dressings.

A cost and clinical effectiveness analysis among moist wound healing dressings versus traditional methods in home care patients with pressure ulcers. Souliotis K, Kalemikerakis I, Saridi M, et al. *Wound Repair Regen* 2016; 24: 596–601.

In this study, 85.56 ± 52.09 days was reported as the average healing time for moist-wound healing dressings group, while it was 121.4 ± 52.21 days for the 'gauze group'. The dressing change frequency per patient was lower in the moist wound healing dressings group, and total treatment cost was lower than the gauze group.

Third-Line Therapies

• Becaplermin gel	A
• Hyperbaric oxygen	E
• Honey	B
• Platelet-rich plasma	B
• Platelet-derived growth factor	C
• Electrical stimulation	A
• Negative pressure wound therapy	C
• Surgical management	D

Cost effectiveness of becaplermin gel on wound closure for the treatment of pressure injuries. Gilligan AM, Waycaster CR, Milne CT. *Wounds* 2018; 30: 197–204.

Becaplermin gel once daily plus good wound care (debridement, infection management, and moisture balance) showed substantially higher-pressure weeks free of ulcers when compared with control patients and had insignificantly increased cost.

Hyperbaric oxygen therapy for chronic wounds. Kranke P, Bennett MH, Martyn-St James M, et al. *Cochrane Database Syst Rev* 2012; 4: CD004123.

There are no satisfactory studies available to prove that hyperbaric oxygen is useful in pressure or arterial ulcers.

Atypical wounds; hyperbaric oxygen therapy (HBO). Benedict Mitnick CD, Johnson-Arbor K. *Clin Podiatr Med Surg* 2019; 36: 525–33.

HBO is the main treatment for decompression sickness, air embolism, and carbon monoxide poisoning, as well as an adjunctive treatment of extra medical conditions, with compromised grafts and flaps, chronic refractory osteomyelitis, and diabetic

foot ulcerations. Pressure ulcers are not one of the HBO indications suggested by the Undersea and Hyperbaric Medical Society.

Nonpharmacologic interventions to heal pressure ulcers in older patients: an overview of systematic reviews (the SENA-TOR-ONTOP series). Vézé-Díaz-Pallarés M, Lozano-Montoya I, Abraha I, et al. *J Am Med Dir Assoc* 2015; 16: 448–69.

The evidence grade is too low or insufficient to support the utilization of any support surface, nutrition intervention, multicomponent interventions, repositioning, or other adjunctive therapy (ultrasound, negative pressure, laser, electromagnetic, light, shock wave, hydrotherapy, radiofrequency, or vibration therapy) to increase the rates of pressure ulcer healing in older patients. Electrotherapy may demonstrate some beneficial effect in the treatment of pressure ulcers, although the quality of evidence is low.

Honey as a topical treatment for wounds. Jull AB, Cullum N, Dumville JC, et al. *Cochrane Database Syst Rev* 2015; 3: CD005083.

Honey has become in vogue for healing partial-thickness burns more quickly than conventional treatment (which included polyurethane film, paraffin gauze, Soframycin-impregnated gauze, sterile linen, and leaving the burns exposed) and healing infected postoperative wounds more quickly than antiseptics and gauze, but the evidence remains unconvincing.

Platelet-rich plasma improves healing of pressure ulcers as objectively assessed by digital planimetry. Volakakis E, Papadakis M, Manios A, et al. *Wounds* 2019; 31: 252–6.

Local applications of platelet-rich plasma (PRP) speed the healing of pressure ulcers when objectively assessed by digital planimetry. A magnificent reduction in the surface area, diameter, and circumference of PUs was seen after the application of PRP compared with conventional treatment.

Optimal use of negative pressure wound therapy (NPWT) in treating pressure ulcers. Gupta S, Ichioka S. *Int Wound J* 2012; 9: 8–16.

Retrospective research or case series were published for NPWT in patients with pressure ulcers. These show the effective use of NPWT on stage 3 and 4 pressure ulcers. The outcomes displayed an increase in granulation tissue formation reduction of fibrin tissue, diminishing necrosis. It is concluded by the writers that NPWT is reliable, effective, and user-friendly.

Negative pressure wound therapy for treating pressure ulcers. Dumville JC, Webster J, Evans D, et al. *Cochrane Database Syst Rev* 2015; 5: CD011334.

There is currently no rigorous randomized, controlled trial evidence available regarding the effects of NPWT compared with alternatives for the treatment of pressure ulcers.

Phototherapy for treating pressure ulcers. Chen C, Hou WH, Chan ES, et al. *Cochrane Database Syst Rev* 2014; 7: CD009224.

Trials compared the use of phototherapy with standard care only (six trials) or sham phototherapy (one trial). Among five studies reporting the rate of change in the ulcer area, three studies found no statistically remarkable difference between the two groups. These are very uncertain as to the effects of phototherapy in treating pressure ulcers. The quality of evidence is very low due to the unclear risk of bias and small number of trials available for analysis.

Electromagnetic therapy for treating pressure ulcers. Aziz Z, Bell-Syer SE. *Cochrane Database Syst Rev* 2015; 9: CD002930.

There is no strong evidence indicating benefits of using electromagnetic therapy to treat pressure ulcers; however, the possibility of a beneficial or harmful effect cannot be eliminated, because there were only two trials included, both with methodologic limitations and small numbers of participants.

Electrical stimulation for pressure injuries: a health technology assessment. Health Quality Ontario. *Ont Health Technol Assess Ser* 2017. PMID: 29201261.

There was a significant difference in wound surface area reduction favoring electrical stimulation compared with standard wound care; however, there was no significant difference in complete pressure injury healing between adjunct electrical stimulation and standard wound care.

Low-level laser therapy (LLT) in the treatment of pressure ulcers: systematic review. Machado RS, Viana S, Sbruzzi G. *Lasers Med Sci* 2017; 32: 937–44.

The use of LLT with a wavelength of 658 nm and a dose of 4 J/cm² showed significant results in the assessed outcomes, and evidence was not found with single wavelengths above it.

A review of the surgical management of heel pressure ulcers in the 21st century. Bosanquet DC, Wright AM, White RD, et al. *Int Wound J* 2016; 13: 9–16.

Surgical interventions, such as simple debridement, partial or total calcanectomy, arterial revascularization in the context of coexisting peripheral vascular disease, or using free tissue flaps may be the only means of encountering successful healing in stage 3 pressure ulcers. Amputation may be necessary for failed surgical intervention or as a definitive first-line procedure in certain high-risk or poor-prognosis patient groups.

A systematic review of complication and recurrence rates of musculocutaneous, fasciocutaneous, and perforator-based flaps for treatment of pressure sores. Sameem M, Au M, Wood T, et al. *Plast Reconstr Surg* 2012; 130: 67e–77e.

Surgery is usually necessary for the descriptive treatment of stage 3 and 4 pressure ulcers. Various reconstructive alternatives are available for skin coverage and filling dead space after debridement of pressure ulcers, containing regional musculocutaneous, fasciocutaneous, and, currently, perforator-based flaps. The writers' view showed no statistically significant difference in terms of recurrence or complication rates among musculocutaneous, fasciocutaneous, or perforator-based flaps.

Surgical treatment and strategy in patients with multiple pressure sores. Chiang IH, Wang CH, Tzeng YS. *Int Wound J* 2018; 15: 900–8.

Conservative management is insufficient for stage 3 or 4 pressure sores and surgery is unavoidable for creating flap coverage. Complete excision of all devitalized tissue in the wound and filling of the defect with a long-lasting and well-perfused flap are included in basic surgical principles to treat pressure sores. A treatment protocol of a multistaged surgery is recommended for old patients who have multiple pressure sores. This may provide a lessened surgery duration, less bleeding, and low complication rate, as well as an increased quality of life for the patient after sepsis control, and reduction of caregiver burden.

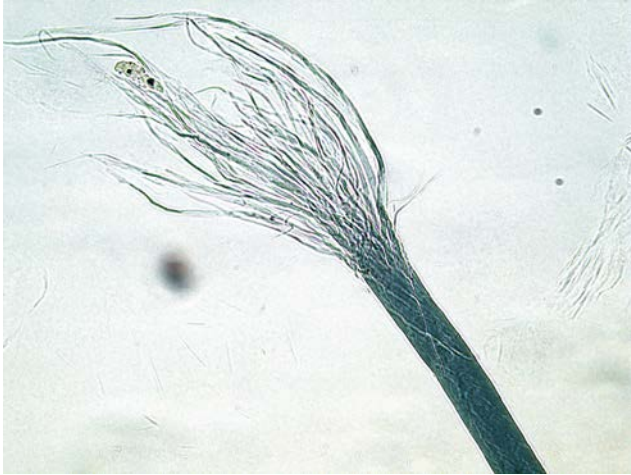
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Delusions of parasitosis

Nicholas D. Brownstone, Quinn Thibodeaux, John Y.M. Koo



Delusions of parasitosis (DOP) is a form of delusional disorder, somatic type. It is a type of monosymptomatic hypochondriacal psychosis and is also known as Morgellons disease, delusions of infestation, and Ekbom disease. Patients with this disorder have cutaneous dysesthesias that cause them to pick at their skin continuously in order to 'extract' a perceived organism or 'foreign body'. The cutaneous findings that result from these attempts to dig out the suspected parasites range from normal skin to excoriations to frank ulcerations. Patients develop elaborate delusional ideations associated with their condition. Frequently, these patients often collect 'samples' in bottles, Ziploc bags, jars, or slides of what is often lint, hair, debris, dead skin, and even common insects found in the home, using these specimens to provide 'evidence'. Many of these patients can also have tactile hallucinatory experiences that are compatible with their delusion. The most characteristic hallucinatory symptom they may experience is formication. Many also complain of pruritus.

It is important early on in diagnosis to make an explicit distinction between primary and secondary DOP. Primary DOP happens spontaneously. Secondary DOP results from many varied causes, including illicit drug use (especially cocaine, narcotics, amphetamines), primary psychotic disorders (schizophrenia, psychotic depression), organic brain injury, and dementia, among other causes. If the patient has a suspected or confirmed history of illicit drug use, then a toxicology screen is useful as confirmation. If the patient has a confirmed or suspected history of an underlying broader mental health disorder, then referral to a psychiatrist is necessary. Secondary DOP are difficult to manage adequately in a dermatology practice. Treatment of the underlying disorder may resolve the DOP. Primary DOP can only be diagnosed once secondary causes have been ruled out.

The condition has a bimodal age distribution, occurring in younger adults (where there is an equal distribution of men and women) and the elderly (mostly women). Primary DOP are

mostly prevalent in older women, whereas secondary DOP are seen in any age group without a predilection for gender. There can be comorbid psychopathologies in DOP, such as depression and anxiety; these can be severe enough to cause the patient to commit suicide.

MANAGEMENT STRATEGY

The management strategy for secondary DOP is a referral to psychiatry. For suspected primary DOP, it is still imperative that the dermatologist carry out a detailed medical history to exclude a bona fide skin condition (e.g., scabies incognito) or other possible organic conditions, such as substance abuse, neurologic, endocrine, hematologic/oncologic, nutritional (e.g., B₁₂ or folate deficiency), or renal (e.g., uremic pruritus) disorders. The condition can also develop after the patient, relative, or pet has had a true parasitic infection, and so ruling out the presence of a real infestation is warranted.

Second, a thorough physical examination should be performed, including examining 'specimens' that the patient may bring. These specimens can be observed under the microscope, which help demonstrate to the patient that his or her concerns are being taken seriously. One should not make any comments that may reinforce their delusional ideation; this may ultimately render the patient more difficult to deal with by making him or her even more firmly fixated on the erroneous beliefs. On the other hand, by definition, rational argument or trying to talk a patient out of a delusion is both not possible and counterproductive. Dermatologists can acknowledge the patient's sensations and suffering as real and that they will do everything they can to help.

It is also important for the dermatologist to treat secondary skin damages in these patients to create a therapeutic alliance with the patient. Dermatologists should consider *soothing baths* and topical agents such as *creams with menthol* or the use of *occlusive dressings* to enhance healing and limit access to involved parts of the skin.

The most effective way to reverse delusional ideation is to start the patient on an *antipsychotic medication*. If this option is offered in a neutral way, emphasizing possible symptom reduction, such as reduced crawling, biting, or stinging sensations, while avoiding discussing pathophysiology or the mechanism of action of these medications, patients may be willing to accept the medication on a 'trial and error' basis.

The medication historically used to treat DOP is pimozide. The fact that pimozide is US Food and Drug Administration (FDA)-indicated only for Tourette syndrome with no psychiatric indications makes pimozide uniquely acceptable to those patients who are often intensely opposed to accepting a psychiatric medication. This medication generally works very well, whether patients have classic DOP or formication without delusions. The trapezoid dosing plan is used to describe the use of pimozide with regard to its dose titrations when treating DOP. The dose of pimozide can be increased by as little as 0.5 mg increments and as slowly as on a biweekly to monthly basis until significant clinical response is noted, which is usually evident at a dose of 3 mg daily or less. It is very rare that a patient will require a dose of more than 5 mg daily. If the patient continues to experience improvement, the dosage of pimozide can eventually be gradually reduced by as little as 0.5 mg every 2–4 weeks until the minimum necessary dosage is determined, or the patient is slowly tapered off the pimozide altogether.

If the clinical state deteriorates again in the future with a new episode of a delusional belief and formication, the patient can be restarted on pimozide and again treated on a time-limited

fashion to control the particular episode. Most patients can be treated on an episodic basis.

Because pimozide blocks dopaminergic receptors, there is the possibility that extrapyramidal side effects such as stiffness or akathisia may develop. If they do develop, however, they can usually be controlled with anticholinergic agents such as benztropine (Cogentin) 1–2 mg up to four times a day as needed, or diphenhydramine (Benadryl) 25 mg up to four times a day as needed. Side effects are not a reason for discontinuing treatment provided they are well controlled. Acute dystonic reaction and tardive dyskinesia are other potential adverse consequences associated with pimozide, although with the relatively low dosages used, these are extremely rare.

The metabolism of pimozide is catalyzed mainly by the cytochrome P450 3A4 (CYP 3A4) enzymatic system and, to a lesser extent, by cytochrome P450 1A2 (CYP 1A2) and cytochrome P450 2D6 (CYP 2D6). Individuals with genetic variations resulting in poor CYP 2D6 metabolism (approximately 10% of the population) exhibit higher pimozide concentrations than extensive CYP 2D6 metabolizers. The time to achieve steady-state pimozide concentrations is expected to be longer (about 2 weeks) in poor CYP 2D6 metabolizers because of the prolonged half-life. Alternative dosing strategies are recommended in patients who are genetically poor CYP 2D6 metabolizers. At doses above 4 mg/day, CYP 2D6 genotyping should be performed. In poor CYP 2D6 metabolizers, pimozide doses should not exceed 4 mg/day, and doses should not be increased earlier than 14 days (see FDA package insert for further information).

Because pimozide can theoretically prolong the QT interval or cause arrhythmias, it is advisable to consider checking electrocardiograms (ECGs) pretreatment and, periodically, during treatment, especially in older patients or those with a history of cardiac arrhythmia. Caution must also be exercised in prescribing pimozide for those with hepatic or renal dysfunction. Hypokalemia or hypomagnesemia is a contraindication to therapy. Therefore, a basic metabolic panel and magnesium (Mg) level should be checked before starting therapy.

Do not prescribe pimozide if a patient has a history of hypersensitivity to it or any components. Further contraindications include history of central nervous system (CNS) depression, history of cardiac arrhythmias, congenital long QT syndrome, and concurrent use with QTc-prolonging agents. Drugs that are inhibitors of CYP3A4 should not be used concurrently. Do not prescribe pimozide if a patient is on a selective serotonin reuptake inhibitor (SSRI) or stimulant.

Atypical antipsychotics, such as *risperidone* and *olanzapine*, have also been used successfully to treat patients with DOP. Atypical antipsychotics block more 5-HT₂ (serotonin) receptors than D₂ receptors. Serotonin has been shown to be a key player in some states of psychosis, most cases of obsessive-compulsive disorder, and self-mutilation, which can all potentially manifest in patients with DOP. Thus, atypical antipsychotics, by blocking both serotonin and dopaminergic receptors, are thought to be an effective choice for treating this condition. Furthermore, the burden of side effects with atypical antipsychotics may be reduced compared with that of older typical antipsychotics. Having the patient agree to go on risperidone or olanzapine, however, may be more difficult than pimozide; the primary indication for risperidone and olanzapine is schizophrenia, with the latter indication likely being unacceptable to many patients with DOP.

Nevertheless, over the past several years, clinicians have reported many successful cases using atypical antipsychotics. It is usually advisable to start at low doses and titrate upward as needed. For example, for risperidone, start from 0.5 mg once to

twice daily, and work up to the effective dose for that particular patient with the usual maximal dose of 5 mg daily. While not widely studied in DOP, the recommended dose for olanzapine ranges from 2.5 mg/day to 7.5 mg/day. The dose should not exceed 10 mg/day.

Even with a skillful interpersonal approach, as described earlier, patients may be reluctant to take a psychotropic medication. It may be helpful to emphasize to them that these medications have worked well with patients with similar symptoms and that, in light of their intense suffering and misery, they are encouraged to try the medication with the spirit of 'trial and error'. Even though managing psychotic patients in dermatologic settings has many challenges, when a dermatologist succeeds in connecting with these patients and dramatically reversing their very miserable situation, these patients often turn out to be the most grateful patients a dermatologist can have in their career.

Specific Investigations

These additional tests may be considered, depending on the patient's clinical presentation:

- Complete blood count
- Complete metabolic panel, including liver function tests
- Thyroid function tests
- Serum B₁₂, ferritin
- ECG before initiation of pimozide and periodically while on pimozide, if indicated
- Drug screen
- Magnesium level
- BMI and waist circumference
- HbA1c and fasting plasma glucose
- Fasting lipid panel

Delusions of parasitosis: a brief review of the literature and pathways for diagnosis and treatment. Laidler N. *Dermatol Online J* 2018; 24(1): 13030/qt1fh739nx.

This review article analyses 17 case reports examining the use of risperidone and olanzapine in the treatment of DOP. These findings are synthesized into a clinical pathway designed to assist dermatologists in effectively managing patients with DOP.

Delusions of parasitosis; suggested dialogue between dermatologist and patient. Patel V, Koo JY. *J Dermatolog Treat* 2015; 26: 456–60.

This article is a practical guide that suggests verbatim how a dermatologist might talk to a delusional patient in order to develop a strong therapeutic rapport. Strategies on how to optimize the initial encounter, build rapport, and prescribe antipsychotic medications that are likely to be accepted by the patient are discussed.

Contemporary diagnosis and management in advanced psychodermatology. Nguyen CM, Beroukhim K, Danesh MJ, et al. *Longboat Key: Handbooks in Health Care*, 2015.

This is a comprehensive handbook on psychodermatology, including diagnosis and management of patients with DOP.

Delusions of parasitosis: ethical and clinical considerations. Fabbro S, Aultman JM, Mostow N. *J Am Acad Dermatol* 2013; 69: 156–9.

A case is presented that demonstrates the dermatologist's dilemma when treating patients with primary psychiatric disease. There is a discussion on the best clinical and ethical action, using principle- and narrative-based approaches in ethical reasoning.

Delusional infestation is typically comorbid with other psychiatric diagnoses: review of 54 patients receiving psychiatric evaluation at Mayo Clinic. Hylwa SA, Foster AA, Bury JE, et al. *Psychosomatics* 2012; 53: 258–65.

This retrospective study found that 74% of patients with delusional infestation have multiple coexisting or underlying psychiatric disorders. Therefore, evaluation by a psychiatrist, when possible, is advised for all patients with delusional infestation.

Diffuse pruritic lesions in a 37-year-old man after sleeping in an abandoned building. Dunn J, Murphy MB, Fox KM. *Am J Psychiatry* 2007; 164: 1166–72.

This is an excellent case presentation of a patient with DOP and contains a thorough discussion of the differential diagnosis.

First-Line Therapy

- Pimozide B

Pimozide in dermatologic practice: a comprehensive review. Lorenzo CR, Koo J. *Am J Clin Dermatol* 2004; 5: 339–49.

This article reviews the utility of pimozide in dermatologic conditions.

Delusional parasitosis: a dermatologic, psychiatric, and pharmacologic approach. Driscoll MS, Rothe MJ, Grant-Kels JM, et al. *J Am Acad Dermatol* 1993; 29: 1023–33.

Pimozide is suggested as the first line of therapy for this psychodermatologic condition. Relapse often occurs upon discontinuation of the drug.

Second-Line Therapies

- Risperidone D
- Olanzapine D
- Quetiapine E
- Aripiprazole E
- Ziprasidone E
- Trifluoperazine E
- Haloperidol E
- Sulpiride E
- Fluphenazine E
- Flupenthixol E
- Promazine E

Second-generation antipsychotics in primary and secondary delusional parasitosis: outcome and efficacy. Freudenmann RW, Lepping P. *J Clin Psychopharmacol* 2008; 28: 500–8.

The first retrospective case-based analysis of 63 cases from 434 available publications to determine the efficacy and outcome of second-generation antipsychotic agents. It was found that risperidone and olanzapine were the most frequently used of these agents, with full or partial remission in 69% and 72% of cases, respectively.

Therapeutic update: use of risperidone for the treatment of monosymptomatic hypochondriacal psychosis. Elmer KB, George RM, Peterson K. *J Am Acad Dermatol* 2000; 43: 683–6.

The authors discuss risperidone as being highly effective for DOP while avoiding the negative long-term side effects of pimozide (as discussed earlier).

Primary delusional parasitosis treated with olanzapine. Freudenmann RW, Schönfeldt-Lecuona C, Lepping P. *Int Psychogeriatr* 2007; 19: 1161–8.

A case report of an elderly woman with DOP successfully and safely treated with olanzapine monotherapy. A dosing regimen is recommended. The authors also present a review of all articles that report the use of atypical antipsychotics for DOP. Of note, dosing regimens for olanzapine are also offered in the two following publications:

Successful treatment of delusions of parasitosis with olanzapine. Meehan WJ, Badreshia S, Mackley CL. *Arch Dermatol* 2006; 142(3): 352–5.

Delusional parasitosis mimicking cutaneous infestation in elderly patients. Le L, Gonski PN. *Med J Aust* 2003; 179(4): 209–10.

Antipsychotic treatment of primary delusional parasitosis: systematic review. Lepping P, Russell I, Freudenmann RW. *Br J Psychiatry* 2007; 191: 198–205.

This article is a systematic review of the use of typical and atypical antipsychotics in patients with DOP. Analyses showed that both typical and atypical antipsychotics were effective in the majority of patients. Particularly effective antipsychotics resulting in full or partial remission were pimozide, trifluoperazine, haloperidol, sulpiride, fluphenazine, and flupenthixol.

Dermatitis artefacta

Bridget Myers, Quinn Thibodeaux, John Y.M. Koo



Dermatitis artefacta (DA), also known as *factitious dermatitis*, is a rare psychiatric condition in which patients self-induce a variety of skin lesions. The motive for creating the lesions is often a conscious or unconscious psychological need to seek attention or play the 'sick role,' possibly due to childhood feelings of abandonment or neglect. DA is unique from *psychogenic excoriation*, a disorder characterized by excessive scratching or picking of one's skin. While both DA as well as psychogenic excoriation can result in significant disfigurement and distress, psychogenic excoriation is used to describe superficial excoriations caused by nail or finger manipulation only. In contrast, DA is used to diagnose self-inflicted cutaneous wounds that are more severe than simple excoriations; it is often generated using sharp instruments, cigarette butts, or injecting feces into one's skin.

Of patients presenting to dermatology with a primary psychiatric condition, 23% of them have DA. DA occurs in a four-to-one ratio of female-to-male patients, with an average age of onset of 12.5 years old. Certain populations, such as healthcare workers and those of lower socioeconomic class, exhibit greater prevalence of DA versus the general population. DA is associated with both childhood abuse and childhood psychiatric disorders. Recent studies suggest that a large proportion of patients with DA have comorbid anxiety, depression, or borderline personality disorder.

To diagnose DA, a detailed history is necessary to uncover any significant stressors, social issues, or underlying psychological diseases. When DA patients are asked about the nature in which their lesions developed, they will often be vague and deny any responsibility. Their disposition is classically described

as inappropriately unconcerned or pleasantly detached, a unique feature termed *hollow history*.

Appearance of DA lesions is variable and depends on what tool or method is used to harm the skin, such as heat, boiling or ice-cold water, chemicals, injection of foreign materials, or tampering with old lesions, such as existing scars or surgical incision sites. Lesions can range in severity from tiny cuts to large areas of trauma, and may include ulcers, burns, erosions, bullae, purpura, hyperpigmentation, ecchymosis, excoriations, or lichenification. Significant disfigurement may result, with more serious lesions posing risk of abscess formation, gangrenous necrosis, or life-threatening infection. Signs of DA-related lesions are different stages of healing, surrounding normal-appearing skin, location in easy to reach areas, and irregular or bizarre morphology. Patients are often otherwise healthy.

The diagnosis of DA is one of exclusion that is difficult to verify, as patients seldom admit to their involvement in producing the lesions. It is important to have a broad differential diagnosis, as DA is capable of mimicking several conditions. First, it is important to consider malingering. If skin lesions are created deliberately for secondary gain, such as to obtain disability or insurance benefits, then the case is no longer considered psychiatrically-based, but instead an act of fraud. However, if skin lesions are created without an underlying material or personal gain, then it is considered an illness warranting medical and psychiatric intervention.

Second, it is important to consider Munchausen syndrome and Munchausen syndrome by proxy, which involves deceptively presenting one's self or another (a victim), respectively, as ill or injured, without obvious external reward. While similar in presentation, Munchausen patients often have an embellished explanation for their condition, with an extensive history of hospital admits and other organ involvement. In Munchausen by proxy, mentally ill individuals make up or cause illness or injury to another, typically a child or even a baby, who are unable to speak for themselves. Finally, since DA frequently occurs in adolescents, it is important to have a low threshold for suspecting physical or sexual abuse in these patients.

MANAGEMENT STRATEGY

Management of DA can be challenging, with most therapeutic options symptomatic and supportive. Topical treatment is first line, and may include bandages, dressings, emollients, baths, or antibiotics. *Protective dressings*, such as an Unna boot, are used to occlude involved areas and protect against further self-injurious behavior.

The mainstay of DA treatment is addressing the patient's underlying psychopathology and behavioral patterns, which could be done with different types of therapy, such as cognitive behavior therapy or psychotherapy. Psychotropic medications are useful in some cases, with appropriate agents depending on patients' underlying psychological issues. *Antidepressant medications*, such as *selective serotonin reuptake inhibitors*, could be helpful for patients with DA and primary or secondary depression. If there is clinical evidence of a psychotic process, *pimozide* could be considered. There have also been case reports of patients responding to *olanzapine*, an atypical antipsychotic, after other therapies failed. A multidisciplinary approach to management, between dermatologists and mental health professionals, is often necessary.

Physicians should be aware that DA patients have a psychiatric illness, and the skin lesions are often a cry for help. However, suggesting the lesions are psychiatrically based often has a negative effect on patient rapport. Direct confrontation should be avoided,

if possible, and instead, a *supportive environment* and *stable physician–patient therapeutic alliance* should be fostered. This is often done with short and frequent office visits.

With an adolescent patient, the clinician should encourage the parents to become involved in identifying psychosocial stressors and helping to modify the patient's environment to meet his or her needs. Certain parents could be resistant to their child's diagnosis and may become angry or critical toward the clinician. If there is intense antagonism between the adolescent patient and the parents, it may be advisable to see the patient alone to optimize the possibility of developing therapeutic rapport. Once the patient establishes trust in his or her physician, through a stable relationship, the physician may then help the patient recognize the psychosocial nature of their disorder and *recommend psychiatric consultation*.

Most DA patients have a chronic waxing and waning course of disease that fluctuates with life circumstances. Even when DA is under control, physicians should continue to follow patients at regular intervals to prevent a relapse in self-destructive behavior. *Regular visits*, whether or not the lesions are present, will help patients feel cared for and diminish the conscious or unconscious desire to self-harm.

Specific Investigations

- Rule out malingering
- Rule out any organic dermatologic disease
- Assess for associated psychiatric disorders (e.g., depression)

Dermatitis artefacta. Lavery MJ, Stull C, McCaw I, et al. Clin Dermatol 2018; 719–22.

An up-to-date review of DA.

Dermatitis artefacta and artefactual skin disease: the need for a psychodermatology multidisciplinary team to treat a difficult condition. Mohandas P, Bewley A, Taylor R. Br J Dermatol 2013; 169(3): 600–6.

Retrospective review of 28 DA cases. Suggests that a combined approach with both dermatology and mental health professionals results in improved patient outcomes.

First-Line Therapies

• Occlusive dressings	D
• Psychotropic agents	D
• Psychotherapy (even if only supportive)	D
• Management of secondary cutaneous complications	D

Second-Line Therapy

• Olanzapine	D

The current management of delusional parasitosis and dermatitis artefacta. Koblenzer CS. Skin Therapy Lett 2010; 15: 1–3.
Review of DA treatment, including the use of aripiprazole.

Self-inflicted skin diseases. A retrospective analysis of 57 patients with dermatitis artefacta seen in a dermatology department. Nielsen K, Jeppesen M, Simmelsgaard L, et al. Acta Derm Venereol 2005; 85: 512–5.

Retrospective analysis of 57 DA patients.

Treatment of self-mutilation with olanzapine. Garnis-Jones S, Collins S, Rosenthal D. J Cutan Med Surg 2000; 4: 161–3.

Three DA patients successfully treated on low-dose olanzapine therapy following failure of other treatment modalities.

Training future dermatologists in psychodermatology. Van Moffaert M. Gen Hosp Psychiatry 1986; 8: 115–8.

Palliative dermatologic measures such as occlusive bandages, ointments, or placebo drugs can therapeutically impact the psychiatric problem by symbolizing the medical attention and care the patient with DA is craving.

Artefactual skin disease in children and adolescents. Rogers M, Fairley M, Santhanam R. Aust J Dermatol 2002; 42(4): 264–270.

DA lesions often on children's head or neck. Non-confrontation with the child is recommended, but parents should be clearly explained the diagnosis so they understand the child's need for psychiatric help.

Dermatitis herpetiformis

Bridget E. Shields, John J. Zone



Dermatitis herpetiformis (DH) is a cutaneous manifestation of celiac disease (CD). More than 85% of patients with DH have a gluten-sensitive enteropathy (CD) that varies in clinical and histologic severity. The skin and intestinal disease both respond to gluten restriction. DH symptoms range from minimally pruritic papules on the elbows and knees to severe, intensely pruritic vesicles over multiple extensor surfaces (see figure). The prevalence of DH is 10–39 per 100,000 persons in the Caucasian population and occurs most frequently in those of northern European descent. CD is rare in those with DH in the Japanese population. One in six patients diagnosed with CD has DH. DH is distinguished from other bullous diseases by characteristic histologic, immunologic, and gastrointestinal findings. Histologically, vesicle formation at the dermal–epidermal junction and infiltration of dermal papillary tips with neutrophils occurs in two-thirds of cases; however, non-specific inflammation is also frequent. Direct immunofluorescence shows granular or fibrillar IgA localized in the dermal papillary tips or along the basement membrane of perilesional skin.

MANAGEMENT STRATEGY

If patients adhere to a strict gluten-free diet, they are likely to undergo long-term remission. Associated intestinal symptoms are minimized and relapses are usually associated with dietary indiscretions. Elevated levels of IgA antibodies to tissue transglutaminase (TG2) are characteristic of CD. Levels correlate with the degree of intestinal inflammation and decrease with gluten restriction. Elevated levels of IgA epidermal transglutaminase (TG3) antibodies are characteristic of DH and are responsible for the diagnostic IgA deposits in skin. Serum levels of both antibodies correlate with response to a gluten-free diet but are not affected by dapsone. DH can be well controlled with medical therapies such as dapsone or sulfapyridine alone, but intestinal symptoms, if present, will continue unabated and contribute to the risk of small intestine lymphoma. Cutaneous disease recurs in 24–72 hours if dapsone is discontinued. Rare patients will enjoy spontaneous DH remission without medical therapy or dietary restriction.

Dapsone is the drug of choice for DH and is currently the only drug approved by the US Food and Drug Administration for DH. We recommend initial treatment with low-dose dapsone at 25 mg daily. Pruritus will usually improve within 24–48 hours and the papulovesicular lesions within 1 week. Correspondingly smaller doses (0.5–1 mg/kg) should be used in children. Maintenance therapy is then adjusted on a weekly basis to maintain adequate suppression of symptoms. The average maintenance dose is 0.5–1.0 mg/kg daily. Despite adequate dapsone dosages, outbreaks of facial and scalp lesions are common.

Adherence to a gluten-free diet (GFD) improves clinical symptoms in patients with DH. Gluten restriction targets the cause of disease as well as the symptoms. Advantages include a reduction in dapsone dosage, improvement in gastrointestinal symptoms, and reduced risk of lymphoma incident to DH and CD, a benefit not seen with dapsone. Strict adherence to a GFD is challenging, and reintroduction of gluten can exacerbate DH. Rare patients will not respond to gluten restriction. In the author's opinion, a useful therapeutic strategy is the initial control of DH symptoms with dapsone coincident with a GFD with subsequent tapering of dapsone. Oats have been found to be non-toxic in most patients with DH and may broaden gluten-free dietary options.

Sulfapyridine is an alternative in patients intolerant to dapsone and offers significant therapeutic efficacy. Sulfapyridine is started at 500 mg three times a day and is increased to a maximum maintenance dose of 1.5 g three times a day. Virtually all DH patients respond to dapsone, but some patients may not respond to sulfapyridine at any dose.

Nicotinamide, tetracycline (or a combination of the two), heparin, ciclosporin, colchicine, rituximab, and systemic corticosteroids have been reported to provide therapeutic benefit in DH. Topical corticosteroid application is generally inadequate when used alone to control DH symptoms. Potent corticosteroids in gel form applied frequently may provide relief for occasional lesions that develop on otherwise adequate dapsone or GFD therapy. Ultraviolet light may provide symptomatic relief. Patients with refractory disease should be screened for iodide ingestion, which can exacerbate DH and has been found in medications, contrast media, dental packing strips, food sources, and dietary supplements.

Specific Investigations

- Lesional biopsy for histology and perilesional biopsy for direct immunofluorescence
- Complete blood count and liver function tests
- Glucose-6-phosphate dehydrogenase levels
- IgA tissue transglutaminase (TG2) antibodies
- IgA epidermal transglutaminase (TG3) antibodies

Deposition of granular IgA relative to clinical lesions in dermatitis herpetiformis. Zone JJ, Meyer LJ, Petersen MJ. Arch Dermatol 1996; 132: 912–8.

Granular IgA deposition in perilesional, clinically normal-appearing skin is the most reliable diagnostic criterion for DH. The diagnosis of DH should not be made without identification of granular IgA in dermal papillae. Linear IgA disease demonstrates identical histology but does not respond to a GFD. These disorders can only be separated on direct immunofluorescence. If direct immunofluorescence is negative and histology is suggestive of DH, a repeat biopsy for direct immunofluorescence is recommended.

Dermatitis herpetiformis: from the genetics to the development of skin lesions. Bonciani D, Verdelli A, Bonciolini V, et al. Clin Dev Immunol 2012; 2012: 239691.

DH is a cutaneous manifestation of CD. The pathogenesis involves an immune response in genetically susceptible individuals (HLA-DQ2 and -DQ8) to dietary gliadin peptides complexed with tissue transglutaminase (TG2). IgA TG2 antibodies are an index of the severity of intestinal involvement and correlate with response to gluten restriction. IgA epidermal transglutaminase (TG3) antibodies are present in the serum of new DH patients and are complexed with TG3 to form the diagnostic immune complexes in the skin of DH patients.

First-Line Therapies

• Dapsone	B
• Gluten-free diet	B

Suggested guidelines for patient monitoring: hepatic and hematologic toxicity attributable to systemic dermatologic drugs. Wolverson SE, Remlinger K. Dermatol Clin 2007; 25: 195–205.

Dapsone may produce a drug hypersensitivity syndrome with liver toxicity in the first 3–12 weeks. Monitoring of the aspartate transaminase (AST), alanine transaminase (ALT), and eosinophil count is indicated. Hepatocellular toxicity may occur in a dose-related fashion, especially with doses greater than 2 mg/kg. AST and ALT should be monitored when dapsone dosage is increased. There are three main hematologic toxicities of dapsone: hemolysis, methemoglobinemia, and agranulocytosis. Methemoglobinemia is usually mild and not problematic unless the patient has underlying cardiopulmonary problems. Agranulocytosis is rare and usually occurs in the first 3–12 weeks of therapy. Symptoms demanding attention include pharyngitis, fever, and oral ulcerations. Virtually all patients have some degree of hemolysis and a decrease in hemoglobin of 1–3 g/dL is expected. Initiation of small doses of dapsone (25 mg daily) and gradual dose increases will minimize these symptoms. A compensatory reticulocytosis occurs. Hemolysis may be severe in patients with glucose-6-phosphate dehydrogenase deficiency. Glucose-6-phosphate dehydrogenase levels should be evaluated prior to the initiation of therapy to avoid catastrophic hemolytic anemia.

Complete blood count and liver function tests should be checked every 2–3 weeks for the first 3 months, then every 3–6 months thereafter.

A long-term gluten-free diet as an alternative treatment in severe forms of dermatitis herpetiformis. Nino M, Ciacci C, Delfino M. J Dermatolog Treat 2007; 18: 10–2.

The treatment of DH with a GFD alone compared to GFD and dapsone was reported. Eighty-seven percent of patients on GFD alone had a complete remission in 18 months (67% of severe patients). A total of 89% of patients on diet and dapsone had remission of skin disease (70% of severe patients) and 11% were improved.

Second-Line Therapies

• Sulfapyridine and sulfasalazine	E
• Elemental diet	C

Management of dermatitis herpetiformis. Cardones AR, Hall RP. Dermatol Clin 2011; 29(4): 631–5. doi: 10.1016/j.det.2011.06.015.

Sulfapyridine is not readily available in the United States but can be prescribed through compounding pharmacies. Sulfasalazine, which is more readily available, is metabolized to 5-amino-salicylic acid and sulfapyridine. Patients have responded to sulfasalazine, 2–6 g/day, administered three times daily.

The effect of elemental diet with and without gluten on disease activity in dermatitis herpetiformis. Kadunce DP, McMurtry MP, Avots-Avotins A, et al. J Invest Dermatol 1991; 97: 175–82.

In refractory DH, elemental diet therapy is effective and produces dramatic clinical improvement within 2–4 weeks. It involves the ingestion of amino acid and carbohydrate alone and is commercially available as Vivonex. It produces rapid healing of the intestine and relief of cutaneous symptoms but was designed for tube feeding and is considered unpalatable by many.

In this author's experience, an elemental diet containing short chain polypeptides is less effective.

Third-Line Therapies

• Tetracycline and nicotinamide	E
• Heparin	E
• Cyclosporin	E
• Colchicine	E
• Systemic corticosteroids	E
• Rituximab	E
• Topical dapsone	E

Dermatitis herpetiformis effectively treated with heparin, tetracycline and nicotinamide. Shah SAA, Ormerod AD. Clin Exp Dermatol 2000; 25: 204–5.

Case report of a patient with severe DH, intolerant to dapsone and sulfapyridine, who achieved DH resolution with subcutaneous low-dose heparin, nicotinamide 1.5 g daily in divided doses, and tetracycline 2 g daily. The patient was on a GFD.

A rare case of dermatitis herpetiformis requiring parenteral heparin for long-term control. Tan CC, Sale JE, Brammer C, et al. Dermatology 1996; 192: 185–6.

A patient with severe DH, intolerant to dapsone and sulfapyridine, was treated with parenteral heparin with complete resolution of her skin lesions within 1 week of therapy. This treatment is not practical for long-term management.

Efficacy of cyclosporine in two patients with dermatitis herpetiformis resistant to conventional therapy. Stenveld HJ, Starink TM, van Joost T, et al. J Am Acad Dermatol 1993; 28: 1014–5.

Two patients with severe DH who were intolerant and/or unresponsive to conventional therapy were treated with cyclosporin (5–7 mg/kg daily) with resolution of skin lesions.

Dermatitis herpetiformis responsive to systemic corticosteroids. Lang PG. J Am Acad Dermatol 1985; 13: 513–5.

A patient with DH was treated successfully with a short course of prednisone and remained clear 4 months after discontinuation. He was successfully re-treated with systemic corticosteroids for recurrence of the skin lesions.

Treatment of dermatitis herpetiformis with colchicine. Silver DN, Juhlin EA, Berczeller PH, et al. Arch Dermatol 1980; 116: 1373–84.

Oral colchicine resulted in significant improvement of skin lesions in three of four patients with DH. The authors suggest that colchicine may be used when dapsone or sulfapyridine is contraindicated.

Rituximab treatment for recalcitrant dermatitis herpetiformis. Albers LN, Zane JJ, Stoff BK, et al. JAMA Dermatol 2017; 153(3): 315–8.

A man with DH unresponsive to dapsone and conventional immunosuppressive therapies was poorly adherent to a GFD. He underwent treatment with rituximab (4 weekly infusions of 375 mg/m²), which resulted in complete and sustained resolution of symptoms. IgA TG2 and TG3 antibody levels returned to normal.

Rituximab treatment for dermatitis herpetiformis in the setting of type 1 diabetes mellitus, celiac disease, vitiligo,

autoimmune hemolytic anemia, and autoimmune thrombocytopenia. Nguyen KT, Gwinn CC, Vary JC. JAAD Case Rep 2020; 6(2): 122–3.

A man with DH and multiple autoimmune diseases (including hemolytic anemia) precluding the use of dapsone was treated with oral prednisone (1–1.5 mg/kg/day) and rituximab (375 mg/m² per week for 4 weeks). He required the addition of a 4-day course of dexamethasone (40 mg daily) and mycophenolate mofetil (500 mg twice daily), which resulted in DH quiescence. The patient remained clear following steroid taper.

Topical dapsone gel as an effective therapy in dermatitis herpetiformis. Burbidge T, Haber RM. J Cutan Med Surg 2016; 20(6): 600–1.

A 66-year-old woman with intermittent flares of DH treated with topical dapsone 5% gel twice daily as she transitioned to a GFD, resulting in dramatic improvement.

Dermatofibrosarcoma protuberans

*Cristian Navarrete-Dechent, Shoko Mori,
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Dermatofibrosarcoma protuberans (DFSP) is a rare soft tissue tumor that represents 0.1% of all cancers and 1.8% of all soft tissue sarcomas. However, it is the most common type of cutaneous sarcoma, mainly affecting adults (30–50 years). Congenital and pediatric cases are rare. DFSP is slightly more common in females (1.14-fold) and Blacks (twofold compared to Whites). The most frequent location is the trunk (42%–49%), followed by the extremities (37%; typically upper extremities), and the head and neck region (13%–16%).

DFSP typically has an indolent growth pattern; however, it has the potential for subclinical extension, morbidity, and local recurrence. DFSP is also associated with a low (2%–5%) risk of metastasis. The 10-year disease-specific survival is 99.1% (97.6%–99.7%). When fibrosarcomatous changes (FS) are found, it is associated with a higher rate of local recurrence, distant metastasis, and decreased survival.

Dermatofibrosarcoma protuberans. Mendenhall WM, Zlotnicki RA, Scarborough MT. *Cancer* 2004; 101: 2503–8.

In this narrative review, the authors discuss the pathophysiology of DFSP as well as its prognosis and histopathological features.

Dermatofibrosarcoma protuberans: a clinicopathologic analysis of patients treated and followed at a single institution. Bowne WB, Antonescu CR, Leung DH, et al. *Cancer* 2000; 88: 2711–20.

In this study with 159 patients, 84% had the classic DFSP variant and 16% had the more aggressive FS-DFSP type. The overall 5-year local recurrence-free survival rate was 75%. Two patients died of metastatic disease.

Incidence and survival of primary dermatofibrosarcoma protuberans in the United States. Kreicher KL, Kurlander DE, Gittleman HR, et al. *Dermatol Surg* 2016; 42 Suppl 1: S24–31.

In this study with almost 7000 patients using the SEER database from 2000 to 2010, the authors found a stable incidence. The trunk was the most common anatomic site. Incidence among women was 1.14 times higher than men. Incidence among Blacks was almost two times the rate among Whites. Ten-year relative survival of DFSP was 99.1% (95% CI: 97.6–99.7).

Prognostic factors, treatment, and survival in dermatofibrosarcoma protuberans. Criscito MC, Martires KJ, Stein JA. *JAMA Dermatol* 2016; 152: 1365–71.

In this study using the SEER database, older age at diagnosis, male sex, and DFSP tumor size were significantly associated with poorer overall survival in a controlled analysis.

Fibrosarcomatous ('high-grade') dermatofibrosarcoma protuberans: clinicopathologic and immunohistochemical study of a series of 41 cases with emphasis on prognostic significance. Mentzel T, Beham A, Katenkamp D, et al. *Am J Surg Pathol* 1998; 22: 576–87.

The fibrosarcomatous variant of dermatofibrosarcoma protuberans (FS-DFSP) represents an uncommon form of DFSP. In this study including 41 cases, FS-DFSP represented a form of tumor progression and was associated with a significantly more aggressive clinical course.

Specific Investigations

- Skin biopsy including subcutis
- Immunostains (e.g., CD34)
- Genetic studies (e.g., FISH)
- Imaging (e.g., magnetic resonance imaging [MRI], ultrasound, PET-CT) to evaluate local and systemic extent of disease

Clinically, DFSP presents as an indurated, irregular, usually skin-colored, subcutaneous tumor, which may display telangiectasia. Rare, pigmented variants exist (Bednar tumor). Differential diagnosis includes dermatofibroma, scar/keloid, epidermal cyst, and lipoma. Definitive diagnosis should be based on biopsy and histopathologic findings. DFSP is frequently misdiagnosed due to inadequate tissue sampling or superficial biopsy. A biopsy, such as a punch or full-thickness incision, needs to include the subcutaneous tissue. Undermining at the time of biopsy is not recommended due to difficulty in reinterpreting re-excisions and possible tumor seeding.

Dermatofibrosarcoma protuberans is a unique fibrohistiocytic tumour expressing CD34. Aiba S, Tabata N, Ishii H, et al. *Br J Dermatol* 1992; 127: 79–84.

On histopathology, a diffuse infiltration of the dermis and subcutaneous adipose tissue with spindle-shaped, tightly packed, neoplastic cells is seen. These cells are arranged in a classic 'storiform' pattern (reminiscent of a straw mat). On immunostains, DFSP typically is diffusely positive for CD34 and negative for Factor XIIIa (FXIIIa). In contrast, dermatofibroma, a benign dermal tumor, is negative for CD34 and positive for FXIIIa.

Subcutaneous dermatofibrosarcoma protuberans, a rare subtype with predilection for the head: a retrospective series of 18 cases. Lombart B, Serra-Guillen C, Rubio L, et al. *J Am Acad Dermatol* 2017; 77: 503–11 e1.

Recently, a purely subcutaneous variant (without dermal involvement) has been described. This subcutaneous DFSP variant more frequently involves the head and neck area, extends to the periosteum, and requires a greater number of stages to clear on Mohs surgery.

Genetics of dermatofibrosarcoma protuberans family of tumors: from ring chromosomes to tyrosine kinase inhibitor treatment. Sirvent N, Maire G, Pedetour F. *Genes Chromosomes Cancer* 2003; 37: 1–19.

DFSP is characterized genetically by a translocation involving chromosome 17 and 22 in greater than 90% of cases. Most commonly, the translocation is caused by a supernumerary ring chromosome.

Deregulation of the platelet-derived growth factor β -chain gene via fusion with collagen gene *COL1A1* in dermatofibrosarcoma protuberans and giant-cell fibroblastoma. Simon MP, Pedetour F, Sirvent N, et al. *Nat Genet* 1997; 15: 95–8.

The t(17:22) mutation leads to collagen type I alpha (*COL1A1*) and platelet-derived growth factor subunit β (*PDGF β*) gene fusion, resulting in the expression of the *COL1A1*-*PDGF β* fusion protein. *PDGF β* is a potent mitogen for mesenchymal cells with autocrine and paracrine activation of the *PDGF* receptor (*PDGFR*) on tumor cells; *PDGF β* activates the Ras MAPK and PI3K-AKT-mTOR pathway leading to uncontrolled cell growth. The identification of the aberrant activation of the *PDGF* pathway led to the utilization of imatinib, a *PDGFR* inhibitor, in the treatment of locally advanced and metastatic DFSP cases.

There is a lack of optimal imaging to assess tumor extension and monitor treatment in DFSP, as evaluation on clinical grounds alone may be inaccurate. This limitation is particularly problematic in patients who do not undergo surgery, either due to significant tumor extension or due to high risk of cosmetic deformity or functional impairment, and who may be eligible for treatment with tyrosine kinase inhibitors.

Correlation between preoperative magnetic resonance imaging and surgical margins with modified Mohs for dermatofibrosarcoma protuberans. Serra-Guillen C, Sanmartin O, Llobart B, et al. *Dermatol Surg* 2011; 37: 1638–45.

MRI with contrast is the likely imaging of choice as it provides better sensitivity than palpation for detecting deep invasion (67% vs 58%); however, MRI can underestimate the depth and area of involvement compared with histopathology. In cases of metastatic disease, a PET-CT may be useful to evaluate systemic dissemination.

MANAGEMENT STRATEGY

Surgery is the standard of care for the majority of DFSP cases. Surgical approaches include wide local excision (WLE), *Mohs micrographic surgery* (MMS), and other modified surgical approaches with comprehensive margin assessment (e.g., Tubingen technique). National Comprehensive Cancer Network (NCCN) guidelines recommend meticulous planning of the surgical approach. Every effort should be made to obtain negative margins as inadequate initial resection may result in local recurrence or increased risk of metastasis. Exhaustive surgery is recommended until margins are clear even if reexcision is required. Resection may be achieved by either WLE with 2–3 cm margins down to the fascia or with surgical techniques that entail a complete circumferential margin assessment (such as MMS or the Tubingen

technique). Reconstruction and tissue rearrangement/flap should be delayed until negative margins are confirmed.

Surgery (either WLE or MMS) is the cornerstone of treatment for DFSP according to the NCCN and every attempt should be made to obtain clear margins. There are cases, however, in which DFSP is unresectable due to tumor extension/size, or risk of cosmetic or functional impairment, such as tumors located on the head and neck, genitalia, or hands and feet. Similarly, some patients may be inoperable due to medical comorbidities.

For larger tumors where surgical resection in the office with local anesthesia is not feasible, surgery with general anesthesia in the operating room may be needed. These cases tend to have a higher recurrence rate and a worse prognosis due to larger size, multiple recurrences, and more aggressive pathology. Differences in cohorts between patients treated in an outpatient setting versus operating room may not be comparable and subject to referral/selection bias.

Radiation therapy (RT) might be considered as a treatment alternative for DFSP. This tumor is considered to be radiosensitive and RT may be used for cases with a high risk of recurrence (microscopic or macroscopic positive margins; adjuvant RT).

Radiation is not recommended in younger patients (under the age of 50 because of increased risk of radiodermatitis, scarring, and second malignancies) or in patients with a previous history of RT. Radiation may be contraindicated in patients with connective tissue diseases or genetic conditions predisposing to skin cancer (e.g., patients with Gorlin syndrome or xeroderma pigmentosum). Combined conservation resection and postoperative radiation could be considered for situations where adequate wide excision alone would result in major cosmetic or functional morbidity. Inoperable, recurrent, and metastatic tumors show significant responses to *imatinib*.

First-Line Therapies

• Mohs micrographic surgery	B
• Wide local excision (2–3 cm)	B

A comparison of Mohs micrographic surgery and wide local excision for treatment of dermatofibrosarcoma protuberans with long-term follow-up: the Mayo Clinic experience. Lowe GC, Onajin O, Baum CL, et al. *Dermatol Surg* 2017; 43: 98–106.

In this non-randomized study, 67 patients treated with MMS and 91 patients with WLE were included. Twenty-eight patients (30.8%) treated with WLE had recurrence (mean time to recurrence, 4.4 years), whereas only two (3.0%) patients treated with MMS recurred (at 1.0 and 2.6 years). Recurrence-free survival rates at 1, 5, 10, and 15 years was significantly higher with MMS ($p < .001$). Mean preoperative lesion sizes were similar between the WLE and MMS groups. Two Mohs layers typically were required for margin control. Surgical excision with meticulous histologic evaluation of all surgical margins is needed for DFSP treatment to achieve long-term high cure rates and low morbidity.

Relapse in dermatofibrosarcoma protuberans: a histological and molecular analysis. Molina AS, Duprat Neto JP, Bertolli E, et al. *J Surg Oncol* 2018; 117: 845–50.

A retrospective study including 61 DFSP patients. There was a recurrence in six patients (9.8% recurrence rate). All recurrences occur in patients who underwent WLE with margins of 2 cm or less. No recurrences were observed when margins of at least 3 cm were used.

Efficacy of Mohs micrographic surgery for the treatment of dermatofibrosarcoma protuberans: systematic review. Foroozan M, Sei JF, Amini M, et al. *Arch Dermatol* 2012; 148: 1055–63.

A systematic review of 23 studies showed that recurrence rate was lower with MMS (1.1%) vs. WLE (6.3%). The mean follow-up period ranged from 26 to 127 months. The mean time to recurrence was 68 months.

Dermatofibrosarcoma protuberans (DFSP): predictors of recurrence and the use of systemic therapy. Fields RC, Hameed M, Qin L-X, et al. *Ann Surg Oncol* 2011; 18: 328–36.

In this large retrospective study, including 244 patients evaluated by oncologic surgery, 70% of patients with primary DFSPs had no evidence of disease (NED) at a median follow-up of 50 months. For recurrent cases, only 47% had NED at the last time of follow-up. On multivariate analysis, depth was associated with disease-free survival (DFS) in primary DFSP. DFS was related to margin status (R1 vs. R0) in the recurrent DFSP group. A total of 22 patients required additional therapy (e.g., RT, systemic therapy).

Second-Line Therapies

- Radiation therapy 50–66 Gy (unresectable, adjuvant if micro- or macroscopic margin involvement) **C**
- Imatinib 400–800 mg (locally advanced, metastatic, unresectable) **C**

S1 guidelines for dermatofibrosarcoma protuberans (DFSP) – update 2018. Ugurel S, Kortmann RD, Mohr P, et al. *J Dtsch Dermatol Ges* 2019; 17: 663–8.

RT can also be considered as a primary treatment modality when there is contraindication for surgery or there is a high risk of cosmetic and functional impairment. A total dose of 60–70 Gy and a 3–5 cm safety margin is used. A lower dose may be used with palliative intent. Adjuvant RT of the tumor bed following a complete surgical excision with negative margins is not recommended.

Dermatofibrosarcoma protuberans: long-term outcomes of 53 patients treated with conservative surgery and radiation therapy. Castle KO, Guadagnolo BA, Tsai CJ, et al. *Int J Radiat Oncol Biol Phys* 2013; 86: 585–90.

The study included 53 consecutive DFSP patients treated with surgery and preoperative or postoperative RT between 1972 and 2010. Radiation dose ranged from 50 to 66 Gy (median dose, 60 Gy). Local control was 98% and 93% at 5 and 10 years, respectively. DFS was 98% and 93% at 5 and 10 years, respectively.

Molecular targeting of platelet-derived growth factor B by imatinib mesylate in a patient with metastatic dermatofibrosarcoma protuberans. Rubin BP, Schuetze SM, Eary JF, et al. *J Clin Oncol* 2002; 20: 3586–91.

In 2002, the first case report showing the efficacy of imatinib in a 25-year-old patient with metastatic DFSP of the lower limb was reported. The patient was severely impaired but was able to walk 2 weeks after initiating treatment; surgery was performed 1 month later. Due to this initial efficacy, numerous case series subsequently evaluated the utility of imatinib in the treatment of DFSP.

Imatinib mesylate in advanced dermatofibrosarcoma protuberans: pooled analysis of two phase II clinical trials. Rutkowski P, Van Glabbeke M, Rankin CJ, et al. *J Clin Oncol* 2010; 28: 1772–9.

The study included a cohort of 24 DFSP patients with tumor size ranging from 1.2 to 49 cm and metastases in seven patients (mainly lungs). Imatinib 400–800 mg/day obtained a partial response in 45.9% of DFSP patients, stable disease in 25% of cases, and progressive disease in 16.6% of patients. Clinical benefit (partial response plus stable disease) from imatinib was 70.9%. The 1-year overall survival rate was 87.5% (range, 66.08%–95.79%). After this phase II study published in 2010 evaluating two different cohorts, the NCCN guidelines incorporated imatinib into their treatment recommendations.

National Comprehensive Cancer Network. Dermatofibrosarcoma protuberans (Version 1.2018) 2017.

The NCCN guidelines recommend imatinib for metastasis/recurrences when ‘disease is unresectable, or unacceptable functional or cosmetic outcomes with resection are predicted’.

Diagnosis and treatment of dermatofibrosarcoma protuberans. European consensus-based interdisciplinary guideline. Saiag P, Grob JJ, Lebbe C, et al. *Eur J Cancer* 2015; 51: 2604–8.

The European consensus-based interdisciplinary guidelines also recommend imatinib for inoperable primary tumors, inoperable locally recurrent disease, and metastatic DFSP.

Imatinib treatment for locally advanced or metastatic dermatofibrosarcoma protuberans: a systematic review. Navarrete-Dechent C, Mori S, Barker CA, et al. *JAMA Dermatol* 2019; 155: 361–9.

A recent systematic review showed a complete response of 5.2% and a partial response of 55.2% when using imatinib in locally advanced or metastatic DFSP. The same study showed no difference between a daily dose of 400 mg or 800 mg. Adverse events were found in 73.5% of cases; severe adverse events were found in 15.1% of cases.

Dermatomyositis

Ruth Ann Vleugels, Scott A. Elman,
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Dermatomyositis (DM) is an idiopathic inflammatory myopathy characterized by cutaneous disease, including a heliotrope eruption, Gottron papules, photodistributed erythema and poikiloderma, and/or periungual changes. Patients with cutaneous lesions of DM often have weakness of the proximal muscles; elevated enzymes such as creatine kinase or aldolase; or abnormal electromyogram, magnetic resonance imaging (MRI), or muscle biopsy findings. Some, however, have cutaneous disease that either precedes the onset of demonstrable muscle disease or occurs in its absence (clinically amyopathic DM). In addition, many patients have persistent cutaneous manifestations long after their muscle disease is adequately controlled. DM in children and adolescents may be complicated by calcinosis, particularly when treatment is delayed. Adults with DM have an increased risk of having or developing a malignancy, usually within the first 3 years after diagnosis.

MANAGEMENT STRATEGY

Before treatment the patient should be thoroughly evaluated to assess the severity of both skin and muscle disease; the presence of systemic involvement such as pulmonary, cardiac, or gastrointestinal involvement; and the presence of malignancy.

The goal of management is to *reverse the weakness, prevent contractures*, and allow the patient to return to normal functional status. The *prevention or treatment of calcinosis* is usually an issue in the management of children and adolescents but may occur in adults as well. Cutaneous disease has a large impact on quality of life; they are troubled by intense *pruritus*, *photosensitivity*, and the *appearance of their skin* and may therefore require treatment even when the muscle disease has been effectively managed or is absent.

For the myopathy, *systemic corticosteroids in conjunction with an immunosuppressive agent* is standard treatment. Most patients respond to this strategy, but for those who do not, *high-dose*

intravenous immune globulin (IVIG) or rituximab may be of benefit. Patients with cutaneous disease are photosensitive and are treated with *photoprotective clothing and wide-brimmed hats, sunscreens, behavior modification, topical corticosteroids*, and occasionally *topical calcineurin inhibitors, oral antimalarials*, and very often an *immunosuppressive agent*. *High-dose IVIG* may also be used for recalcitrant cutaneous disease. Ultimately, the therapeutic goal is to provide relief from the cutaneous inflammation and associated symptoms utilizing a combination of medications selected after considering comorbidities.

Assessment of response of cutaneous dermatomyositis has been hampered by a lack of validated assessment tools. To this end, three such measures have been developed: the Cutaneous Dermatomyositis Area and Severity Index (CDASI) (Arch Dermatol Res 2008; 300: 3–9, and Br J Dermatol 2012; 162: 669–73), the Dermatomyositis Skin Severity Index (DSSI) (Br J Dermatol 2008; 158: 345–50), and a cutaneous assessment tool in juvenile dermatomyositis (Arthritis Rheum 2008; 59: 352–6); however, the tools are being utilized more frequently and will ideally become incorporated as standard practice in the future as a means to assess cutaneous disease response.

Specific Investigations

- A thorough evaluation to exclude other causes of myopathy
- Malignancy evaluation, including computed tomography (CT) scans of chest, abdomen, and pelvis; transvaginal pelvic ultrasound; stool occult blood testing and age-appropriate endoscopy; Papanicolaou smear; mammography; complete blood count; comprehensive metabolic panel; CA-125; CA 19-9; urinalysis; and full physical examination
- Serum creatine kinase and aldolase
- Electromyogram, MRI, or ultrasound of muscle
- Muscle biopsy
- Assessment for the presence of systemic involvement (e.g., pulmonary, esophageal, and cardiac)
- Myositis-specific antibodies

Treatment

Scalp involvement in dermatomyositis. Often overlooked or misdiagnosed. Kasteler JS, Callen JP. JAMA 1994; 272: 1939–41.

Skin lesions in patients with DM, particularly those of the scalp, are often confused with psoriasis or seborrheic dermatitis. Additionally, DM skin disease may simulate cutaneous lupus erythematosus or lichen planus.

Influence of age on characteristics of polymyositis and dermatomyositis in adults. Marie I, Hatron PY, Levesque H, et al. Medicine (Baltimore) 1999; 78: 139–47.

This group compared characteristics of younger versus older adults and found that the incidence of malignancy was much higher in the older population, resulting in a poorer prognosis for this subset of patients.

Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Hill CL, Zhang Y, Sigurgeirsson B, et al. Lancet 2001; 357: 96–100.

This study demonstrated that malignancies of the ovaries, pancreas, stomach, colon, and rectum and non-Hodgkin lymphoma were overrepresented in patients with DM. The malignancy

risk decreased with each passing year after DM diagnosis and approached background levels at 3 years.

Malignancy evaluations should be repeated annually for at least 3 years. For details on suggested malignancy screening, please see specific investigations above.

A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. Love LA, Leff RL, Fraser DD, et al. *Medicine* (Baltimore) 1991; 70: 360–74.

This study compared the usefulness of myositis-specific autoantibodies (anti-aminoacyl-tRNA synthetases, antisignal recognition particle [anti-SRP], and anti-Mi-2) to the standard clinical categories (polymyositis, DM, overlap myositis, cancer-associated myositis, and inclusion body myositis) in predicting clinical signs and symptoms and prognosis in 212 adult patients. Compared with those without these antibodies, patients with anti-aminoacyl-tRNA synthetase autoantibodies ($n=47$) had significantly more frequent arthritis, fever, interstitial lung disease, and ‘mechanic’s hands’; higher mean prednisone dose at survey; higher proportion of patients receiving cytotoxic drugs; and higher death rates. Those with anti-SRP antibodies ($n=7$) had more frequent palpitations, myalgias, severe refractory disease, and higher death rates. Patients with anti-Mi-2 antibodies ($n=10$) had increased ‘V-sign’ and ‘shawl-sign’ rashes and cuticular overgrowth, as well as a good response to therapy. These findings suggest that myositis-specific autoantibody status is a more useful guide than clinical group in assessing patients with myositis.

Dermatomyositis: an update on diagnosis and treatment. Cobos GA, Femia A, Vleugels RA. *Am J Clin Dermatol* 2020 Feb 24 [Epub ahead of print].

This review takes an in-depth look at myositis-specific autoantibodies, many of which are associated with specific phenotypes, which may help the clinician prognosticate as well as identify more common DM systemic manifestations.

Currently, the anti-aminoacyl-tRNA synthetase autoantibodies are those antibodies most frequently incorporated into clinical practice. The recently described antibodies are becoming more widely available although interlaboratory concordance is thought to be highly variable.

A novel dermato-pulmonary syndrome associated with MDA-5 antibodies: report of 2 cases and review of the literature. Chaisson NE, Park J, Orbai AM, et al. *Medicine* (Baltimore) 2012; 91: 220–8.

This work describes the clinical features typically associated with a novel autoantibody termed *melanoma differentiation-associated protein 5* (MDA-5), including interstitial lung disease that can be rapidly progressive, arthritis, and a characteristic cutaneous phenotype, including ulcerations in Gottron papules; Gottron sign; and along the lateral nailfold, painful palmar papules, and prominent alopecia (this phenotype was first described in 2011 by Fiorentino et al. The mucocutaneous and systemic phenotype of dermatomyositis patients with antibodies to MDA5 (CADM-140): a retrospective study. *J Am Acad Dermatol* 2011; 65: 25–34). Most patients with the MDA-5 antibody have clinically amyopathic DM. Although this entity was first recognized in Asian populations, it has since been described in others.

Most patients with cancer-associated dermatomyositis have antibodies to nuclear matrix protein NXP-2 or transcription intermediary factor 1- γ . Fiorentino DF, Chung LS, Christopher-Stone L, et al. *Arthritis Rheum* 2013; 65: 2954–62.

In two large DM cohorts, reactivity against either transcription intermediary factor-1 γ (TIF-1 γ) or NXP-2 identified 83% of patients with cancer-associated DM. In these cohorts, malignancy was associated with older age, male sex, and antibodies to either TIF-1 γ or NXP-2 on multivariate analysis (OR 3.78).

The MDA-5 and TIF-1 γ autoantibodies are not yet routinely available in all commercial laboratories. They define distinct clinical subsets and therefore may be useful in predicting patient outcomes in DM. Specific antibodies may potentially help prognosticate and alter screening practices for patients with DM in the future.

Interstitial lung disease in classic and skin-predominant dermatomyositis: a retrospective study with screening recommendations. Morganroth PA, Kreider ME, Okawa J, et al. *Arch Dermatol* 2010; 146: 729–38.

In this retrospective cohort study, 23% of patients had interstitial lung disease (ILD) based on CT findings, and all of these had a reduced diffusion capacity (DLCO) on pulmonary function tests as well. Prevalence of ILD was not statistically different between patients with and without muscle disease. The authors conclude that serial DLCO testing is reasonable in all patients with DM to screen for pulmonary involvement.

Incidence of dermatomyositis and clinically amyopathic dermatomyositis: a population-based study in Olmstead County, Minnesota. Bendewald MJ, Wetter DA, Li X, et al. *Arch Dermatol* 2010; 146: 26–30.

This retrospective population-based study found that 20% of the dermatomyositis cases were amyopathic in this population.

This epidemiologic study supports other data demonstrating that 20%–30% of adult DM patients lack muscle involvement.

First-Line Therapies

1 For cutaneous disease

- Sunscreens E
- Topical corticosteroids E
- Antimalarials – hydroxychloroquine (HCQ) or chloroquine (CQ) D
- Combination antimalarial therapy (quinacrine plus either HCQ or CQ) E
- Methotrexate D

2 For muscle disease

- Systemic corticosteroids B
- Immunosuppressive agents – methotrexate, mycophenolate mofetil, azathioprine A

The use of pulse corticosteroid therapy for juvenile dermatomyositis. Paller AS. *Pediatr Dermatol* 1996; 13: 347–8.

This report notes that pulse administration of systemic corticosteroids might result in less toxicity, and further that this therapy aids in the prevention of calcinosis.

Cutaneous lesions of dermatomyositis are improved by hydroxychloroquine. Woo TY, Callen JP, Voorhees JJ, et al. *J Am Acad Dermatol* 1984; 10: 592–600.

Seven patients with cutaneous lesions of DM that had not responded to therapy with corticosteroids and/or immunosuppressive agents were treated with hydroxychloroquine 200 mg once or twice daily in an open study. The response to the

addition of hydroxychloroquine was good in all patients, and three had total resolution of their skin lesions. In two patients the corticosteroid dosage could be tapered. Therapy with hydroxychloroquine did not appear to have any beneficial effect on the myositis.

Combination antimalarials in the treatment of cutaneous dermatomyositis: a retrospective study. Ang GC, Werth VP. Arch Dermatol 2005; 141: 855–9.

In this retrospective analysis, seven of 17 patients experienced at least near clearance of cutaneous symptoms with the use of antimalarial therapy alone: four of them required combination therapy (hydroxychloroquine 200 mg once or twice daily + quinacrine 100 mg daily; or chloroquine 250 mg daily + quinacrine 100 mg daily), and three of them responded well to antimalarial monotherapy. The median time required to efficacy was 3 months.

When considering combination antimalarial agents as a therapeutic option, it is critical to use quinacrine in addition to either hydroxychloroquine or chloroquine, given that quinacrine lacks ocular toxicity. Hydroxychloroquine and chloroquine both have ocular toxicity and should not be given concurrently.

Systemic treatment for clinically amyopathic dermatomyositis at 4 tertiary care centers. Pinard J, Femia AN, Roman M, et al. JAMA Dermatol 2019; 155(4): 494–6.

In this study, patients with cutaneous dermatomyositis rarely responded sufficiently to antimalarial therapy alone (10/88 or 11.4% responded adequately). Therefore, patients with moderate-to-severe skin disease were treated more aggressively, either with methotrexate or mycophenolate mofetil as initial therapy, alone or in conjunction with hydroxychloroquine.

Adverse cutaneous reactions to hydroxychloroquine are more common in patients with dermatomyositis than in patients with cutaneous lupus erythematosus. Pelle MT, Callen JP. Arch Dermatol 2002; 138: 1231–3.

In this case-control study, 31% of patients with dermatomyositis developed a cutaneous reaction to hydroxychloroquine, compared with 2.5% of those with cutaneous lupus.

Given the fact that hydroxychloroquine is utilized as a first-line therapy for cutaneous DM, awareness of the increased risk of cutaneous reactions in approximately one-third of DM patients is critical, as this can lead to worsening of the cutaneous DM and warrants cessation of hydroxychloroquine. A pretreatment warning is helpful in order to allow patients to alert the clinician to the development of a cutaneous reaction.

Second-Line Therapies

3 For cutaneous disease

- Topical calcineurin inhibitors (tacrolimus or pimecrolimus) **D**
- Mycophenolate mofetil **D**

4 For muscle disease

- IVIG **A**
- IVIG **A**
- Rituximab **A**
- Other immunosuppressive agents – cyclophosphamide, chlorambucil, cyclosporin, tacrolimus **D**

Topical tacrolimus 0.1% ointment for refractory skin disease in dermatomyositis: a pilot study. Hollar CB, Jorizzo JL. J Dermatol Treat 2004; 15: 35–9.

This open-label study of six patients with cutaneous DM treated with topical tacrolimus noted a very good to excellent response in two patients, a moderate response in one, and essentially no response in three.

This agent is worthy of a trial but does not seem to be highly effective.

Low-dose methotrexate administered weekly is an effective corticosteroid-sparing agent for the treatment of the cutaneous manifestations of dermatomyositis. Kasteler JS, Callen JP. J Am Acad Dermatol 1997; 36: 67–71.

The records of 13 patients who received oral methotrexate in doses ranging from 2.5 mg to 30 mg weekly were reviewed. Their skin lesions had not been completely responsive to sunscreens, topical corticosteroids, oral prednisone, oral antimalarial therapy, or, in one patient each, chlorambucil and azathioprine. Four of these 13 patients had complete clearance of cutaneous manifestations, and another four had almost complete clearance. In the remaining five patients, methotrexate induced moderate clearing of their cutaneous lesions. In all patients, the addition of methotrexate allowed a reduction in or discontinuation of other therapies, including prednisone.

Mycophenolate mofetil as an effective corticosteroid-sparing therapy for recalcitrant dermatomyositis. Edge JC, Outland JD, Dempsey JR, et al. Arch Dermatol 2006; 142: 65–9.

Mycophenolate mofetil in dermatomyositis: is it safe? Rowin J, Amato AA, Deisher N, et al. Neurology 2006; 66: 1245–7.

These two open-label studies suggest that in 60%–75% of patients with myositis, mycophenolate mofetil 1–1.5 g twice daily is an effective steroid-sparing agent for skin and muscle disease. Toxicity was noted in these relatively small case series, including in the former study an Epstein–Barr virus–associated lymphoma of the central nervous system, which resolved upon cessation of therapy, and opportunistic infections in the latter study, one of which was fatal.

This agent appears to be useful in some patients with refractory DM yet needs careful monitoring for the development of infection and potentially neoplasia.

Mycophenolate mofetil for interstitial lung disease in dermatomyositis. Morganroth PA, Kreider ME, Werth VP. Arthritis Care Res 2010; 62: 1496–501.

In this study, all three patients with at least one year of follow-up on mycophenolate mofetil experienced complete normalization of pulmonary functions tests and resolution of dyspnea.

This agent appears to be useful in patients with DM-associated ILD. It is often used as the steroid-sparing agent of choice in DM patients with ILD or at high risk of ILD based on phenotype (ex: MDA-5 DM patients).

A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. Dalakas MC, Illa I, Dambrosia JM. N Engl J Med 1993; 329: 1993–2000.

These authors conducted a double-blind, placebo-controlled trial of IVIG in 15 patients with biopsy-proven treatment-resistant DM. The patients continued to receive prednisone (mean daily dose 25 mg) and were randomly assigned to receive one infusion of immunoglobulin (2 g/kg body weight) or placebo monthly for 3 months, with the option of crossing over to the alternative

therapy for three more months. The eight patients assigned to immunoglobulin showed significant improvement in scores of muscle strength ($p < 0.018$) and neuromuscular symptoms ($p < 0.035$), whereas the seven patients assigned to placebo did not. With crossovers, a total of 12 patients received immunoglobulin. Of these, nine with severe disabilities showed a major improvement to near-normal function. Of 11 placebo-treated patients, none had a major improvement, three had a mild improvement, three had no change in their condition, and the condition of five worsened. Skin disease also responded in the treated patients, with 8 of 12 demonstrating 'marked clearance' of cutaneous disease as assessed through clinical photographs.

Intravenous immunoglobulin for refractory cutaneous dermatomyositis: a retrospective analysis from an academic medical center. Femia AN, Eastham AB, Lam C, et al. *J Am Acad Dermatol* 2013; 69: 654–7.

Clinical efficacy of intravenous immunoglobulins for the treatment of dermatomyositis skin lesions without muscle disease. Bounfour T, Bouaziz JD, Bezier M, et al. *J Eur Acad Dermatol Venereol* 2014; 28: 1150–7.

Since the time of the small, randomized, controlled trial by Dalakas et al., two retrospective studies investigated the role of IVIG specifically in refractory cutaneous DM. The first study (Femia et al.) included 13 patients who received IVIG to specifically treat cutaneous DM. All patients, except two, had previously been treated with various systemic immunosuppressive and immunomodulatory therapies, photoprotection, and topical agents. The validated CDASI was utilized when available to determine treatment response, in addition to review of clinical photography. All 13 patients demonstrated improvement on IVIG, with a complete clinical response noted in eight patients. IVIG allowed for discontinuation of all concurrent immunosuppressive medications except in two patients.

A second retrospective study (Bounfour et al.) of 27 patients treated with IVIG for refractory cutaneous DM also found promising results. Utilizing clinical examination and photography, 19 of 27 patients were determined to have a major response to therapy, four demonstrated a partial response, and four had no response.

Cyclosporine A and intravenous immunoglobulin treatment in polymyositis/dermatomyositis. Danieli MG, Malcangi G, Palmieri C, et al. *Ann Rheum Dis* 2002; 61: 37–41.

This is a retrospective review of 20 patients, including 12 with DM. It suggests that combining prednisone, cyclosporin, and IVIG was the most useful regimen.

A pilot trial of rituximab in the treatment of patients with dermatomyositis. Chung L, Genovese MC, Fiorentino DF. *Arch Dermatol* 2007; 143: 763–7.

In this open-label pilot study with seven evaluable patients who received 1-g infusions administered 2 weeks apart, only three had partial response of their muscle disease. Skin disease using the validated DSSI did not demonstrate notable improvement over the study period.

Rituximab in the treatment of refractory adult and juvenile dermatomyositis (DM) and adult polymyositis (PM): a randomized, placebo-phase trial (the RIM Study). Oddis CV, Reed AM, Aggarwal R, et al. *Arthritis Rheum* 2013; 65: 314.

This multicenter, randomized, controlled trial of 200 participants, including 76 with DM, 48 with juvenile DM, and 76 with

polymyositis, randomized participants to either a 'rituximab early' arm, receiving the drug at weeks 0 and 1 and placebo at weeks 8 and 9, or a 'rituximab late' arm, receiving placebo at weeks 0 and 1 and rituximab at weeks 8 and 9. The primary end point, time to achieve improvement based on specifically defined muscle parameters, was not met, nor were the secondary end points, which were also based on muscle involvement. Despite this, 83% of patients met the definition of improvement (DOI) by week 44. In addition, a steroid-sparing effect of rituximab was noted in both groups. The authors propose that the trial design, particularly the short placebo phase of 8 weeks, may have reduced the ability to detect differences between the groups given the median time to DOI from rituximab. Of note, a validated DM skin index was not used.

Cutaneous improvement in refractory adult and juvenile dermatomyositis after treatment with rituximab. Aggarwal R, Loganathan P, Koontz D, et al. *Rheumatology* 2017; 56: 247–54.

Using the same subjects and methodology of the RIM Study, cutaneous disease activity was assessed on a visual analog scale (VAS), which is not a validated DM skin index. The VAS improved in both adult and juvenile DM, with erythroderma, erythematous rashes without secondary changes, heliotrope eruption, and Gottron sign/papules improving most significantly.

Although design concerns with the RIM Study make recommendations regarding the use of rituximab in DM challenging, it is used for refractory muscle disease. At this time, however, the data to support the use of rituximab for cutaneous DM is weaker, especially without the use of a validated DM skin index in this study.

Third-Line Therapies

• Rituximab for cutaneous disease	D
• Tofacitinib, ruxolitinib (JAK inhibitors)	D
• Leflunomide	D
• Diltiazem for calcinosis	D
• Total body irradiation	D
• Stem cell transplantation	D
• Anakinra	D
• Sirolimus	E
• Tocilizumab	E
• Antiestrogen medication for cutaneous disease	E
• Thalidomide for cutaneous disease	E
• Apremilast	E
• Dapsone for cutaneous disease	E

Calcinosis cutis occurring in association with autoimmune connective tissue disease: the Mayo Clinic experience with 78 patients, 1996 to 2009. Balin SJ, Wetter DA, Andersen LK. *Arch Dermatol* 2012; 148: 455–62.

This retrospective study found that DM and systemic sclerosis were the most common autoimmune connective tissue diseases associated with calcinosis cutis. Therapy with diltiazem resulted in partial benefit in nine of 17 patients. Of 28 patients who had surgical excision of one or more lesions, 22 noted complete response, five had partial response, and one patient did not respond.

A wide variety of agents have been used in the treatment of DM-associated calcinosis, although none is uniformly effective.

A randomized, pilot trial of etanercept in dermatomyositis. Amato A. *Ann Neurol* 2011; 70: 427–36.

In this randomized, double-blind, placebo-controlled trial of 16 participants with DM on prednisone (11 randomized to etanercept arm 50mg subcutaneously weekly for 52 weeks and 5 to placebo arm), a steroid-sparing effect was demonstrated in five patients in the treatment arm. There was no statistically significant difference in skin disease response assessed by CDASI between the groups. In addition, cutaneous disease worsened in five etanercept-treated patients.

In addition to the potential worsening of muscle disease in patients with DM treated with anti-TNF- α therapy, there were reports of TNF inhibitor-associated DM. For these reasons, anti-TNF therapy is not typically utilized in patients with DM.

Improvement in dermatomyositis rash associated with the use of antiestrogen medication. Sereda D, Werth VP. Arch Dermatol 2006; 142: 70–2.

In this report, two women experienced improvement in their DM-associated skin eruptions while taking antiestrogen medication, either tamoxifen, a selective estrogen receptor modulator, or anastrozole, an aromatase inhibitor. When tamoxifen therapy was discontinued after 4 years of use in the first patient, her cutaneous DM worsened and remained difficult to control with conventional immunosuppressive agents.

This observation offers a novel approach to consider for women with DM; however, no further reports of either medication have appeared in the literature.

Efficacy and safety of leflunomide as an adjuvant drug in refractory dermatomyositis with primarily cutaneous activity. de Souza RC, de Souza FHC, Miossi R, et al. Clin Exp Rheumatol 2017; 35:1011–3.

In this retrospective, single-center cohort study of 18 adults, patients were started on leflunomide and followed for 6 months. Leflunomide proved effective and safe in 66.6% of patients with control of cutaneous activity and the ability to taper oral glucocorticoids. Two patients with muscle involvement had improved strength with leflunomide. Importantly, no validated skin index was used.

Rapamycin (sirolimus) as a steroid-sparing agent in dermatomyositis. Nadiminti U, Arbiser JL. J Am Acad Dermatol 2005; 52: 17–9.

A single case of dermatomyositis that was recalcitrant to prior therapies responded to this antirejection agent 5mg/day for 2 weeks, then 2mg/day. Both muscle disease and skin manifestations were noted to improve.

Anakinra treatment in patients with refractory inflammatory myopathies and possible predictive response biomarkers: a mechanistic study with 12 months of follow-up. Zong M, Dorph C, Dastmalchi M, et al. Ann Rheum Dis 2014; 73: 913–20.

An open-label trial of 15 patients with refractory myositis, four of whom had DM, received anakinra for a 12-month period. Three of the four DM patients had improvement in their cutaneous disease, but no validated skin index was used.

Remission of recalcitrant dermatomyositis treated with ruxolitinib. Hournung T, Janzen V, Heidgen FJ, et al. J. N Engl J Med 2014; 371: 2537–8.

A case of refractory DM was incidentally noted to have complete resolution of both muscle weakness and cutaneous disease based on CDASI scores after being treated with ruxolitinib, a JAK 1 and 2 selective inhibitor, for concurrent myelofibrosis. The patient was able to discontinue systemic corticosteroids, mycophenolate mofetil, and IVIG while taking ruxolitinib.

Tofacitinib citrate for refractory cutaneous dermatomyositis: an alternative treatment. Kurtzman DJ, Wright NA, Lin J, et al. JAMA Dermatol 2016; 152: 944–5.

Three patients with refractory DM were identified and treated with tofacitinib. Clinical response was observed after 4 weeks; mean treatment period was 9.6 months. Mean improvement in CDASI activity scores was 12 points. All patients reported decreased pruritus, and two patients reported subjective improvement in strength and fatigue.

Successful treatment of extensive calcifications and acute pulmonary involvement in dermatomyositis with the Janus-Kinase inhibitor tofacitinib – a report of two cases. Wendel S, Venhoff N, Frye BC, et al. J Autoimmun 2019; 100: 131–6.

In two cases of patients observed over 28 weeks, both patients had no progression of calcinosis and also had either stability or regression in their disease. One patient had improvement in ILD. Both patients were able to taper concomitant glucocorticoids.

Larger studies of JAK inhibitors might add another agent to our therapeutic armamentarium for DM.

Apremilast as a potential treatment for moderate to severe dermatomyositis: a retrospective study of 3 patients. Bitar C, Maghfour J, Ho-Pham H, et al. JAAD Case Rep 2019; 5: 191–4.

Three patients with refractory cutaneous DM were treated with apremilast. All patients were treated with 30mg twice daily; overall, patients had 85% improvement in CDASI score at 3 months of therapy. Two patients were able to discontinue all other medications. One patient with muscle involvement had normalization in CK values.

Larger studies or observations of PDE4 inhibition may add another agent to our therapeutic ladder.

Efficacy of allogeneic mesenchymal stem cell transplantation in patients with drug-resistant polymyositis and dermatomyositis. Wang D, Zhang H, Cao M, et al. J Ann Rheum Dis 2011; 70: 1285–8.

An open study of 10 patients with refractory DM ($n=4$) or polymyositis who underwent stem cell transplantation (SCT) noted recurrence of disease in three patients and death in two patients. The remaining patients had improvement in muscle disease, pulmonary disease, and chronic cutaneous ulcers.

Other reports of patients with adult and juvenile DM have noted improvement in both skin disease and calcinosis after SCT in severe cases. Given infection risks, SCT is considered only in highly refractory cases.

Diaper dermatitis

Dawn Z. Eichenfield, Lawrence F. Eichenfield



Diaper (napkin) dermatitis encompasses a broad set of conditions, although the most common form is irritant contact dermatitis (ICD). ICD usually presents as erythema and mild scaling on the convex surfaces of the inner upper thigh, lower abdomen, and buttock, classically sparing the inguinal folds where the skin is not in contact with irritants. It may present as early as a few days after birth to as late as several years of age. Diaper use in older disabled and geriatric patients may be identical in pathogenesis and physical findings. Many other dermatoses such as psoriasis, seborrheic dermatitis, allergic contact dermatitis, acrodermatitis enteropathica, infections (*Candida*, *Staphylococcus*, and *Streptococcus*), and Langerhans cell histiocytosis can affect the diaper area and need to be excluded. Prevalence and severity of infant and toddler diaper dermatitis varies greatly internationally, influenced

by age of toilet-training, regional diaper care habits, frequency of diaper changes, time spent overnight without diaper changes, and prophylactic use of topical products.

MANAGEMENT STRATEGY

ICD is triggered by irritants present in the area covered by the diaper, which acts as an occlusive surface. Moisture from urine and feces causes damage from friction, increased pH from urine and fecal enzymes, and physical erosion. Skin barrier dysfunction and increase in pH contribute to the increased susceptibility to infections with microorganisms such as *C. albicans*. Management is aimed at preventing overhydration and frictional damage, and addressing inflammation or infection.

Prevention

Frequent diaper changes, particularly after defecation, reducing moisture, and minimizing irritants are important steps in managing diaper dermatitis. Disposable diapers containing superabsorbent gelling materials and breathable backsheets are preferred. The evolving diaper technology, including mesh-like apertures, variable topsheet construction, and use of 'natural' or 'organic' materials, has prompted development of 'enhanced' disposable diapers, which can be associated with a lower incidence of diaper dermatitis. Cloth diapers are associated with an increased incidence of irritant diaper dermatitis compared with disposable diapers.

The skin in an area of active diaper dermatitis may be cleaned with water alone, with mild soap, or with commercial wipes. Optimally, wipes should not contain fragrance, isothiazolinones, iodopropynyl butylcarbamate, or alcohol. Rubbing of the area can cause damage to the skin and should be avoided.

A *barrier cream* such as zinc oxide cream maybe applied at every diaper change. This can provide a barrier between the skin and irritants in order to reduce friction and contact with stool and urine.

A *low-potency topical steroid* such as hydrocortisone 1% ointment can be used in more severe cases of diaper dermatitis, but should be used sparingly to avoid skin atrophy and systemic absorption. High-potency steroids should be avoided in diaper dermatitis, including the use of compound formulations containing potent steroids and antimicrobial agents.

Topical antifungal preparations are recommended for use in proven or suspected cases of *C. albicans* infection.

Specific Investigations

- Inquiry about recent antibiotic usage (predisposing to *Candida*)

In selected cases:

- KOH preparation, fungal and bacterial cultures
- Serum zinc and biotin levels
- Skin biopsy
- Patch testing

Diaper dermatitis: clinical characteristics and differential diagnosis. Coughlin CC, Eichenfield LF, Frieden IJ. *Pediatr Dermatol* 2014; 31(Suppl 1): 19–24.

This article characterizes three subgroups: skin conditions caused by the presence of the diaper, eruptions exacerbated by the diaper, and rashes present regardless of the presence of the diaper.

Those caused by the presence of the diaper include irritant diaper dermatitis and its different presentations, as well as allergic contact dermatitis. The conditions exacerbated by the diaper include infectious causes (yeast and bacteria), seborrheic dermatitis, and psoriasis. The third group includes infantile hemangiomas, Langerhans cell histiocytosis, zinc deficiency, Kawasaki disease, and Coxsackie virus.

Potential allergens in disposable diaper wipes, topical diaper preparations and disposable diapers: under-recognized etiology of pediatric perineal dermatitis. Yu J, Treat J, Chaney K, Brod B. *Dermatitis* 2016; 27: 110–8.

Botanical extracts, which include members of the Compositae family, were the top potential allergens in both diaper wipes and topical preparations. Others identified include tocopherol, fragrances, propylene glycol, parabens, iodopropynyl butylcarbamate, and lanolin.

The role of allergic contact dermatitis in diaper dermatitis. Smith WJ, Jacob SE. *Pediatr Dermatol* 2009; 26: 369–70.

Allergens include the many chemicals added to diapers, as well as preservatives in baby wipes. For example, sorbitan sesquioleate, fragrances, and disperse dye have been reported to cause contact dermatitis in the diaper area. Rubber additives, cyclohexylthiophthalimide and mercaptobenzothiazole, tend to cause ‘lucky Luke’ dermatitis, a pattern that resembles a cowboy’s holster due to elastic bands coming into contact with the skin. Patch testing is recommended in diaper dermatitis that fails to improve despite treatment.

First-Line Therapies

• Water-repellent barrier cream	A
• Frequent changing of diapers	B
• Superabsorbent disposable diapers	A

Prevention and treatment of diaper dermatitis. Blume-Peytavi U, Kanti V. *Pediatr Dermatol* 2018; 35(Suppl 1): s19–23.

Non-medical skincare practices that support healthy skin barrier function can prevent or alleviate diaper dermatitis. The usage of barrier emollients and improved diaper technology may minimize dermatitis.

Modern diaper performance: construction, materials, and safety review. Dey S, Kenneally D, Odio M, et al. *Int J Dermatol* 2016; 55(Suppl 1): 18–20.

Typical modern diapers do not contain concerning ingredients such as latex and disperse dyes, but use spandex and pigments with a favorable safety profile. Today’s disposable diapers are designed with layers and liners for optimal urine and feces absorption.

Clinical approaches to skin cleansing of the diaper area: practice and challenges. Coughlin CC, Frieden IJ, Eichenfield LF. *Pediatr Dermatol* 2014; 31(Suppl 1): 1–4.

The authors review important factors in diaper area care, including skin pH, the local microbiome, irritant and allergic potential of certain products, and application of topical agents. The use of wet wipes is concluded to be a widespread practice, which is well tolerated and effective in several populations, including preterm infants.

Diaper dermatitis prevalence and severity: global perspective on the impact of caregiver behavior. Carr AN, DeWitt T, Cork MJ, et al. *Pediatr Dermatol* 2020; 37(1): 130–6.

This article compares the prevalence and severity of diaper dermatitis across three countries: China, United States, and Germany. Diaper dermatitis was significantly lower in babies in China, highest in Germany, and intermediate in the United States. Lower prevalence of diaper dermatitis in China was associated with lower skin pH and transepidermal water loss (TEWL) on diapered skin and decreased relative humidity in the diaper. Chinese caregivers had the highest rate of prophylactic topical product usage, the most robust cleaning of the diapered area, lack of cleansing after urine-only diaper changes, and Chinese infants spent the least time in an overnight diaper.

Neonatal skin care: developments in care to maintain neonatal barrier function and prevention of diaper dermatitis. Burdall O, Willgress L, Goad N. *Pediatr Dermatol* 2019; 36(1): 31–5.

This article emphasizes the importance of reducing moisture at skin level and utilization of barrier creams for both prevention and cure, but not as a substitute for frequent diaper changes.

Second-Line Therapies

• 1% hydrocortisone ointment	D
• Topical antifungal agent (miconazole, clotrimazole, nystatin, ketoconazole)	A

A prospective two-year assessment of miconazole resistance in *Candida* spp. with repeated treatment with 0.25% miconazole nitrate ointment in neonates and infants with moderate to severe diaper dermatitis complicated by cutaneous candidiasis. Blanco D, van Rossem K. *Pediatr Dermatol* 2013; 30: 717–24.

This multicenter, open-label, long-term, phase IV study investigated the potential resistance of *Candida* spp. to repeated topical use of 0.25% miconazole nitrate in infants age 15 months and younger with moderate-to-severe candidal diaper dermatitis. Results showed that about half of the patients achieved clinical cure, 45.8% mycologic cure, and 29.2% overall cure (clinical and mycologic). The treatment with 0.25% miconazole nitrate ointment was effective and generally well tolerated. There was no evidence of candidal resistance to miconazole.

Efficacy and safety of two different antifungal pastes in infants with diaper dermatitis: a randomized, controlled study. Hoeger PH, Stark S, Jost G. *J Eur Acad Dermatol Venereol* 2010; 24: 1094–8.

This double-blinded, multicenter trial compared 1% clotrimazole versus nystatin with 20% zinc oxide for the treatment of diaper dermatitis complicated by *Candida* infection. Clotrimazole was superior to nystatin in symptom reduction. Both clotrimazole and nystatin had microbiologic cure rates of 100%, and were safe and well tolerated.

Absorption and efficacy of miconazole nitrate 0.25% ointment in infants with diaper dermatitis. Eichenfield LF, Bogen ML. *J Drugs Dermatol* 2007; 6: 522–6.

Twenty-four infants with moderate-to-severe diaper dermatitis were evaluated for relative safety from systemic absorption of topical miconazole. Nineteen received 0.25% miconazole nitrate ointment, and five received 2% miconazole nitrate cream for 7 days. Blood concentrations in the 0.25% miconazole nitrate treatment group were undetectable in 83% and minimal in 17%, demonstrating its safety as a treatment for diaper dermatitis.

Pediatricians who prescribe clotrimazole-betamethasone dipropionate (Lotrisone) often utilize it in inappropriate settings regardless of their knowledge of the drug's potency. Railan D, Wilson JK, Feldman SR, et al. *Dermatol Online J* 2002; 8: 3.

High-potency topical corticosteroids can cause skin atrophy and systemic absorption. Products combining antibiotics with high-potency corticosteroids should be avoided in the diaper area.

Third-Line Therapies

- Continuous administration of petrolatum and zinc oxide by disposable diaper **A**
- Oral antifungal agent **E**

Skin benefits from continuous topical administration of a zinc oxide/petrolatum formulation by a novel disposable diaper. Baldwin S, Odio MR, Haines SL, et al. *J Eur Acad Dermatol Venereol* 2001; 1: 5–11.

A double-blind, randomized trial comparing regular diapers to diapers designed to continuously deliver zinc oxide and petrolatum in 268 infants over a 4-week period. The ointment formulation was effectively transferred to the skin, and a significant reduction in skin erythema and rash was observed in the treatment group compared with controls.

Consultation with the Specialist: Contact dermatitis. Friedlander SF. *Pediatr Rev* 1998; 19: 166–71.

Some diaper dermatitis persists despite first- and second-line therapies. In these recalcitrant cases, oral Mycostatin may be beneficial. In addition, an evaluation of the mother for infections of the nipples or genital tract should be considered, as continuous reinoculation of the infant is possible. If positive, a short course of oral fluconazole (5–7 days) can help eradicate the infection.

Discoid (nummular) eczema

Ian H. Coulson



Discoid eczema comprises relatively well-defined, usually multiple, coin-sized plaques. In the acute stages they often weep or ooze; in the chronic phase lesions are discrete, hyperkeratotic, or lichenified. Itching is usual. It primarily affects the limbs (especially the legs), sometimes the trunk, and rarely the face or flexures.

MANAGEMENT STRATEGY

Discoid eczema (nummular dermatitis) has many causes. It is usually idiopathic in older patients, but similar lesions may occur due to contact allergic reactions, as a pattern of hand and foot eczema, in atopic dermatitis (AD), as an 'id' eruption related to venous eczema, or locally (e.g., after trauma, insect bite reactions, 'halo eczema' around melanocytic nevi, and after breast reconstruction). Discoid eczema has been reported as a manifestation of drug reaction to gold, tumor necrosis factor antagonists, interferon, and retinoids. Comparisons among studies may be limited if the site(s) and etiology are not stated or represent a mixed spectrum.

There are few publications on the pathophysiology of discoid eczema to inform treatment. An association with dry skin (xerosis) is documented, and discoid lesions may appear during treatment with isotretinoin (which reduces sebum secretion). However, dry skin is not consistently present, and the morphology of discoid eczema differs from that of xerosis or asteatotic eczema.

One study suggested that patients with discoid eczema have a degree of xerosis similar to that of age-matched controls but have stronger delayed hypersensitivity to allergens that permeate the skin as a result of scratching. A link with atopy has been proposed, but serum IgE levels are generally normal.

Occult infections (e.g., dental abscess) and infections causing dry skin (e.g., leprosy) have rarely been linked with discoid eczema. *Helicobacter pylori* has been implicated, but the evidence is weak.

It is difficult to provide specific therapeutic strategies because of the various different causes and the paucity of pertinent publications; most reports are retrospective from individual departments or are anecdotal, rather than formal, trials. The main therapeutic issues are:

- Other disorders may need to be excluded, especially mycoses, psoriasis, Bowen disease, mycosis fungoides, and sarcoidosis
- A medication and alcohol history should be taken
- Patch testing may be useful; metals and medicaments (such as fusidic acid, lanolin, neomycin, and cetostearyl alcohol) are most implicated
- The management of discoid eczema is generally similar to that of other eczemas; *emollients* appear to be helpful due to the link with dry skin
- The mainstay of treatment is *topical corticosteroids*. Severe itch in discoid eczema usually dictates that strong agents are applied; this is safe because the individual lesions are small, rarely affect thin skin sites such as the face or flexures, and usually respond to this approach. Chronic lichenified lesions may respond better to steroid-impregnated tapes or by using a potent steroid with hydrocolloid dressing or paste bandage occlusion
- *Calcineurin antagonists* have been used successfully both as monotherapy and in combination with topical steroids, but trials specifically looking at efficacy in discoid eczema exclusively, rather than atopic eczema generally, are lacking
- If weeping is present, the use of soaks (with, e.g., 1 in 10,000 *potassium permanganate* solution) will help dry lesions up and prevent lesions from sticking to clothes or dressings
- Secondary impetiginization, particularly in the exudative phase, is common, and combining with a *topical antibiotic or antiseptic*, or the use of an *oral antistaphylococcal antibiotic*, helps
- *Tar-based treatments* and impregnated bandages to minimize the effects of scratching may help
- *Sedating antihistamines* before retiring will help nocturnal scratching and minimize excoriation
- *Phototherapy and systemic immunosuppressive therapies* are usually not required, but there is a literature relating to ultraviolet B (UVB) and methotrexate

Newer drugs such as *biological agents* (dupilumab) and small molecules such as *apremilast* and *topical PDE 4 antagonists*, and *Janus kinase (JAK) inhibitors* show efficacy in atopic eczema, but specific reports relating to discoid eczema are lacking to date.

Specific Investigations

- None usually required, except to exclude differential diagnoses
- Consider medications as a cause
- Consider mycology
- Consider patch testing
- Bacteriology if secondary infection likely
- Consider occult infections in resistant cases

Pityriasis rosea and discoid eczema: dose related reactions to treatment with gold. Wilkinson SM, Smith AG, Davis MJ, et al. *Ann Rheum Dis* 1992; 51: 881–4.

Discoid eczematous lesions occur in up to 30% of patients on gold therapy and may be dose related.

Severe, generalized nummular eczema secondary to interferon alpha-2b plus ribavirin combination therapy in a patient with chronic hepatitis C virus infection. Moore MM, Elpern J, Carter DJ. Arch Dermatol 2004; 140: 215–7.

Study on dermatoses and their prevalence in groups of confirmed alcoholic individuals in comparison to a non-alcoholic group of individuals. Bruno MC, Vilela MA, Oliveira CA. An Bras Dermatol 2013; 8: 368–75.

Discoid eczema, along with psoriasis, pellagra, and pigmented purpuric eruptions, were felt to be potential indicators of alcoholism.

Nummular eczema of breast: a potential dermatologic complication after mastectomy and subsequent breast reconstruction. Iwahira Y, Nagasao T, Shimizu Y, et al. Plast Surg Int 2015, Article ID 209458, 6 pages, 2015. <https://doi.org/10.1155/2015/209458>.

Almost 3% of postmastectomy reconstructions resulted in peri-wound or breast discoid eczema.

Patch testing in discoid eczema. Fleming C, Parry E, Forsyth A, et al. Contact Dermatitis 1997; 36: 261–4.

Retrospective study of persistent and severe discoid eczema; 24 of 48 cases were positive (16 relevant) to rubber chemicals, formaldehyde, neomycin, chromate, and nickel.

Nummular eczema and contact allergy: a retrospective study. Bonamonte D, Foti C, Vestita M, et al. Dermatitis 2012; 23: 153–7.

Nickel, cobalt, and chromate allergy was found in 32% of discoid eczema patients. Irritants may also be relevant as perpetuating factors.

Dental infection associated with nummular eczema as an overlooked focal infection. Tanaka T, Satoh T, Yokozeki H. J Dermatol 2009; 36: 462–5.

Thirteen cases of extensive discoid eczema with moderate-to-severe odontogenic infections detected by panoramic X-ray screening test. In 11 patients, skin lesions partially or completely improved after the dental treatment.

First-Line Therapies

• Topical corticosteroids ± antibacterial agents	C
• Emollients	C
• Tar-based preparations	C
• Oral antibiotics	C
• Oral antihistamines	C
• Topical doxepin	A

Most of these are standard treatments for discoid eczema; however, in terms of evidence grading, most studies include a variety of different eczemas, few specifically identify results for discoid eczema, and no comparative trials have been identified. *Potent and ultrapotent topical steroids are needed short term; maintenance therapy may only need 1 or 2 applications a week.* Chronically lichenified lesions may benefit from topical steroid occlusion under hydrocolloid dressings.

The use of antibacterial agents (e.g., clioquinol) or antibiotics is based on the fact that lesions are often moist and crusted. Secondary staphylococcal infection, as in AD, may aggravate the eczematous process.

Occlusion over a topical corticosteroid has been reported to lead to lesion clearance in previously therapy-resistant patients with discoid lesions due to AD; soaking in water for 20 minutes before treatment application has been recommended for a range of eczemas.

As with other itchy dermatoses, *sedating antihistamines* may help symptoms; the increase in mast cells in lesions provides the rationale for this approach. However, histamine itself has not been shown to be important.

Successful treatment of therapy-resistant atopic dermatitis with clobetasol propionate and a hydrocolloid occlusive dressing. Volden G. Acta Derm Venereol 1992; 176: 126–8.

Nummular AD lesions cleared rapidly.

Topical corticosteroids are the usual first-line therapy. Trial evidence is limited to pharmaceutically sponsored studies that are not specific to discoid eczema. Alternate day treatment left on for 24 h can be used; often only three or four treatments will transform symptoms.

Nummular eczema. A review, follow-up and analysis of a series of 325 cases. Cowan MA. Acta Derm Venereol 1961; 41: 453–60.

5–10% Crude coal tar preparations were the main treatment. Recurrent crops of lesions occurred in 25% of cases, and relapse occurred when treatment was discontinued in 53% of patients, presumably representing the natural history of the disease, but possibly reflecting the limitations of therapy available at the time (other options were hydrocortisone or superficial X-ray therapy).

Tar preparations, historically used in the treatment of discoid eczema, have been largely superseded by potent topical corticosteroids as first-line therapy.

The antipruritic effect of 5% doxepin cream in patients with eczematous dermatitis. Drake LA, Millikan LE. Arch Dermatol 1995; 131: 1403–8.

Significant improvement in itch after 1 day, not at 7 days.

Studies suggest that twice daily doxepin has a short-term effect on itch only.

Second-Line Therapies

• Phototherapy (broadband or narrowband ultraviolet B [NB-UVB], 311 nm)	E
• Photochemotherapy (psoralen plus UVA [PUVA])	E
• Topical immune modulators	E
• Ciclosporin	E
• Intralesional corticosteroid injection	E
• Oral corticosteroids	E

Formal trials of these treatments in discoid eczema are lacking, and therefore the evidence gradings are weak; however, all are useful in AD or other dermatitis (see gradings in Atopic dermatitis, Chapter 17) and are therefore likely to be effective in discoid eczema. Personal experience is that NB-UVB or ciclosporin is useful if required.

Photochemotherapy beyond psoriasis. Honig B, Morison WL, Karp D. J Am Acad Dermatol 1994; 31: 775–90.

Review article. Nothing specific to discoid eczema, but several eczemas respond to PUVA.

Half-side comparison study on the efficacy of 8-methoxypsoralen bath-PUVA versus narrow-band ultraviolet B phototherapy in patients with severe chronic atopic dermatitis. Der-Petrossian M, Seeber A, Honigsmann H, et al. Br J Dermatol 2000; 142: 39–43.

Both were equivalent (at equi-erythemogenic doses) in AD.

Phototherapies also reduce staphylococci and superantigens and therefore may improve eczema with weeping and infection.

Antimicrobial effects of phototherapy and photochemotherapy in vivo and in vitro. Yoshimura M, Namura S, Akamatsu H, et al. *Br J Dermatol* 1996; 135: 528–32.

Antimicrobial effects are apparent after a single exposure.

Suppressive effect of ultraviolet (UVB and PUVA) radiation on superantigen production by *Staphylococcus aureus*. Yoshimura-Mishima M, Namura S, Akamatsu H, et al. *J Dermatol Sci* 1999; 19: 31–6.

Hand dermatitis: a review of clinical features, therapeutic options, and long-term outcomes. Warshaw E, Lee G, Storrs FJ. *Am J Contact Dermat* 2003; 14: 119–37.

One review recommends topical tacrolimus or pimecrolimus twice daily for nummular hand dermatitis. No evaluable evidence presented.

Long-term efficacy and safety of ciclosporin in severe adult atopic dermatitis. Berth-Jones J, Graham-Brown RA, Marks R, et al. *Br J Dermatol* 1997; 136: 76–81.

An open study of 100 patients with AD, with mostly good responses at 3–5 mg/kg/day.

Side effects (drug interactions, hypertension, nephrotoxicity) limit ciclosporin therapy in older patients with discoid eczema, compared with AD. It is possibly useful for intermittent short-term treatment.

Oral corticosteroids are generally unnecessary. Intralesional corticosteroid injection is impractical, except in patients who have a small number of persistent thickened lesions.

Third-Line Therapies

• Azathioprine	E
• Methotrexate	C
• Mycophenolate mofetil	E
• Hypnosis	D
• Relaxation therapy	D

As for second-line therapies, formal trials of these treatments in discoid eczema are lacking, and therefore the evidence gradings are weak; however, all are useful in AD or other dermatitis (see gradings in Atopic dermatitis, Chapter 17) and are therefore likely to be effective in discoid eczema.

Azathioprine in dermatologic practice. An overview with special emphasis on its use in nonbullous inflammatory dermatoses. Scerri L. *Adv Exp Med Biol* 1999; 445: 343–8.

Documents the efficacy of azathioprine in AD and pompholyx.

Azathioprine in dermatology: a survey of current practice in the UK. Tan BB, Lear JT, Gawkrödger DJ, et al. *Br J Dermatol* 1997; 136: 351–5.

A questionnaire to 248 dermatologists showed that none was using azathioprine for discoid eczema.

Azathioprine is used in the treatment of several dermatoses, including various eczemas. It is likely to be beneficial in discoid eczema, although a study of azathioprine prescribing by UK dermatologists did not identify this as a current indication.

Methotrexate for severe nummular eczema in children: efficacy and tolerability in a retrospective study of 28 patients. Knöpfel N, Noguera-Morel L, Hernández-Martín, et al. *Pediatr Dermatol* 2018; 35: 611–5.

In this retrospective study, 35% had greater than 90% improvement; 46% had moderate improvement. The standard dose of oral methotrexate in children is 0.4 mg/kg once weekly. Treatment was well tolerated; 18% had mild transaminitis.

Hypnosis in dermatology. Shenefelt PD. *Arch Dermatol* 2000; 136: 393–9.

Hypnosis as a complementary therapy may improve lesions or itch in discoid eczema.

Treatment of atopic dermatitis: a comparison of psychological and dermatologic approaches to relapse prevention. Ehlers A, Stangier U, Gieler J. *Consult Clin Psychol* 1995; 63: 624–35.

Although this study is related to adults with atopic eczema, it may be applicable to discoid eczema too. Relaxation therapy produced a sustained benefit over a year and significantly reduced topical steroid use.

Discoid lupus erythematosus

Spandana Maddukuri, Daisy Yan, Victoria P. Werth



Discoid lupus erythematosus (DLE) is the most common type of chronic cutaneous lupus erythematosus (CCLE). Lesions typically occur on the scalp, face, and ears, although they can be generalized. The lesions are photodistributed and are scaly, erythematous plaques and papules, which can be hypertrophic/hyperkeratotic. Late-stage lesions result in atrophy and scarring accompanied by dyspigmentation and permanent alopecia.

MANAGEMENT STRATEGY

Although the chance of progression of DLE to systemic lupus erythematosus (SLE) is low, a thorough workup is needed to rule out systemic disease. SLE is also more likely to occur with generalized DLE lesions. This includes inquiring about symptoms of systemic disease such as fever, fatigue, arthralgia, arthritis, myalgia, weight loss, and loss of appetite. Laboratory workup should include urinalysis, complement levels, CBC, and autoantibodies such as antinuclear antibodies (ANA) and double-stranded DNA (dsDNA). Primary counseling includes smoking cessation and sun avoidance and protection.

In localized disease, topical and intralesional steroids are first line. Intralesional injection of corticosteroids can also treat alopecia due to early-stage lesions on the scalp. However, if new lesions are appearing despite local treatment or are widespread, systemic treatment is warranted. Antimalarials are first-line systemic therapy and afford a measure of photoprotection and are highly effective, despite their relatively slow onset of action. Calcineurin inhibitors are also considered a first-line therapy and are important for use on delicate skin, where corticosteroids may not be used.

For refractory DLE, there is a lack of rigorous, randomized studies. However, immunosuppressive agents such as methotrexate (MTX) and mycophenolate mofetil (MMF) clear lesions and act

as steroid-sparing agents for SLE. Retinoids are effective in hypertrophic DLE. Thalidomide, and its derivative lenalidomide, are also effective but can have serious adverse effects.

Specific Investigations

- Autoantibodies
- Indicators of systemic disease: urinalysis, complement levels, CBC

First-Line Therapies

• Sunscreen	B
• Topical or intralesional steroids	A
• Calcineurin inhibitors	A

Review of treatment for discoid lupus erythematosus. Garza-Mayers AC, McClurkin M, Smith GP. *Dermatol Ther* 2016; 29: 74–83.

Potential allergenicity of commonly sold high SPF broad spectrum sunscreens in the United States; from the perspective of patients with autoimmune skin disease. Keyes E, Werth VP, Brod B. *Int J Womens Dermatol* 2019; 5: 227–32.

DLE can be precipitated and exacerbated by ultraviolet (UV) light exposure. Generous sunscreen use with regular reapplication has been shown to be efficacious in preventing UV-induced DLE lesions. A retrospective study confirmed that sunscreen prevented photoprovocation and pigment changes of lesions. Data suggests that higher sun protection factor (SPF 70 or greater) with broad-spectrum UVA and UVB coverage or physical blockers are effective in prevention of UV-induced DLE lesions. Although sunscreen usage is crucial in patients with autoimmune skin conditions, these patients have an increased risk of reaction to allergenic ingredients and developing contact dermatitis. Most sunscreens found on Amazon, Target, and CVS are not allergen-free, but many have no high-prevalence allergens.

Drugs for discoid lupus erythematosus. Jessop S, Whitelaw DA, Grainge MJ, et al. *Cochrane Database Syst Rev* 2017; 5: CD002954.

Topical steroids can be used for localized DLE lesions. In a study comparing fluocinonide 0.05% (potent steroid) and hydrocortisone 1% (low-potency steroid) there was complete resolution of skin lesions in 27% of participants using fluocinonide and 10% using hydrocortisone. Side effects included skin irritation and burning.

Effectiveness of topical calcineurin inhibitors as monotherapy or in combination with hydroxychloroquine in cutaneous lupus erythematosus. Avgerinou G, Papafragkaki DK, Nasiopoulou A, et al. *J Eur Acad Dermatol Venereol* 2012; 26: 762–7.

Review of treatment for discoid lupus erythematosus. Garza-Mayers AC, McClurkin M, Smith GP. *Dermatol Ther* 2016; 29: 74–83.

The macrolactam immunosuppressive agents, tacrolimus and pimecrolimus, are steroid-sparing agents that are effective in the topical treatment of lesions of DLE lesions. Tacrolimus 0.03% or 0.1% and pimecrolimus 1% cream are important in thin-skinned areas where corticosteroids are not appropriate, such as the

eyelids and in areas of atrophy resulting from the disease itself. Hypertrophic lesions may not respond well to calcineurin inhibitors or to other topical therapies because of limited penetration. Topical calcineurin inhibitors can also be used in combination with systemic therapy (e.g., hydroxychloroquine).

Second-Line Therapy

- Hydroxychloroquine

A

Update on recommendations for screening for hydroxychloroquine retinopathy. Couturier A, Giocanti-Aurégan A, Dupas B, et al. *J Fr Ophtalmol* 2017; 40: 793–800.

At recommended doses, the risk of retinopathy is <1% at 5 years and <2% at 10 years but increases to about 20% after 20 years of treatment. Current guidelines for hydroxychloroquine call for a baseline visual field exam and again after 5 years, followed by yearly exams. Although the guidelines are the same for chloroquine, consider more frequent visual field exams (every 4–6 months) due to increased risk of retinopathy.

The effect of increasing the dose of hydroxychloroquine (HCQ) in patients with refractory cutaneous lupus erythematosus (CLE): an open-label prospective pilot study. Chasset F, Arnaud L, Costedoat-Chalumeau N, et al. *J Am Acad Dermatol* 2016; 74: 693–9.

Effects of hydroxychloroquine in patients with cutaneous lupus erythematosus: a multicenter, double-blind, randomized, parallel-group trial. Yokogawa N, Eto H, Tanikawa A, et al. *Arthritis Rheumatol* 2017; 69: 791–9.

Antimalarial drugs are favored for long-term treatment of DLE and are effective in many patients for whom topical therapy alone is unsuccessful or impractical. Hydroxychloroquine is dosed at <5 mg/kg actual body weight/day and chloroquine is dosed at <2.3 mg/kg/day. Quinacrine was widely used in the past but is currently not available in the United States. Antimalarials typically take 2 months before improvement is noticed.

Third-Line Therapies

- Immune response-modifying agents
- Systemic retinoids
- Thalidomide
- Lenalidomide
- Azathioprine

B

B

B

D

D

Efficacy and safety of methotrexate in recalcitrant cutaneous lupus erythematosus: results of a retrospective study in 43 patients. Wenzel J, Brähler D, Bauer R, et al. *Br J Dermatol* 2005; 153: 157–62.

Therapeutic options for cutaneous lupus erythematosus: recent advances and future prospects. Chang J, Werth V. *Expert Rev Clin Immunol* 2016; 12: 1109–21.

MTX and MMF are second-line immunosuppressive agents for refractory DLE. A study by Gammon et al. found nearly all patients responded to MMF, with 37% of patients demonstrating a complete response. For MTX, Wenzel et al. found that 98%

of CLE patients experienced significant improvement. Clinical response to MTX is seen within weeks, and some potential side effects include oral ulcers, transaminitis, nausea, and cytopenias. MTX is titrated up to an average of 15–25 mg/week and MMF can be dosed up to 1500 mg twice daily. Screening of latent infections such as tuberculosis and hepatitis is necessary before treatment initiation.

Isotretinoin for refractory lupus erythematosus. Shornick J, Formica N, Parke A. *J Am Acad Dermatol* 1991; 24: 49–52.

Efficiency of acitretin in the treatment of cutaneous lupus erythematosus. Ruzicka T, Meurer M, Bieber T. *Arch Dermatol* 1988; 124: 897–902.

Oral retinoids, either isotretinoin 1 mg/kg/day or acitretin 25–50 mg/day, are useful in the hypertrophic DLE subtype. Patient counseling must include the teratogenic effects. Long-term adverse effects like hypertriglyceridemia and possible bony abnormalities are especially relevant, as lesions can recur after drug discontinuation.

Thalidomide therapy: an open trial. Naafs B, Faber WR. *Int J Dermatol* 1985; 24: 131–4.

Thalidomide in the treatment of refractory cutaneous lupus erythematosus: prognostic factors of clinical outcome. Cortés-Hernández J, Torres-Salido M, Castro-Marrero J, et al. *Br J Dermatol* 2012; 166: 616–23.

Thalidomide in the treatment of sixty cases of chronic discoid LE. Knop J, Bonsmann G, Happle R, et al. *Br J Dermatol* 1983; 108: 461–6.

Efficacy and tolerance profile of thalidomide in CLE: a systemic review and meta-analysis. Chasset F, Tounsi T, Cesbron E, et al. *J Am Acad Dermatol* 2018; 78: 342–50.

Lenalidomide in treatment-refractory cutaneous LE: efficacy and safety in 52-week trial. Okon L, Rosenbach M, Krathen M, et al. *J Am Acad Dermatol* 2014; 70: 583–4.

Thalidomide has been used in the treatment of cutaneous lupus refractory to other modalities. Thalidomide is dosed at 100 mg daily, decreasing to a lower maintenance dose when lesions are well controlled. A derivative, lenalidomide, can be dosed at 5 mg/day. Patients must be counseled on their teratogenic potential, increased risk of clotting, and peripheral neuropathy. Response rate for thalidomide can be as high as 90%, but lesion clearance is dependent on drug continuation.

Azathioprine. An effective, corticosteroid-sparing therapy for patients with recalcitrant cutaneous lupus erythematosus or with recalcitrant cutaneous leukocytoclastic vasculitis. Callen JP, Spencer LV, Burruss JB, et al. *Arch Dermatol* 1992; 127: 515–22.

Successful treatment of generalized discoid skin lesion with azathioprine. Tsokos GC, Caughman SW, Klippel JH. *Arch Dermatol* 1985; 121: 1323–5.

There is limited data for azathioprine as a CLE treatment. However, azathioprine is one of the few suitable alternatives for refractory CLE treatment during pregnancy.

Dissecting cellulitis of the scalp

Donna Cummins, Matthew Harries



Dissecting cellulitis (*perifolliculitis capitis abscedens et suffodiens*) is a rare inflammatory disease of the scalp characterized by multiple fluctuant nodules and abscesses over the vertex and occipital region associated with interconnecting sinus tract formation and purulent discharge. Dissecting cellulitis of the scalp (DCS) follows a progressive relapsing course eventually resulting in permanent hair loss and hypertrophic scarring. The condition predominantly affects men aged 20–40 and is more common in those of African descent. Dissecting cellulitis may occur in association with hidradenitis suppurativa, pilonidal sinus, and acne conglobata to form the ‘follicular occlusion tetrad’. The suggested common pathogenic mechanism is of follicular occlusion triggering a folliculitis with neutrophilic or granulomatous inflammation in the dermis and subcutis, leading to formation of sinus tracts, abscesses, and progressive fibrosis. An abnormal host response to (possibly commensal) bacteria may also be a factor in disease development.

MANAGEMENT STRATEGY

Dissecting cellulitis is characterized by a chronic, progressive course with temporary improvement on treatment followed by relapses when treatment is discontinued. There are no large therapeutic clinical trials, and recommendations for therapy are based on case reports or case series. Inflammatory tinea capitis and the very rare complication of squamous cell carcinoma should be excluded. Although no specific pathogenic organisms have been isolated, swabs should be obtained for cultures and the antibiotic sensitivity of organisms reviewed.

In mild cases or when disease is limited, improved scalp hygiene and the use of antiseptics, topical antibiotics, intralesional corticosteroid injections, and aspiration of fluctuant lesions may be adequate. At an early stage, systemic antibiotics

such as tetracyclines or azithromycin reduce inflammation and can control disease. In more severe cases a combination of systemic antibiotics, such as clindamycin with rifampicin, may be effective. However, recognition that oral isotretinoin (with or without corticosteroids) can provide sustained remission has led many to now regard it as first-line therapy in DCS. Recent reports highlight success with anti-tumor necrosis factor (TNF) therapy in those unresponsive to standard treatment. Alitretinoin, finasteride, compression therapy and photodynamic therapy are new additions to the therapeutic armamentarium.

In those unresponsive to medical therapy, a surgical approach may be considered. *X-ray epilation* of affected areas has largely been superseded by *laser epilation* techniques. The most resistant cases may require *surgical excision and skin grafting*.

Specific Investigations

- Swabs for bacteriology
- Scrapings and plucked hairs for mycology
- Scalp biopsy for histology and fungal culture

Tinea capitis mimicking dissecting cellulitis in three children. Shastry J, Ciliberto H, Davis DM. *Pediatr Dermatol* 2018; 35: e79–83.

Three cases of inflammatory tinea capitis mimicking DCS are reported. As fungal elements are not always visible on histology, the authors advise that fungal microscopy and culture should be performed in all inflammatory alopecias.

Squamous cell carcinoma arising in dissecting perifolliculitis of the scalp. Curry SS, Gaither DH, King LE. *J Am Acad Dermatol* 1981; 4: 673–8.

The rare complication of squamous cell carcinoma arising in DCS is presented.

First-Line Therapy

- Isotretinoin (oral)

C

Dissecting cellulitis of the scalp: response to isotretinoin. Scerri L, Williams HC, Allen BR. *Br J Dermatol* 1996; 134: 1105–8.

Three patients with DCS showed a sustained response to isotretinoin. The authors recommend isotretinoin initially at 1 mg/kg daily and maintained at 0.75 mg/kg daily for at least 4 months after clinical remission is achieved.

Dissecting cellulitis of the scalp: a retrospective study of 51 patients and review of literature. Badaoui A, Reygagne P, Cavelier-Balloy B, et al. *Br J Dermatol* 2016; 174: 421–3.

A retrospective analysis of 51 patients with DCS treated from 1996 to 2013. Thirty-five patients received treatment with isotretinoin at 0.5–0.8 mg/kg/day with complete remission being achieved in 92%.

Approach to treatment of refractory dissecting cellulitis of the scalp: a systematic review. Thomas J, Aguh C. *J Dermatolog Treat.* 2021; 32: 144–149.

A systematic review summarizing 57 published articles. The authors propose isotretinoin as first-line treatment for DCS, although they highlight that the response can be inconsistent and relapse is common.

Second-Line Therapies

• Systemic antibiotics	C
• Intralesional corticosteroid injection	D
• Incision and drainage	D
• Adalimumab/anti-TNF therapy	D
• Topical antibiotic/retinoid	E

Dissecting cellulitis (perifolliculitis capitis abscedens et suffodiens): a comprehensive review focusing on new treatments and findings of the last decade with commentary comparing the therapies and causes of dissecting cellulitis to hidradenitis suppurativa. Scheinfeld N. *Dermatol Online J* 2014; 20: 22692.

Various treatment strategies for DCS are reviewed. Oral antibiotics and oral isotretinoin, either as monotherapy or in combination, represent the mainstay of treatment. Addition of intralesional corticosteroids or incision and drainage may improve local control. Reported antibiotic regimens include rifampicin 300 mg BID and clindamycin 300 mg BID, tetracyclines (e.g., doxycycline 100–200 mg/day), ciprofloxacin 250–500 mg BID, and trimethoprim-sulfamethoxazole 960 mg BID. Responses and relapse rates are variable and depend on the regimen chosen.

Epidemiology, clinical presentation and therapeutic approach in a multicenter series of dissecting cellulitis of the scalp. Segurado-Miravalles G, Camacho-Martínez FM, Arias-Santiago S, et al. *J Eur Acad Dermatol Venereol* 2017; 31: e199–200.

A retrospective series of 21 patients with DCS. Successful monotherapy included doxycycline (100 mg daily), azithromycin (500 mg 3 × week), isotretinoin, and finasteride (1 mg daily).

Dissecting folliculitis (dissecting cellulitis) of the scalp: a 66-patient case series and proposal of classification. Lee CN, Chen W, Hsu CK, et al. *J Dtsch Dermatol Ges* 2018; 16: 1219–26.

The authors present a classification system for disease severity assessment. Oral tetracyclines or isotretinoin, with intralesional or oral corticosteroids used as short-term adjunctive therapies, were the main treatments used.

Three cases of dissecting cellulitis of the scalp treated with adalimumab. Navarini AA, Trüeb RM. *Arch Dermatol* 2010; 146: 517–20.

Rapid improvement with adalimumab, but relapse occurred on stopping treatment due to persistent underlying structural disease. The authors suggest continuous therapy or surgical excision of involved areas to prevent recurrence.

Perifolliculitis capitis abscedens et suffodiens successfully controlled with topical isotretinoin. Karpouzis A, Giatromanolaki A, Sivridis E, et al. *Eur J Dermatol* 2003; 13: 192–5.

A case of DCS controlled with topical isotretinoin and clindamycin gel.

Third-Line Therapies

• PDT	D
• Excision surgery	D
• Laser epilation	D
• Radiotherapy epilation	E
• Dapsone	E
• Alitretinoin	E
• Oral zinc	E
• Finasteride	E
• Compression therapy	E

Treatment of dissecting cellulitis of the scalp with 10% ALA-PDT. Feng Y, Zhang Y, Guo H, et al. *Lasers Surg Med* 2019; 51: 332.

The authors report using 10% ALA-PDT (plus microneedling) 2-weekly for three sessions in seven males. At 3-month follow-up, two patients achieved remission, four patients had significant improvement, and one had minor improvement.

Dissecting cellulitis of the scalp. Williams CN, Cohen M, Ronan SG, et al. *Plast Reconstruct Surg* 1986; 77: 378–82.

Four patients with extensive scalp disease responded to wide excision and split-thickness skin grafting.

Cutting out the tracts: staged excisions for dissecting cellulitis of the scalp. Powers MC, Mehta D, Ozog D. *Dermatol Surg* 2017; 43: 738–40.

Two patients with extensive scarring and sinus tract disease responded to multiple staged excisions under local anesthetic using a pulley-suture closure technique.

Dissecting cellulitis treated with the long-pulsed Nd:YAG laser. Krasner BD, Hamzavi FH, Murakawa GJ, et al. *Dermatol Surg* 2006; 32: 1039–44.

Four patients achieved sustained improvement at 1 year, with some regrowth of hair at treated sites.

Modern external beam radiation therapy for refractory dissecting cellulitis of the scalp. Chinnalayan P, Tena LB, Brenner MJ, et al. *Br J Dermatol* 2005; 152: 777–9.

Rapid improvement in four cases treated with electron beam therapy. No relapses reported after 4- to 13-year follow-up.

Successful treatment with alitretinoin of dissecting cellulitis of the scalp in keratitis-ichthyosis-deafness (KID) syndrome. Prasad SC, Bygum A. *Acta Derm Venereol* 2013; 93: 473–4.

Alitretinoin was given at 10 mg daily for 2 months followed by 20 mg daily in a patient with DCS and KID syndrome. Significant improvement was noted after 5 months of therapy.

Successful treatment of dissecting cellulitis and acne conglobata with oral zinc. Kobayashi H, Aiba S, Tagami H. *Br J Dermatol* 1999; 141: 1136–8.

A patient with DCS and acne conglobata responded to oral zinc sulfate 135 mg three times a day for 12 weeks followed by a reduced maintenance dose.

Innovative management of recalcitrant dissecting cellulitis with compression therapy. Asemota E, Chang YC, Goldberg LJ. *JAMA Dermatol* 2016; 152: 1280–1.

A bespoke compression dressing was used by one patient that promoted drainage and accelerated healing, possibly by reducing the potential space within the tissue.

DRESS syndrome: drug reaction with eosinophilia and systemic symptoms/ drug-induced hypersensitivity syndrome (DiHS)

Roni P. Dodiuk-Gad, Nidhi Shah, Neil H. Shear



Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug-induced hypersensitivity syndrome (DiHS), is considered to result from complex interactions between genetic predisposition, exposure to drug, and viral reactivation. DRESS is characterized by multiorgan involvement with cutaneous, mucosal, hematological, and solid organ manifestations. The cutaneous involvement in DRESS is typically extensive and symptomatic. Delayed onset of 2–8 weeks after drug administration followed by a stepwise development of manifestations is characteristic. Two types of diagnostic criteria are available: the Japanese study group of severe cutaneous adverse reactions to drugs and the RegiSCAR network. Symptoms are usually present for several weeks even after discontinuation of the offending agent and appropriate treatment. Late complications, including mostly

autoimmune diseases and end-organ failure, should be closely monitored. Mortality in DRESS has been estimated at 10%, with most patients dying from liver failure.

MANAGEMENT STRATEGY

DRESS/DiHS is a severe adverse drug reaction with multiorgan involvement that is potentially fatal. Hence, prompt diagnosis and management are essential.

Initial management of DRESS/DiHS requires withdrawal of the culprit drug and assessment of the extent and severity of cutaneous, mucosal, and systemic involvement (hematological and solid organs).

DRESS presents with a combination of fever, diffuse rash, and signs of systemic involvement (any internal organ can be affected) – this triad is often the key to diagnosis. Delayed onset of 2–8 weeks after drug administration followed by a stepwise development of manifestations is characteristic. Fever is the most common sign, followed by a skin rash. The cutaneous involvement in DRESS is typically extensive and symptomatic (pruritus, burning, and pain), with morbilliform eruption being most common. However, various dermatological features may appear. Facial edema and diffuse lymphadenopathy are observed in most patients and mucosal involvement, mainly of the lips and oral cavity, may be demonstrated.

DRESS is considered to occur as a result of complex interactions between genetic predisposition (such as HLA-B*13:01 with dapsone hypersensitivity), exposure to drug, and viral reactivation.

According to the above, thorough investigations are to be conducted by history-taking, skin and full body exam (including assessment of mucous membranes and lymph nodes), blood work, and additional assessment for systemic involvement, viral reactivation, and to exclude alternative diagnosis.

Differential diagnosis must be done with other diseases that may present with skin rash, systemic symptoms, hematologic abnormalities, adenopathy, and fever. These include other severe drug reactions, viral and bacterial infections, autoimmune diseases, hypereosinophilic syndromes, Sézary syndrome, pseudolymphoma, and lymphomas.

Histological assessment is mandatory. Histopathology of cutaneous lesions in DRESS syndrome are variable. However, most commonly include perivascular dense lymphocytic infiltrate in the papillary dermis, with eosinophils, atypical lymphocytes, and spongiosis of the epidermis.

The RegiSCAR group developed a validated and practical scoring system for the diagnosis of DRESS. A severity score is an additional clinical tool to guide treatment options and assist in predicting outcomes.

Proper identification of the culprit drug is of utmost importance for avoiding it and all drugs that may cross-react with this agent and for providing the patient with reassurance to use other drugs that are safe.

The following methods are helpful to establish whether there is a causal relationship between the suspected drug and the clinical event: 1) patient history: the patient should be questioned about former drug eruptions and whether discontinuing the drug improved the eruption; 2) analysis of the literature: PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) and Litt's D.E.R.M. Drug Eruptions and Reactions Manual and database (<http://www.drugeruptiondata.com/>); and 3) in vitro and in vivo diagnostic assessments, including human leukocyte antigen (HLA) genetic tests.

Specific Investigations

- Assessment of skin: extent of cutaneous involvement and morphology of the primary lesion based on four main categories: maculopapular (exanthem, enanthem), urticarial, bullous, and pustular
- Assessment of mucous membranes involvement: ocular, oral, genital
- Assessment of systemic involvement based on patient's signs and symptoms: fever, facial edema, enlarged lymph nodes, malaise, dysphagia, appetite loss, chills, dyspnea, cough, palpitations, nausea, vomiting, diarrhea, sore throat, and arthralgia
- Assessment of systemic involvement based on patient's laboratory screen: full blood count, peripheral blood smear for evaluation of atypical lymphocytes, liver function tests (AST, ALT, GGT, alkaline phosphatase, total bilirubin), kidney function tests (creatinine, serum urea), blood electrolytes, amylase and lipase, serum creatine phosphokinase (CPK), C-reactive protein, and urine analysis. Further laboratory evaluation to be conducted based on patient's signs and symptoms
- Assessment of systemic involvement based on additional evaluation: chest X-ray, ECG, and further investigations based on patient's signs and symptoms
- Assessment of viral reactivation: viral serology and polymerase chain reaction for HHV-6, HHV-7, CMV, EBV
- Assessment to exclude alternative diagnosis according to clinical relevance: serology for hepatitis (A, B, C) and *Mycoplasma/Chlamydia pneumoniae*, blood cultures, and ANA
- Skin biopsy for histopathology and, if relevant, direct immunofluorescence studies
- Usage of RegiSCAR DRESS validation score (classification into definite, probable, possible, or no diagnosis of DRESS)
- Establishment of a differential diagnosis that considers all possible diagnoses
- Usage of DRESS severity score to guide treatment options and assist in predicting outcomes
- Drug exposure analysis: determination of the lag period and creation of a timeline
- Determination of probabilities for the associations between the suspected drug and the clinical event according to the patient's history, literature, and in vitro and in vivo diagnostic assessments, including HLA genetic tests

Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. *Br J Dermatol* 2007; 156: 609–11.

RegiSCAR DRESS validation score is presented.

Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms severity score: a useful tool for assessing disease severity and predicting fatal cytomegalovirus disease. Mizukawa Y, Hirahara K, Kano Y, et al. *J Am Acad Dermatol* 2019; 80(3): 670–8.

DRESS severity score is presented with implications regarding treatment options and predicting outcomes, including CMV-related complications.

Sensitivity and specificity of the lymphocyte transformation test in drug reaction with eosinophilia and systemic symptoms causality assessment. Cabañas R, Calderón O, Ramírez E, et al. *Clin Exp Allergy* 2018; 48(3): 325–33.

An observational retrospective analysis was performed on 41 patients diagnosed with DRESS syndrome and 35 additional patients with non-immediate drug-induced reactions in which a re-exposition drug test was performed. Sensitivity and specificity of the lymphocyte transformation test (LTT) in the recovery phase of DRESS were 73% and 82%, respectively, whereas in the acute phase, they were only 40% and 30%, respectively. The data indicate that LTT has a good sensitivity and specificity and is a reliable tool for diagnosis of drug causality, mainly when performed in the recovery phase in DRESS syndrome.

A combined approach using a detailed case history, LTT, and skin tests is advised to identify the causative drug.

Making a diagnosis in severe cutaneous drug hypersensitivity reactions. Ardern-Jones MR, Mockenhaupt M. *Curr Opin Allergy Clin Immunol* 2019; 19(4): 283–93.

Diagnostic algorithm for drug allergy testing in cutaneous drug hypersensitivity reactions is presented.

First-Line Therapies

• Discontinue the offending drug and avoidance of cross-reacting medications	B
• Supportive care: fluid and electrolyte replacement, nutritional supplementation, hemodynamic balance, and pain control	B
• Skin care and treatment with topical high potency corticosteroids	C
• Systemic corticosteroids	C
• Ciclosporin	C
• Antivirals	D

Therapeutic management of DRESS: a retrospective study of 38 cases. Funck-Brentano E, Duong TA, Bouvresse S, et al. *J Am Acad Dermatol* 2015; 72(2): 246–52.

In this retrospective, single-center, observational study of 50 consecutive patients with DRESS, topical steroid treatment alone was initiated in 66% of cases. The treatment protocol included topical steroids (betamethasone or clobetasol applied once or twice daily) for symptoms of DRESS-related skin disorders in the absence of life-threatening organ involvement; otherwise, systemic steroids were given (orally or intravenously). Complications of DRESS, such as relapse, viral reactivation, and sepsis, were less frequent with topical steroid than with systemic steroids. None of the patients died during their stay in hospital. It was found that systemic steroids may not be required for the management of mild forms of DRESS and may thus be reserved for more severe cases.

Drug reaction with eosinophilia and systemic symptoms (DRESS): how far have we come? Martínez-Cabrales SA, Rodríguez-Bolaños F, Shear NH. *Am J Clin Dermatol* 2019; 20(2): 217–36.

A very comprehensive review including detailed causality assessment tests, treatment guidelines, and summary of all original articles reporting patients with DRESS treated with systemic corticosteroids.

Management of drug reaction with eosinophilia and systemic symptoms (DRESS). Descamps V, Ben Saïd B, Sassolas B, et al. *Ann Dermatol Venerol* 2010; 137(11): 703–8.

This management protocol for DRESS of the French Society of Dermatology was tailored according to the severity and extent of systemic involvement, and the diagnosis of viral reactivation of herpesviruses (mostly HHV-6). The protocol includes four visceral involvement severity categories and corresponding treatment:

1. No severe systemic involvement: topical corticosteroids (potent or very potent), emollients, H1-antihistamines
2. Severe systemic involvement (transaminases >5 times normal, renal involvement, pneumonia, hemophagocytosis, cardiac, etc.): systemic corticosteroids equivalent to 1 mg/kg/day of prednisone and multidisciplinary evaluation
3. Life-threatening signs (hemophagocytosis with bone marrow failure, encephalitis, severe hepatitis, renal failure, and respiratory failure): systemic steroids with intravenous immunoglobulin (IVIG) at a dose of 2 g/kg over 5 days. The IVIG should not be used without associated steroids. The treatments are to be conducted under multidisciplinary supervision
4. Severe systemic involvement and confirmation of a major viral reactivation: combining steroids and antiviral (such as ganciclovir) and/or IVIG

The management of DRESS was not assessed in a prospective study. These guidelines are clinically practical. Systemic steroids need to be slowly tapered over 6–8 weeks to prevent a flare of the disease.

Spanish guidelines for diagnosis, management, treatment and prevention of DRESS syndrome. Cabañas R, Ramírez E, Sendagorta E, et al. *J Investig Allergol Clin Immunol* 2020; 30(4): 229–53.

A comprehensive review including drugs reported in association to DRESS, causality assessment for identifying the culprit drug by the Spanish Pharmacovigilance System, in vitro and in vivo tests, treatment guidelines (consensus of experts) of acute interstitial nephritis and liver injury in DRESS, management of anti-TB DRESS, and Spanish guidelines for the treatment of DRESS including consensus of experts.

Evaluation of cyclosporine for the treatment of DRESS syndrome. Nguyen E, Yanes D, Imadojemu S, et al. *JAMA Dermatol* 2020 Mar 11 [Epub ahead of print].

This retrospective case-control study of adult patients with DRESS compared treatment with intravenous or oral ciclosporin (3–5 mg/kg divided twice daily for 7 days, tapered to 1.5–2.5 mg/kg divided twice daily for 7 days) and four age- and sex-matched controls treated with intravenous methylprednisolone, 1–2 mg/kg daily, with variable prednisone taper dose. The cohort included five patients on treatment with ciclosporin and 21 patients that received systemic corticosteroids. Ciclosporin treatment was associated with shorter time from treatment initiation to cessation of progression and erythema. Ciclosporin treatment resulted in shorter duration of hospitalization and faster normalization of fevers and systemic involvement. Patients in the control group experienced eruption recrudescence on prednisone taper, requiring dosage escalation.

In the following clinical settings, treatment with ciclosporin as first- or second-line treatment is to be considered: when systemic steroids are contraindicated; when there is an inadequate response to steroids; or when a prolonged course of steroids is not ideal. Renal function is important to assess prior and during this treatment.

Second-Line Therapies

• Intravenous immunoglobulin G	E
• Plasmapheresis	E
• Cyclophosphamide	E

Drug reaction with eosinophilia and systemic symptoms (DRESS) in the pediatric population: a systematic review of the literature. Kim GY, Anderson KR, Davis DMR, et al. *J Am Acad Dermatol* 2000; 83: 1323–30.

This systematic literature review on pediatric DRESS found that the majority of patients experienced skin involvement and that the liver was the second most common organ involved. Regarding treatment, the majority were treated with systemic steroids, IVIG alone failed to improve symptoms, and those treated with IVIG and steroids showed rapid clinical improvement. The mortality rate was low, and complications included multiorgan failure and acute respiratory distress syndrome.

Severe DRESS syndrome managed with therapeutic plasma exchange. Alexander T, Iglesia E, Park Y, et al. *Pediatrics* 2013; 131(3): e945–9.

A pediatric case of DRESS syndrome leading to multiorgan involvement and life-threatening complications of respiratory failure and cardiac arrest. After failing to improve with systemic corticosteroids, the patient showed dramatic, sustained clinical response to therapeutic plasma exchange.

Cyclophosphamide therapy for corticoreistant drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome in a patient with severe kidney and eye involvement and Epstein–Barr virus reactivation. Laban E, Hainaut-Wierzbicka E, Pourreau F, et al. *Am J Kidney Dis* 2010; 55(3): e11–4.

A case of severe DRESS with acute tubulointerstitial nephritis in the context of reactivation of Epstein–Barr virus infection. Owing to resistance of the skin and kidney manifestations to prolonged corticosteroid therapy, a 6-month course of oral cyclophosphamide was given and resulted in complete recovery.

Other Therapies

• Counsel the patient and family	C
• Report the event to the patient's healthcare provider, the manufacturer, and regulatory agencies	C
• Conduct medical follow-up to assess long-term emotional and physical complications	C

Long-term sequelae of drug reaction with eosinophilia and systemic symptoms: a retrospective cohort study from Taiwan. Chen YC, Chang CY, Cho YT, et al. *J Am Acad Dermatol* 2013; 68(3): 459–65.

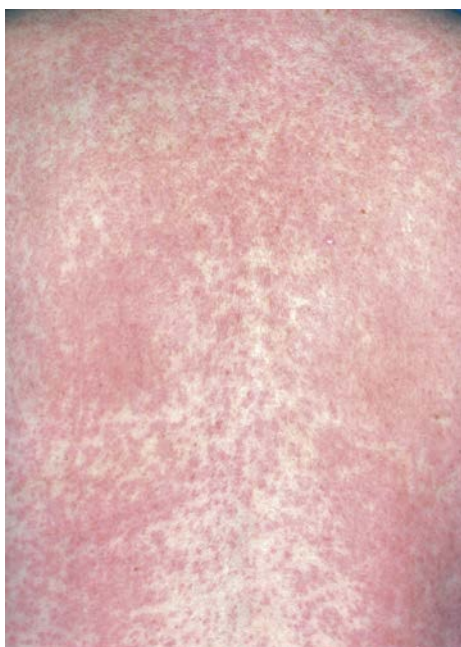
This retrospective cohort study of patients for at least 1 year following DRESS found that the sequelae of DRESS can be divided into two major types occurring in different age groups: young patients tend to develop autoimmune diseases, whereas elderly patients are more vulnerable to end-organ failure.

Post-traumatic stress disorder following drug reaction with eosinophilia and systemic symptoms. Lew TT, Creamer D, Mackenzie J, et al. *Br J Dermatol* 2015; 172(3): 836–7.

This retrospective pilot study on a cohort of 19 patients with DRESS found that most patients experience psychological symptoms consistent with posttraumatic stress disorder, anxiety, and depression following DRESS.

Drug eruptions

Roni P. Dodiuk-Gad, Nidhi Shah, Neil H. Shear



Drug eruptions are among the most frequent adverse reactions in patients receiving drug therapy. They have a wide spectrum of clinical manifestations, are caused by various drugs, and result from varied pathophysiologic mechanisms. Hence, their diagnosis and management are challenging. Drug eruptions can range from a mild, simple eruption involving only the skin to severe complex eruptions with systemic involvement, such as toxic epidermal necrolysis. Systemic involvement should be explored even in a mild cutaneous eruption due to a drug because the severity of skin manifestation does not necessarily mirror the severity of the systemic involvement. The figure above shows a widespread eruption of erythematous macules and papules coalescent into ill-defined plaques on the trunk – maculopapular (exanthem, enanthem) morphology of cutaneous drug eruption. This can be localized to the skin with no systemic involvement (simple drug eruption) or be associated with systemic involvement (complex drug eruption).

MANAGEMENT STRATEGY

The following is the authors' protocol to approaching a patient with a drug eruption: the **4Ds**.

Diagnosis

Diagnosis of the adverse event is based on three key clinical elements:

1. Appearance: the morphology of the drug eruption based on four main categories of the primary lesion: maculopapular (exanthem, enanthem), urticarial, bullous, and pustular.

2. Systemic signs that differentiate between a simple reaction involving only the skin and a complex reaction that comprises systemic involvement in addition to the skin. Systemic involvement is evaluated by assessing the patient's symptoms such as fever, facial edema, malaise, chills, dyspnea, cough, palpitations, nausea, vomiting, diarrhea, sore throat, and arthralgia, and a basic laboratory screen, which includes a full blood count, liver and renal function tests, and urine analysis.

3. Histology: histopathology and, if relevant, direct immunofluorescence studies of skin biopsies to confirm the clinical impression and to distinguish between a drug eruption and other skin diseases.

In addition, it is valuable to use validated diagnostic criteria of specific types of drug eruptions, if available. Currently, only acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) have published validated diagnostic criteria.

Differential Diagnosis

Establishing a differential diagnosis, which considers all possible diagnoses, is essential.

Drug Exposure (Timing)

All medications, regardless of route of administration, must be considered, particularly new drugs taken in the 8 weeks before the drug eruption. Assessment of the lag period, the time between initiation of the drug and onset of the cutaneous reaction, is essential in view of the different lag times for different drug eruptions. A recommended method for drug exposure analysis is to chart a timeline to visualize the chronology and facilitate comprehension of the event.

Determine Probabilities

An important step in assessing a drug eruption is to establish whether there is a causal relationship between the suspected drug and the clinical event. The following methods are helpful:

1. Patient history: the patient should be questioned about previous drug eruptions and whether dechallenging with the drug improved the eruption.
2. Analysis of the literature: PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) and Litt's DERM (*Drug Eruptions and Reactions Manual*) and database (<http://www.drugeruptiondata.com/>).
3. In vitro and in vivo diagnostic assessments, including human leukocyte antigen (HLA) genetic tests.

An important progress in understanding the underlying mechanisms of several types of drug eruptions has been achieved by the discovery of an association between a specific HLA allele, a drug, an ethnic background, and a drug eruption. These tests are best utilized as genetic screening before drug prescription. However, they may serve as a simple, safe, and reliable method for establishing causality in specific cases of drug eruptions such as toxic epidermal necrolysis and DRESS induced by specific drugs, such as carbamazepine and allopurinol. In some countries in Asia, genetic tests are performed prior to prescription of high-risk drugs, and this strategy was proven to reduce the incidence of severe drug eruptions caused by these drugs. Unfortunately, although available in other places, these tests are not yet incorporated as a genetic screening tool to assess the risk of developing a severe drug eruption. In vitro tests, such as the lymphocyte transformation test and basophil activation test, exhibit varying

sensitivity depending on the drug involved and clinical phenotype. In vivo tests, such as patch test and delayed intradermal testing, may also be used in assessment of a drug eruption. Caution should always be exercised regarding false-positive and false-negative results of these in vitro and in vivo tests.

After the diagnosis of a drug eruption, the physician must provide the patient with clear information on the drug eruption, the name of the offending drug, potential cross-reacting drugs, and drugs that can be safely taken as an alternative to the offending drug. In cases of complex reactions, it is also necessary to explain to the patient the need for long-term medical follow-up, to provide information on support groups, and to conduct family counseling because the predisposition may be genetic. The physician must also report the event to the patient's healthcare provider, the manufacturer, and regulatory agencies.

Specific Investigations

- Determination of the morphology of the primary lesion based on four main categories: maculopapular (exanthem, enanthem), urticarial, bullous, and pustular
- Assessment of mucous membrane involvement: ocular, oral, genital
- Assessment of systemic involvement based on patient's signs and symptoms: fever, facial edema, malaise, chills, dyspnea, cough, palpitations, nausea, vomiting, diarrhea, sore throat, and arthralgia
- Assessment of systemic involvement based on patient's basic laboratory screen: full blood count, liver and renal function tests, and urine analysis
- Skin biopsy for histopathology and, if relevant, direct immunofluorescence studies
- In cases of complex drug eruptions, further investigations by multidisciplinary medical team based on the patient's signs and symptoms
- Usage of validated diagnostic criteria, if available (AGEP and DRESS)
- Establishment of a differential diagnosis that considers all possible diagnoses
- Drug exposure analysis: determination of the lag period and creation of a timeline
- Determination of probabilities for the associations between the suspected drug and the clinical event according to the patient's history, literature, and in vitro and in vivo diagnostic assessments, including HLA genetic tests

Phenotype standardization for immune-mediated drug-induced skin injury. Pirmohamed M, Friedmann PS, Molokhia M, et al. Clin Pharmacol Ther 2011; 89: 896–901.

A drug-induced skin injury (DISI) expert working group defined the minimum phenotypic criteria for selected forms of DISI (Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), AGEP, and DRESS). In addition, an algorithm to aid appropriate clinical categorization is presented.

Severe cutaneous adverse reactions to drugs. Duong TA, Valeyrie-Allanore L, Wolkenstein P, et al. Lancet 2017; 28: 390(10106): 1996–2011.

This review summarizes the clinical approach to patients with severe cutaneous adverse reactions to drugs.

Acute generalized exanthematous pustulosis (AGEP) – a clinical reaction pattern. Sidoroff A, Halevy S, Bavinck JN, et al. J Cutan Pathol 2001; 28: 113–9.

AGEP validation score is presented in this manuscript.

Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. Br J Dermatol 2007; 156: 609–11.

Scoring system for classifying DRESS cases is presented in this manuscript.

Controversies in drug allergy: in vitro testing. Mayorga C, Ebo DG, Lang DM, et al. J Allergy Clin Immunol. 2019; 143: 56–65.

International consensus on in vitro testing to assess drug allergy.

Controversies in drug allergy: testing for delayed reactions. Phillips EJ, Bigliardi P, Bircher AJ, et al. J Allergy Clin Immunol. 2019; 143: 66–73.

International consensus on in vitro testing to assess delayed immunologically mediated adverse drug reactions, which includes a summary table on the various tests available for different types of reactions.

HLA association with drug-induced adverse reactions. Fan WL, Shiao MS, Hui RC, et al. J Immunol Res 2017; 2017: 3186328.

This review summarizes the alleles of HLA genes, which have been proposed to have association with adverse drug reactions induced by different drugs.

First-Line Therapies

• Discontinue the offending drug	B
• Supportive care	B
• Simple drug eruption (involving only the skin): oral antihistamines and topical corticosteroids	C
• Complex drug eruption (systemic involvement in addition to the skin): specific treatments based on the type of the drug eruption	C

Clinical practice. Exanthematous drug eruptions. Stern RS. N Engl J Med 2012; 366: 2492–501.

Identifying and discontinuing the causative drug are the most important steps in management of a drug eruption. In simple drug eruptions, symptomatic treatment with antihistamines and potent topical glucocorticoids may be helpful. A decision can be made to continue the drug and offer symptomatic treatment if the drug is of paramount importance, but the risk:benefit ratio of this option must be carefully weighed, and the evolution of the eruption must be meticulously monitored. In cases of complex drug eruptions, it is always essential to discontinue the drug.

Severe delayed cutaneous and systemic reactions to drugs: a global perspective on the science and art of current practice. Peter JG, Lehloeny R, Dlamini S, et al. J Allergy Clin Immunol Pract 2017; 5: 547–63.

The review summarizes various types of delayed cutaneous and systemic reactions to drugs including common offending drugs, images of different clinical phenotypes, and management.

Second-Line Therapies

• Cyclosporine	B
• Systemic steroids	C
• TNF inhibitors	E
• Intravenous immunoglobulin G	E
• Mucous membrane treatment	E
• Skin treatment	E
• Pain control	E

Open trial of cyclosporine treatment for Stevens–Johnson syndrome and toxic epidermal necrolysis. Valeyrie-Allanore L, Wolkenstein P, Brochard L, et al. *Br J Derm* 2010; 163: 847–53.

Death rate and progression of detachment appeared lower than expected in 29 patients with a diagnosis of SJS or TEN who received ciclosporin (3 mg/kg/day for 10 days and tapered over a month).

A meta-analysis of cyclosporine treatment for Stevens–Johnson syndrome/toxic epidermal necrolysis. Ng QX, De Deyn MLZQ, Venkatanarayanan N, et al. *J Inflamm Res* 2018; 11: 135–42.

A meta-analysis of ciclosporin treatment for Stevens–Johnson syndrome/toxic epidermal necrolysis found improved mortality with efficacy, safety, and beneficial effects in SJS/TEN patients.

Randomized, controlled trial of TNF- antagonist in CTL-mediated severe cutaneous adverse reactions. Wang CW, Yang LY, Chen CB, et al. Taiwan Severe Cutaneous Adverse Reaction (TSCAR) Consortium. *J Clin Invest* 2018; 128: 985–96.

In this randomized trial, participants with SJS/TEN were consecutively enrolled and randomly assigned at a 1:1 ratio to receive either etanercept by subcutaneous injection 25 mg (or 50 mg administered to patients who weighed more than 65 kg) twice a week or 1–1.5 mg/kg/day prednisolone by intravenous injection until their skin lesions were healed. Etanercept was found to improve clinical outcomes in patients with SJS/TEN.

Stevens–Johnson syndrome and toxic epidermal necrolysis: risk factors, causality assessment and potential prevention strategies. Lin CC, Chen CB, Wang CW, et al. *Expert Rev Clin Immunol* 2020; 2: 1–15.

This review presents the current therapeutic approaches to SJS and TEN and includes a summary of studies using ciclosporin and TNF- α antagonist for SJS/TEN.

Spanish guidelines for diagnosis, management, treatment and prevention of DRESS syndrome. Cabañas R, Ramírez E, Sendagorta E, et al. *J Investig Allergol Clin Immunol* 2020; 30(4): 229–53.

Spanish guidelines on DRESS syndrome including expert consensus protocols for management and treatment. Gives advice on suitable alternatives to causative anticonvulsants and allopurinol, and evidence relating to in vivo and in vitro drug tests.

Other Therapies

- Counsel the patient and family C
- Report the event to the patient's healthcare provider, the manufacturer, and regulatory agencies C
- In cases of DRESS and SJS/TEN, conduct medical follow-up to assess long-term emotional and physical complications C

Health-related quality of life and long-term sequelae in survivors of epidermal necrolysis: an observational study of 57 patients. Ingen-Housz-Oro S, Alves A, Colin A, et al. *Br J Dermatol* 2020; 182: 916–26.

TEN-specific sequelae in survivors 3.6 years after the acute event were cutaneous (77%), ocular (70%), psychological (60%), dental/oral (49%), genital (30%), and respiratory (18). Anxiety and depression were similar to survivors of severe septic shock requiring ITU admission.

Eosinophilic fasciitis

Elizabeth Tkachenko, Alisa Femia, Ruth Ann Vleugels



Eosinophilic fasciitis (EF), also known as *Shulman syndrome*, is a rare fibrosing disorder characterized by the rapid onset of symmetric induration of the extremities. The trunk and neck are affected less commonly; the distal digits and face are typically spared. The condition overlaps with plaque morphea in 35% of patients. Clinically, EF is marked by an early, edematous phase with erythema, followed by progressive sclerosis and a *peau d'orange* appearance. Depressions over superficial veins produce the characteristic 'groove' sign. Ultimately, woody induration and stiffness of the limbs develop, leading to decreased range of motion. Joint contractures are a major cause of morbidity and occur in 50%–56% of patients.

Laboratory investigations may reveal peripheral blood eosinophilia, present in 58% of patients, and an elevated erythrocyte sedimentation rate, but these are not essential in securing a diagnosis. EF has been reported in association with hematologic disorders, including monoclonal gammopathy, aplastic anemia, hemolytic anemia, thrombocytopenia, leukemias, and lymphomas; as such, abnormalities in complete blood count and immunofixation and/or protein electrophoresis may be seen. Histologically, EF presents with fascial thickening associated with a mixed inflammatory infiltrate composed of lymphocytes, plasma cells, histiocytes, and occasionally eosinophils. Dermal sclerosis can be seen in more advanced disease. Although the etiology remains unknown, vigorous physical activity and infection have been reported prior to EF onset in select cases, presumably triggering an aberrant immune response; however, these factors may be present in a minority of patients, with preceding trauma or intense exercise reported in only 28% of cases.

EF is differentiated from systemic sclerosis by the relative absence of sclerodactyly, Raynaud disease, nailfold capillary changes, and serologic markers. In addition, patients with EF traditionally lack visceral involvement. This clinical distinction is critical given that data supports avoiding systemic corticosteroids,

a first-line agent for EF, in systemic sclerosis. EF must also be distinguished from the eosinophilia-myalgia syndrome, which is characterized by diffuse muscle pain and weakness, polyneuropathy, respiratory and pulmonary involvement, and most notably a history of contaminated L-tryptophan ingestion.

MANAGEMENT STRATEGY

The constellation of clinical, laboratory, imaging, and histologic findings establish the diagnosis of EF. Histopathologic examination from a full-thickness skin-to-muscle biopsy has been considered the gold standard for diagnosis. Diagnostic biopsy can be challenging to obtain due to feasibility issues, concerns regarding healing, and sampling error. *Magnetic resonance imaging* (MRI) is increasingly used by experts as a non-invasive modality to establish the diagnosis and monitor the effectiveness of treatment. On MRI, findings typically show high signal intensity of the deep and superficial fasciae on T₁, T₂, and short tau inversion recovery imaging with enhancement after intravenous contrast administration. Ultrasound and positron emission tomography/computed tomography (PET/CT) are additional non-invasive tools to aid in diagnosis, but are utilized less frequently. Serum aldolase levels have also been proposed as a useful indicator of disease activity.

Though spontaneous remission of EF has rarely been reported, treatment is crucial to help prevent the progression of sclerosis and development of contractures and limited mobility. Although a validated skin index does not exist, clinical response is usually defined as resolution of erythema and edema with improvement in skin thickening. As fibrosed tissue becomes softer and looser, it allows for increased range of motion. The primary goal of EF management is to halt disease progression. Softening of recently involved areas of sclerosis is possible with appropriate early treatment. Complete resolution of induration is rare and not routinely expected, particularly in patients with longstanding disease. Importantly, when patients are appropriately diagnosed and treated during the early, edematous phase, avoidance of induration and joint contractures is often possible, underscoring the need for prompt diagnosis and management.

Although responsive to *oral steroids*, EF will typically flare upon taper of steroids, and thus EF requires long-term treatment with a *steroid-sparing immunosuppressive* agent for durable clinical response and to avoid sequelae of prolonged steroid use. The combination of systemic corticosteroids and either *methotrexate* or *mycophenolate mofetil* should be considered first line for EF, initiated simultaneously at the time of diagnosis. This regimen consists of high-dose oral corticosteroids (*prednisone* 1 mg/kg/day, slowly tapered over 3–6 months depending on disease severity) or *pulse methylprednisolone* (1000 mg/day for 3 days, followed by prednisone taper). The authors utilize pulse methylprednisolone in moderate-to-severe cases as there are data to support this results in improved outcomes. Simultaneously, therapy with *methotrexate* (target dose 25 mg weekly) or *mycophenolate mofetil* (target dose 2–3 g daily, often 3 g in moderate-to-severe cases) is initiated. *Pulse methotrexate* has also been efficacious (4 mg/kg/month with 25 mg/day folinic acid 24 hours after administration) with or without systemic corticosteroids for five treatment months. The addition of *hydroxychloroquine* (200–400 mg/day) to this regimen can also be considered.

Although methotrexate has traditionally been considered the steroid-sparing agent of choice for EF, novel data reveals that *mycophenolate mofetil* (2–3 g/day) is efficacious both first line and in cases where methotrexate fails or is contraindicated. *Intravenous immunoglobulin* (2 g/kg over 2 days, monthly) may also be considered in refractory cases as an adjuvant to corticosteroids

and/or methotrexate, or as monotherapy in patients with contraindications to *methotrexate* or *mycophenolate mofetil*. Use of *cyclosporin* monotherapy (3.7–5 mg/kg/day) is supported by several case reports. *Ultraviolet A1 (UVA1)* at cumulative doses of 1750–1930 J/cm² was efficacious in one case as monotherapy and in a second case with concomitant methylprednisolone.

Infliximab, *sirolimus*, *D-penicillamine*, *ketotifen*, *chloroquine*, *psoralen and ultraviolet light (PUVA)*, *azathioprine*, *griseofulvin*, *dapsone*, *rituximab*, *tocilizumab*, *tofacitinib*, and *sulfasalazine* have all been reported to have beneficial effects in case reports or series. *Mepolizumab*, an antiinterleukin-5 antibody, is being evaluated in a clinical trial (NCT04305678) given the role of IL-5 in hyper-eosinophilia. Additionally, physical therapy should be routinely recommended to prevent and/or improve joint contractures and related functional morbidity.

Specific Investigations

- Careful physical examination to differentiate from systemic sclerosis
- Complete blood count with differential
- Wedge excision to muscle (including fascia) and/or MRI
- In select cases, ultrasound or fludeoxyglucose (FDG) PET/CT
- History to exclude tryptophan, simvastatin, or trichloroethylene ingestion

Epidemiology and treatment of eosinophilic fasciitis: an analysis of 63 patients from 3 tertiary care centers. Wright NA, Mazori DR, Patel M, et al. *JAMA Dermatol* 2016; 152: 97–9.

In this large cohort of EF patients, peripheral eosinophilia was present in 58% of cases. Seventy-nine percent of patients were initially misdiagnosed, most frequently with systemic sclerosis. Although 50% of patients had joint contractures, only 37% were referred for physical therapy.

The use of an elevated aldolase in diagnosing and managing eosinophilic fasciitis. Nashel J, Steen V. *Clin Rheumatol* 2015; 34: 1481–4.

In this retrospective review of 15 patients, the aldolase level was the last parameter to normalize and the first to rise during a flare compared with eosinophilia and inflammatory markers.

Eosinophilic fasciitis: spectrum of MRI findings. Moulton SJ, Kransdorf MJ, Ginsburg WW, et al. *Am J Roentgenol* 2005; 184: 975–8.

In this case series of six patients with histologically proven EF, MRI revealed characteristic findings, including thickening, signal abnormalities, and contrast enhancement of the superficial and, to a lesser extent, deep muscle fasciae.

Eosinophilic fasciitis: typical abnormalities, variants and differential diagnosis of fasciae abnormalities using MR imaging. Kirchgessner T, Dallaudiere B, Omoumi P, et al. *Diagn Interv Imaging* 2015; 96: 341–8.

This review summarizes the MRI findings in EF and other subcutaneous conditions on the differential diagnosis of entities that produce abnormal fascial signal intensities.

Ultrasound assessment of subcutaneous compressibility: a potential adjunctive diagnostic tool in eosinophilic fasciitis. Kissin EY, Garg A, Grayson PC, et al. *J Clin Rheumatol* 2013; 19: 382–5.

A cross-sectional study of 12 patients with EF revealed a significant reduction in subcutaneous compressibility quantified by ultrasound.

Usefulness of FDG PET/CT in the diagnosis of eosinophilic fasciitis. Kim HJ, Lee SW, Kim GJ, et al. *Clin Nucl Med* 2014; 39: 801–2.

In one case report, increased uptake of FDG on PET/CT along the superficial and deep fasciae suggested FDG PET/CT may be a non-invasive tool to illustrate more detailed anatomic involvement of the disease, especially if MRI is contraindicated.

Eosinophilic fasciitis. A pathologic study of twenty cases. Barnes L, Rodnan GP, Medsger TA, et al. *Am J Pathol* 1979; 96: 493–517.

Deep fascia and subcutaneous tissue are infiltrated with lymphocytes, plasma cells, histiocytes, and eosinophils early in the course of the disease. Sclerosis of the dermis with increased collagen occurs later in the course of the disease.

Clinicopathologic and immunophenotypic features of eosinophilic fasciitis and morphea profunda: a comparative study of 27 cases. Onajin O, Wieland CN, Peters MS, et al. *J Am Acad Dermatol* 2018; 78: 121–8.

While EF and morphea profunda share clinical and pathologic features, EF patients are more likely to have forearm involvement and peripheral eosinophilia. Histopathologically, fascia in patients with EF is more likely to reveal eosinophils and focal loss of CD34 staining.

Baseline characteristics and long-term outcomes of eosinophilic fasciitis in 89 patients seen at a single center over 20 years. Mango RL, Bugdayli K, Crowson CS, et al. *Int J Rheum Disease* 2020; 23(2): 233–9.

This retrospective review of 89 EF patients revealed complete treatment response in 60% of patients at 3 years. While diagnostic delay was inversely associated with treatment response, no baseline characteristics correlated with response, although there was a trend toward positive association with elevated aldolase, hypergammaglobulinemia, and hematologic disorders.

First-Line Therapies

• Systemic corticosteroids and methotrexate	B
• Systemic corticosteroids	B
• Pulsed methylprednisolone	D
• Methotrexate	D
• Mycophenolate mofetil	D
• Adjunctive physical therapy	Expert opinion (no studies have evaluated this)

Epidemiology and treatment of eosinophilic fasciitis: an analysis of 63 patients from 3 tertiary care centers. Wright NA, Mazori DR, Patel M, et al. *JAMA Dermatol* 2016; 152: 97–9.

A retrospective review of 63 EF patients revealed that complete response was more likely in those treated with a combination of corticosteroids and methotrexate (64%), compared with corticosteroid monotherapy (30%), other treatment combinations (29%), and without steroids (17%).

Eosinophilic fasciitis: clinical spectrum and therapeutic response in 52 cases. Lakhanpal S, Ginsburg WW, Michet CJ, et al. *Semin Arthritis Rheum* 1988; 17: 221–31.

Of the 52 patients, 34 were treated with prednisone (40–60 mg/daily). The remaining 18 were treated with hydroxychloroquine, colchicine, D-penicillamine, or no medication. Twenty of the 34 patients treated with prednisone had a partial response, and five had complete resolution. Eight of the nine patients who had a poor response were treated with the addition of hydroxychloroquine (200–400 mg/daily). Two responded completely, two had an improvement of over 50%, and three were lost to follow-up. Eight patients also responded to treatment with hydroxychloroquine alone. Relapses occurred in some patients.

Eosinophilic fasciitis (Shulman disease): new insights into the therapeutic management from a series of 34 patients. Lebeaux D, Francés C, Barete S, et al. *Rheumatology (Oxford)* 2012; 51: 557–61.

Prednisone served as a first-line therapy for all 34 patients. Before treatment initiation, 15 patients received methylprednisolone pulses (MPPs), which increased the probability of complete remission. After treatment initiation, 12 patients received methotrexate as a second-line therapy. A poor outcome was present in 10 patients and was associated with a diagnosis time delay of more than 6 months and a lack of MPPs at treatment initiation. Overall, complete remission was achieved in 69% of patients.

Eosinophilic fasciitis: clinical characteristics and response to methotrexate. Berianu F, Cohen MD, Abril A, et al. *Rheum Dis* 2015; 18: 91–8.

Of 15 prednisone-dependent patients with biopsy-proven EF, 13 (87%) were able to discontinue prednisone after receiving methotrexate for a mean of 14.5 months, with 9/13 (69%) achieving disease remission after a mean of 31.4 months on methotrexate.

High-dose intravenous pulse methotrexate in patients with eosinophilic fasciitis. Mertens JS, Zweers MC, Kievit W, et al. *JAMA Dermatol* 2016; 152: 1262–5.

In this study, 12 patients with biopsy-proven EF received intravenous methotrexate (4 mg/kg) monthly for 5 months with folinic acid rescue 24 hours after administration. Median modified skin scores improved significantly from baseline on this regimen.

Mycophenolate mofetil for eosinophilic fasciitis: a retrospective analysis from 3 tertiary care centers. Tkachenko E, Steuer AB, Lo K, et al. *JAMA Dermatol* 2020; 156: 595–7.

Fourteen EF patients were treated with mycophenolate mofetil (2–3 g daily), with 13 responding favorably and eight ultimately achieving complete clinical response. Concomitant systemic corticosteroids were discontinued in the majority (69%) of patients and tapered from an average of 48 mg to average 11.25 mg daily in the remaining 31%. Gastrointestinal distress was the only adverse event noted.

Four prolonged cases of eosinophilic fasciitis in children. Hui-Yuen J, Lauren C, Garzon M, et al. *Arthritis Rheumatol* 2014; 66: S85.

Four pediatric patients with EF confirmed the efficacy of corticosteroids as a first-line therapy. All patients required either methotrexate or mycophenolate mofetil, and three required both, suggesting a more severe course within the pediatric population.

Second-Line Therapies

• Hydroxychloroquine	C
• Prednisone and D-penicillamine	C
• Intravenous immunoglobulin	D
• Ciclosporin	E

Eosinophilic rheumatic disorders. Clauw DJ, Crofford LJ. *Rheum Clin North Am* 1995; 21: 231–46.

Hydroxychloroquine at a dose of 200–400 mg daily can be used either alone or in combination with corticosteroids.

Eosinophilic fasciitis successfully treated with cyclosporine. Bukiej A, Dropiński J, Dyduch G, et al. *Clin Rheumatol* 2005; 24: 634–6.

A 45-year-old female unresponsive to treatment with prednisone followed by cimetidine experienced clinical remission after a regimen of ciclosporin at 5 mg/kg daily for 4 weeks tapered to 2.5 mg/kg daily.

Severe eosinophilic fasciitis: comparison of treatment with D-penicillamine plus corticosteroids vs. corticosteroids alone. Mendoza FA, Bai R, Kebede AG, et al. *Scand J Rheumatol* 2015; 73: 1010.

A prospective, non-randomized, open-label trial of 16 patients with a clinicohistopathologic diagnosis of severe EF revealed that the combination treatment of D-penicillamine plus corticosteroids was more efficacious than corticosteroids alone. Proteinuria was the most common adverse event in both groups. Four of 10 patients in the D-penicillamine-arm had to discontinue treatment due to adverse events.

Intravenous immunoglobulin for refractory eosinophilic fasciitis: a retrospective analysis from 3 tertiary care centers. Tkachenko E, Steuer AB, Lo K, et al. *J Am Acad Dermatol* 2019; S0190-9622(19)33297-9.

Five patients with recalcitrant EF were successfully treated with intravenous immunoglobulin (IVIG) (2 g/kg divided evenly over 2–3 consecutive days, every 4 weeks). All patients were able to discontinue oral corticosteroids once receiving IVIG. Adverse effects were headache in two patients.

Third-Line Therapies

• PUVA	E
• Ultraviolet A1 (UVA1) phototherapy	E
• Combination UVA1–retinoid–corticosteroid	E
• Extracorporeal photochemotherapy	E
• D-penicillamine	E
• Azathioprine	E
• Chloroquine	E
• Sulfasalazine	E
• Surgery	E
• Infliximab	E
• Rituximab	E
• Dapsone	E
• Cimetidine	C
• Tocilizumab	E
• Sirolimus	E
• Tofacitinib	E
• Mepolizumab	E

Eosinophilic fasciitis treated with psoralen-ultraviolet A bath photochemotherapy. Schiener R, Behrens-Williams SC, Gottlob P, et al. *Br J Dermatol* 2000; 142: 804–7.

After 35 sessions of PUVA, induration and mobility improved in a 56-year-old patient, with resolution of induration after 50 sessions.

Extracorporeal photochemotherapy in the treatment of eosinophilic fasciitis. Romano C, Rubegni P, De Aloe G, et al. *J Eur Acad Dermatol Venereol* 2003; 17: 10–3.

Three patients were treated with extracorporeal photochemotherapy on 2 consecutive days at 2-week intervals for 3 months, then every 4 weeks. After 1 year of therapy, two patients showed a considerable improvement in clinical parameters.

Eosinophilic fasciitis: a report of two cases treated with ultraviolet A1 phototherapy. Silny W, Osmola-Mankowska A, Czarnecka-Operacz M, et al. *Photodermatol Photoimmunol Photomed* 2009; 25: 325–7.

In one patient for whom immunosuppression was contraindicated, UVA1 monotherapy improved skin elasticity on the forearms but not the trunk after a cumulative dose of 1750J/cm². A second patient reduced concomitant methylprednisolone dose and experienced clinical improvement with a total UVA1 dose of 1930J/cm².

Surgical management of eosinophilic fasciitis of the upper extremity. Suzuki G, Itoh Y, Horiuchi Y. *J Hand Surg* 1997; 22: 405–7.

All four patients experienced improved mobility a few weeks after fasciectomy with follow-up oral prednisolone.

Infliximab may be effective in the treatment of steroid-resistant eosinophilic fasciitis: report of three cases. Khanna D, Agrawal H, Clements PJ. *Rheumatology (Oxford)* 2010; 49: 1184–8.

Three patients refractory to initial treatment with prednisone (60 mg/daily), two of whom also received methotrexate (20 mg/week), noticed clinical improvement within 8 weeks of starting

infliximab (3 mg/kg every 8 weeks), leading ultimately to drug-free remission.

Rituximab as a therapeutic consideration for refractory eosinophilic fasciitis. Nahhas AF, Alam M, Lim HW. *Int J Dermatol* 2018; 57: 614–5.

A 67-year-old man with biopsy and MRI-proven refractory EF was treated with oral corticosteroids, methotrexate, and rituximab (1 g IV, 2 weeks apart) in two courses 5 months apart. Range of motion and skin thickness improved, and peripheral eosinophilia resolved.

The use of tocilizumab in the treatment of refractory eosinophilic fasciitis: a case-based review. Vilchez-Oya F, Sánchez-Schmidt JM, Agustí A, et al. *Clin Rheumatol* 2020 Jan 23 [Epub ahead of print].

A 60-year-old man who failed corticosteroids, subcutaneous methotrexate, and intravenous immunoglobulins for EF was initiated on 8 mg/kg monthly tocilizumab with improved Rodnan skin scores and functional range of motion after 5 months. This case and two additional cases in the literature used concomitant prednisone and methotrexate with tocilizumab in refractory EF.

Treatment of eosinophilic fasciitis with sirolimus. Oza VS, Walsh R, North J, et al. *JAMA Dermatol* 2016; 152: 488–90.

A man in his 30s failed combined prednisone and methotrexate for biopsy-proven EF. He started sirolimus 2 mg/day (with 5 mg/day prednisone), experiencing improved pain and skin thickening within 6 weeks. Clinical and functional improvement continued throughout 9 months on this regimen.

Treatment of generalized deep morphea and eosinophilic fasciitis with the Janus kinase inhibitor tofacitinib. Kim SR, Charos A, Damsky W, et al. *JAAD Case Rep* 2018; 4: 443–5.

Tofacitinib (5 mg twice weekly) in combination with methotrexate (10 mg weekly) and prednisone (15 mg daily tapered and discontinued over 3 months) resulted in marked improvement of induration and range of motion after 1 year of treatment in a 66-year-old female.

Epidermal nevi

Jeffrey M. Weinberg



Epidermal nevi (EN; OMIM162900) are congenital hamartomas of embryonal ectodermal origin classified on the basis of their major component. The components may be sebaceous, apocrine, eccrine, follicular, or keratinocytic. An estimated one-third of individuals with EN have involvement of other organ systems. In these cases, the condition is termed *epidermal nevus syndrome*.

The most common EN are verrucous epidermal nevi (VEN), which are best treated with an ablative procedure using either surgical or laser technology. Inflammatory EN may respond to topical or systemic therapy.

The pluripotential stem cell in the embryonic ectoderm can develop into any of the cell types found within the epidermis and skin adnexa. Therefore many potential nevi may develop from these cell types. EN may be classified according to the predominant cell type. However, there may be different cell populations or overlap between different areas within the same nevus.

The focus of this chapter will be on nevi derived from keratinocytes. Of these, VEN are the most common. Other forms include an inflammatory linear verrucous epidermal nevus (ILVEN), an acantholytic or Darier-like nevus, an epidermolytic form, and linear porokeratosis. Very rarely an epidermal nevus may be associated with other birth defects, and a number of epidermal nevus syndromes have been described.

VEN may be localized, segmental, and rarely systematized. The individual lesions are verrucous papules, which may be pink, brown, or gray. These may develop as a result of mosaicism, and, if there is gonadal mosaicism, EN may be transmitted to future offspring.

There are very rare case reports of malignant change within EN, including squamous cell carcinoma and basal cell carcinoma.

MANAGEMENT STRATEGY

The major focus of therapy is improved cosmesis. A possible role for the dermis in the development of EN is suggested by the difficulty experienced in ablating these lesions surgically without destroying the underlying dermis. *Surgical management* of these lesions presents challenges. Superficial treatments, which remove only the epidermis, have a high recurrence rate, whereas excision or more aggressive ablative procedures may produce unacceptable scarring. *Laser* technology provides the surgeon with more precise tools to maximize efficacy while minimizing scarring. Alternatively, for very widespread lesions, a variety of *topical regimens*, as well as *systemic retinoids*, have been reported to produce some benefit.

ILVEN presents in early childhood as a pruritic, erythematous, linear plaque. It shares many features with psoriasis, and certain cases respond to antipsoriatic therapies such as *topical vitamin D analogs*, *corticosteroids*, and *dithranol*. This has led some authors to suggest that this condition is a nevusoid form of psoriasis. Epidermolytic and acantholytic nevi are more likely to respond to treatment with *retinoids*.

Specific Investigations

- Skin biopsy
- X-ray, imaging studies (magnetic resonance imaging [MRI], computed tomography scans), and ophthalmologic examinations

An epidermal nevus can most often be diagnosed solely on the clinical presentation and distribution of the lesion. A skin biopsy can be used both to confirm the diagnosis if necessary and to determine the predominant cell type and the presence of inflammatory changes, acantholysis, or dysplasia. This can be helpful in determining which therapeutic modality is most likely to succeed. If histopathology demonstrates an epidermolytic nevus, the individual should be counseled that there is a possibility that the mutation could be transmitted to offspring, with the risk that their children may have generalized cutaneous involvement. Biopsy can also indicate the rare occurrence of squamous or basal cell carcinoma, which can develop in EN.

Epidermal nevus syndromes refer to the association of EN with extracutaneous manifestations involving the central nervous system, eyes, or bones. The evaluation for systemic involvement should be based on the clinical extent of the EN and the presence of any extracutaneous signs and symptoms.

Generalized epidermolytic hyperkeratosis in two unrelated children from parents with localized linear form, and prenatal diagnosis. Chassaing N, Kanitakis J, Sportich S, et al. *J Invest Dermatol* 2006; 126: 2715–7.

The authors report two unrelated children with epidermolytic hyperkeratosis, both born to a parent affected with epidermolytic epidermal nevi (EEN); prenatal diagnosis in two successive pregnancies of one of the patients with EEN is described.

Squamous cell carcinoma arising in a verrucous epidermal naevus. Ichikawa T, Saiki M, Kaneko M, et al. *Dermatology* 1996; 193: 135–8.

A case report of a squamous cell carcinoma arising in a 74-year-old man with an epidermal nevus, plus a review of the literature, which revealed 18 previous reports of malignant change in EN.

Basal cell carcinoma developing in verrucous epidermal nevus. De D, Kanwar AJ, Radotra BD. *Indian J Dermatol Venereol Leprol* 2007; 73: 127–8.

A 58-year-old farmer with a hyperpigmented, soft verrucous plaque on the right temporoparietal region since birth presented with an ulcer of 8 months' duration. A diagnosis of basal cell carcinoma (BCC) arising in a verrucous epidermal nevus was made. Biopsy was consistent with BCC.

Epidermal nevus syndromes: new insights into whorls and swirls.

Asch S, Sugarman JL. *Pediatr Dermatol* 2018; 35 :21–9. The authors review recent genetic discoveries involving EN, including nevus sebaceous, keratinocytic epidermal nevus, nevus comedonicus, congenital hemidysplasia with ichthyosiform nevus and limb defects syndrome, phakomatosis pigmentokeratotic, Becker nevus, porokeratotic adnexal ostial nevus, ILVEN, and cutaneous-skeletal hypophosphatemia syndrome. Several mutations have been identified in EN, including mutations in Ras, fibroblast growth factor receptor 3 (FGFR3), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), and keratins.

Epidermal nevus syndromes: clinical findings in 35 patients.

Vidaurre-de la Cruz H, Tamayo-Sanchez L, Duran-Mckinster C, et al. *Pediatr Dermatol* 2004; 21: 432–9. Of patients with EN, 10%–18% may have disorders of the eye and skeletal and nervous systems.

Does inflammatory linear verrucous epidermal nevus represent a segmental type 1/type 2 mosaic of psoriasis?

Hofer T. *Dermatology* 2006; 212: 103–7. The author hypothesizes that inflammatory linear verrucous eruption besides nevoid psoriasis/linear psoriasis represents a further segmental type 1/type 2 mosaic of psoriasis, which, if a (verrucous) epidermal nevus exists, shows a high affinity of occurrence in close context to such a nevus. Heritability is thought to be possible.

Papular epidermal nevus with skyline basal cell layer (PENS): three new cases and review of the literature.

Luna PC, Pannizardi AA, Martin CI, et al. *Pediatr Dermatol* 2016; 33: 296–300. Papular epidermal nevus with skyline basal cell layer (PENS) is a recently described type of epidermal nevus with characteristic histopathologic findings. The authors note that cases of Blaschko distribution, associated extracutaneous manifestations, and familial cases have been reported. The probability of having extracutaneous manifestations is 6.3 times greater in those with more than four lesions. Therefore these patients require closer follow-up.

Verrucous Epidermal Nevus

First-Line Therapies

- Excision under local anesthetic **D**
- Shave or curettage under local anesthetic **D**
- Cryotherapy **C**

Epidermal nevus: surgical treatment by partial-thickness skin excision.

Dellon AL, Luethke R, Wong L, et al. *Ann Plast Surg* 1992; 28: 292–6. A case report of treatment of a systematized epidermal nevus by partial-thickness skin excision. This cleared the nevus but led to extensive hypertrophic and keloidal scarring.

Treatment of VEN: experience with 71 cases.

Lapidoth M, Israeli H, Ben Amitai D, et al. *Dermatology* 2013; 226: 342–6. Of the 71 cases reviewed, 62 responded well to cryotherapy alone, and nine facial VEN required CO₂ laser treatment. Small VEN required relatively few treatments (mean 3.4). Larger lesions required more treatments (mean 7.4) and did not respond as well.

Assessment of cryotherapy for the treatment of verrucous epidermal nevi.

Panagiotopoulos A, Chasapi V, Nikolaou V, et al. *Acta Derm Venereol* 2009; 89: 292–4. Nine patients with VEN and two with extensive unilateral epidermal nevus were treated with cryosurgery. Ten patients had their nevi treated successfully in two to five sessions, in which two cycles of open spray technique were used, 10–15 seconds each, depending on the size and extent of the nevus. The authors reported that the cosmetic result was excellent, with no scarring.

Second-Line Therapies

- Laser ablation **B**
- Dermabrasion **E**
- Ruby laser **E**
- Erbium:YAG laser **C**

Laser treatment of epidermal nevi: a multicenter retrospective study with long-term follow-up.

Alkhalifah A, Fransen F, Le Duff F, et al. *J Am Acad Dermatol* 2019 Jun 13. pii: S0190-9622(19)30976-4. doi: 10.1016/j.jaad.2019.06.013 [Epub ahead of print].

Patients were treated for different types of EN, mostly with ablative lasers, including 23 VEN, 16 nevi sebaceous, 26 Becker nevi, and 2 ILVEN. The follow-up period was a median of 37 months. Better results, fewer recurrences, and higher patient satisfaction were noted in treatments for VEN than for nevi sebaceous.

Epidermal nevi treated by carbon dioxide laser vaporization: a series of 25 patients.

Paradela S, Del Pozo J, Fernández-Jorge B, et al. *J Dermatol Treat* 2007; 18: 169–74.

A total of 25 patients were treated with the CO₂ laser in the superpulsed mode. Good results were achieved in 92% of patients with soft, flattened nevi but in only 33% of patients with keratotic nevi. The authors concluded that the CO₂ laser in the superpulsed mode is an effective and safe treatment for VEN and provides fewer recurrences than other laser therapies. They noted that the main determining factor for the cosmetic result is thickness of the nevus.

Er:YAG laser treatment of verrucous epidermal nevi.

Park JH, Hwang ES, Kim SN, et al. *Dermatol Surg* 2004; 30: 378–81. Twenty patients with VEN were treated with the erbium:YAG laser. After a single treatment, successful elimination of the VEN was observed in 15 patients. Five patients (25%) showed a relapse within the first year after treatment.

Successful treatment of dark-colored epidermal nevus with ruby laser.

Baba T, Narumi H, Hanada K, et al. *J Dermatol* 1995; 22: 567–70. Five darkly pigmented EN were successfully cleared after one to four treatments with a ruby laser in the normal mode. Two patients subsequently had hypopigmentation at the treatment site.

Third-Line Therapies

• Systemic retinoids	D
• Topical retinoids plus 5-fluorouracil	E
• Photodynamic therapy	E
• Sirolimus	E

A case of verrucous epidermal naevus successfully treated with acitretin. Taskapan O, Dogan B, Baloglu H, et al. Acta Derm Venereol 1998; 78: 475–6.

Report of a case of VEN in a 20-year-old patient who responded to acitretin 75 mg daily. The nevus started to recur 6 weeks after cessation of therapy.

Topical tretinoin and 5-fluorouracil in the treatment of linear verrucous epidermal nevus. Kim JJ, Chang MW, Shwayder T. J Am Acad Dermatol 2000; 43: 129–32.

In a 7-year-old boy with an extensive facial epidermal nevus, there was significant improvement using a combination of topical tretinoin 0.1% cream and 5-fluorouracil.

Verrucous epidermal nevus successfully treated with photodynamic therapy. Sim JH, Kang Y, Kim YC. Eur J Dermatol 2010; 20: 814–5.

A 9-year-old girl presented with asymptomatic linear papillomatous and hyperkeratotic papules on the right thigh. She had no history of previous therapy. Treatment with methyl-aminolevulinate–photodynamic therapy (MAL-PDT) was performed. After four treatments, the lesion almost completely resolved, with mild residual hyperpigmentation. At 3 months' follow-up, cosmetic and clinical response was excellent. At 5 months' follow-up, no recurrence had been observed.

Topical sirolimus therapy for epidermal nevus with features of acanthosis nigricans. Dodds M, Maguiness S. Pediatr Dermatol 2019; 36: 554–5.

A 4-year-old male presented with widespread expanding epidermal nevus with features of acanthosis nigricans. He demonstrated a mosaic mutation in FGFR3, the R248C variant. Despite several treatments, there was progressive growth, fissuring, and bleeding of the affected skin. Topical sirolimus was attempted and found to improve thickness and overall symptoms.

Inflammatory/Dysplastic Epidermal Nevi

First-Line Therapy

• Topical corticosteroids	D

Successful treatment of inflammatory linear verrucous epidermal nevus with tacrolimus and fluocinonide. Mutasim DF. J Cutan Med Surg 2006; 10: 45–7.

Successful treatment of ILVEN with potent topical steroid and tacrolimus ointments.

Nevi that have inflammatory, epidermolytic, acantholytic, or dysplastic features may respond more effectively to medical therapy than to surgical treatment. ILVEN is a relatively rare entity that presents during childhood and can be difficult to treat. Topical corticosteroids are often used as first-line therapy, but the response is variable.

Second-Line Therapies

• Topical calcipotriol/tacalcitol	D
• Topical retinoids	E
• Systemic retinoids	E
• Topical dithranol	E

Topical calcipotriol for the treatment of inflammatory linear verrucous epidermal nevus. Zvulunov A, Grunwald MH, Halvy S. Arch Dermatol 1997; 133: 567–8.

A report on the use of calcipotriol in the treatment of an ILVEN.

Acitretin treatment of a systematized inflammatory linear verrucous epidermal nevus. Renner R, Rytter M, Sticherling M. Acta Derm Venereol 2005; 85: 348–50.

In this case treatment with oral acitretin was initiated at a dose of 25 mg daily but was reduced to 20 mg, with increasing erythema on the face and left leg. The dose was slowly increased to 30 mg daily. After 2 weeks, the erythema had almost entirely resolved, and the hyperkeratosis was distinctly reduced. After 8 weeks, the inflammatory and hyperkeratotic lesions had almost disappeared.

Dithranol in the treatment of inflammatory linear verrucous epidermal nevus. De Mare S, van de Kerkhof PC, Happle R. Acta Derm Venereol 1989; 69: 77–80.

Treatment with dithranol resulted in complete relief from pruritus and clearing of all linear lesions, except for a small verrucous band on the shin.

Third-Line Therapies

• Pulsed-dye laser	E
• CO ₂ laser	E
• Surgical excision	D
• Etanercept	E
• Photodynamic therapy	E
• Crisaborole	E
• Excimer laser	E

Inflammatory linear verrucous epidermal nevus responsive to 308-nm excimer laser treatment. Grgurich E, Gupta N, Owen R, et al. Cutis 2018; 102: 111–4.

The authors report a 20-year-old woman with lesions on the right leg since infancy. After failing treatments, including ablative CO₂ laser, the patient was treated with a UV 308-nm excimer laser and showed noticeable clinical improvement.

Inflammatory linear verrucous epidermal nevus treated successfully with crisaborole ointment in a 5-year-old boy. Barney E, Prose NS, Ramirez M. Pediatr Dermatol 2019; 36(3): 404–5. doi: 10.1111/pde.13793. 2019 Mar 5 [Epub ahead of print].

The authors present a case of ILVEN in a 5-year-old-boy, treated successfully with crisaborole 2% ointment.

Pulsed dye laser for inflammatory linear verrucous epidermal nevus. Sidwell RU, Syed S, Harper JL. Br J Dermatol 2001; 144: 1267–9.

Three cases of ILVEN in children (ages 2–8) were treated successfully with the pulsed-dye laser. The authors surmise that the destruction of capillaries by the laser reduces the release of inflammatory mediators.

Carbon dioxide laser therapy for an inflammatory linear verrucous epidermal nevus: a case report. Ulkur E, Celikoz B, Yuksel F, et al. *Aesthet Plast Surg* 2004; 28: 428–30.

A case of ILVEN was treated with the CO₂ laser. All symptoms, including erythema, excoriation, granulation, and pruritus, disappeared, and a pale pigmentation remained.

Full-thickness surgical excision for the treatment of inflammatory linear verrucous epidermal nevus. Lee BJ, Mancini AJ, Renucci J, et al. *Ann Plast Surg* 2001; 47: 285–92.

The authors report four patients with extensive ILVEN treated successfully with full-thickness surgical excision.

Successful treatment of a widespread inflammatory verrucous epidermal nevus with etanercept. Bogle MA, Sobell JM, Dover JS. *Arch Dermatol* 2006; 142: 401–2.

A 55-year-old woman diagnosed with widespread inflammatory epidermal verrucous nevi was presented. She had a history of multiple therapies, including emollients, topical and intramuscular steroids, and isotretinoin.

Etanercept therapy was initiated at 25 mg biweekly. After 1 month, good improvement in pruritus and erythema was observed. Etanercept was increased to 50 mg biweekly, which provided nearly 50% improvement over 3 months. After a total of 6 months, she achieved almost complete resolution of pruritus and a significant improvement in roughness and erythema. The dose was then reduced to 25 mg biweekly, and disease activity remained quiescent at follow-up.

Inflammatory linear verrucous epidermal nevus successfully treated with methyl-aminolevulinate photodynamic therapy. Parera E, Gallardo F, Toll A, et al. *Dermatol Surg* 2010; 36: 253–6.

Treatment with MAL-PDT was performed for a 67-year-old man with ILVEN who had failed multiple modalities. Almost complete resolution of the lesions after three weekly PDT sessions was observed. No recurrence was observed after follow-up of 15 months.

Epidermodysplasia verruciformis

Helen Lee, Anthony A. Gaspari



Epidermodysplasia verruciformis (EV) is a rare genetic disease characterized by an impaired immune response to human papillomavirus (HPV) and HPV-associated cutaneous oncogenesis. The exact prevalence of EV is unknown; however, about 500 cases have been described worldwide. Because of the rarity of EV, there are few controlled trials of therapeutic interventions. Thus, the treatments described herein are predominantly anecdotal. The therapies applied to EV are usually extensions of treatments for HPV infections and skin cancers in the general population, or treatments successfully used for other immunodeficiency diseases in which HPV infections are prominent.

The disease is manifested by development of widespread flat-wart and pityriasis versicolor-like lesions in early childhood, which persist throughout adulthood. Other lesions may be more verrucous or resemble seborrheic keratoses. In the fourth and fifth decades, 50%–70% of patients begin to develop multiple cutaneous malignancies, mainly squamous cell carcinomas (SCCs).

EV has been associated with increased susceptibility to specific HPV types, primarily involving β -human papillomaviruses (β -HPVs). Most β -HPVs are considered non-pathogenic in the general population and viewed as commensal viruses of the human skin. In EV, however, HPV-5 and HPV-8 genotypes account for up to 90% of EV-associated SCC. Malignant transformation has also been associated with HPV subtypes 17, 20, and 47. Other non-oncogenic HPV types commonly seen in EV include 4, 9, 12, 14, 15, 19, 21–25, 36–38, and 50. EV patients generally are concomitantly infected with more than one genotype. Notably, Merkel cell polyomavirus particles have been recently identified in EV lesions as well. Advancement in HPV typing systems has proven to be beneficial in discerning potentially oncogenic HPV types from non-pathologic types. Such HPV detection methods involving polymerase chain reaction protocols can further assist in confirming the diagnosis of EV when histology is unrevealing.

Inherited EV harbors autosomal recessive mutations of two genes located on chromosome 17: *EVER1/TCM6* and *EVER2/*

TCM8, both coding transmembrane proteins located in the endoplasmic reticulum and involved in zinc transportation. However, about 25% of EV cases are not associated with these genetic mutations. Various case reports presenting novel mutations such as *MST-1*, *RHOH*, *CORO1A*, *DOCK8*, *DCLRE1C*, *RASGRP1*, *ANKRD26*, *IL2RG*, and *TPP2* have emerged. Loss of function gene mutation of *CIB1* (calcium and integrin-binding protein 1), which is an integral part of the *EVER1/EVER2* complex, has gained recent notoriety in its role in atypical EV cases. All associated mutations are thought to result in defective cell-mediated immune response to HPV, ultimately leading to formation of skin lesions.

A more novel entity is the occurrence of the EV phenotype in immunosuppressed individuals, which has been coined *acquired epidermodysplasia verruciformis*. This EV-like syndrome has been described in patients with HIV infection, organ transplantation, Hodgkin disease, common variable immunodeficiency, systemic lupus erythematosus, immunoglobulin M deficiency, adult T-cell leukemia, some cases of graft-versus-host reaction, and others. Although this condition affects a diverse range of immunocompromised patients, AEV is reported less frequently than congenital EV, which may be due to a yet unidentified, higher genetic predisposition to EV infections in affected individuals only. The high risk of malignant transformation in genetic EV seems to be reduced in the acquired variety.

MANAGEMENT STRATEGY

There is no definitive treatment for EV that can produce a complete and sustained clearing of both benign wart-like and keratotic lesions that possess potential for oncogenic transformation. In addition, these EV lesions can be locally destructive when left untreated. Arguably the most vital aspect in the management of EV is protection from ultraviolet radiation, which contributes to carcinogenesis. Ultraviolet light-avoiding behavior and topical sunscreens (sun protection factor >50) are indicated. Other cancer cofactors (radiotherapy, immunosuppressive drugs) must be avoided. Premalignant and troublesome benign lesions can be treated by a variety of destructive techniques: surgical (cryotherapy, shave excision, curettage, laser, full excision, Mohs micrographic surgery) or chemical (trichloroacetic acid, 5-fluorouracil, cidofovir, glycolic acid).

For more widespread lesions with signs of premalignancy or malignancy, agents that modify keratinization are indicated, such as oral or topical retinoids, vitamin D₃ analogs, interferons, and imiquimod. Photodynamic therapy (PDT) can be useful in the treatment of early malignant lesions. Larger malignancies can necessitate skin autografts.

The role of HPV vaccination in EV patients has not been fully elucidated. Recent literature has been divided on the therapeutic benefit of HPV vaccines in immunosuppressed patients. Some cases have reported clinical resolution of cutaneous warts with anecdotal use, while others have shown limited results. There are evolving studies examining the effects of investigational vaccinations such as HPV-16-derived L-2 vaccine, which can generate antibodies that exhibit potential to cross-neutralize other cutaneous genotypes including HPV-5 and HPV-8. The efficacy of such vaccines in preventing cutaneous malignancies has not been fully assessed and ongoing work will be needed to confirm the protective and therapeutic potential of HPV vaccination in EV patients.

Specific Investigations

- Family history and examination of other family members
- Skin biopsy
- HPV typing to identify potentially oncogenic and non-oncogenic HPV types
- Evaluation of immune status and the presence of factors producing or enhancing immunosuppression: HIV, congenital and acquired immunodeficiency syndromes, iatrogenic immunosuppression

Generalized verrucosis: a review of the associated diseases, evaluation, and treatments. Sri JC, Dubina MI, Kao GF, et al. *J Am Acad Dermatol* 2012; 66: 2292–311.

Generalized verrucosis and distinct diseases (including EV) associated with generalized warts are defined. The indications for histopathologic examination, HPV typing, and other laboratory tests, as well as potential treatment options, are discussed.

Acquired epidermodysplasia verruciformis: a comprehensive review and proposal for treatment. Zampetti A, Giurdanella F, Manco S, et al. *Derm Surg* 2013; 39: 974–9.

The treatment of acquired EV is not standardized, and several approaches have been described in the literature. Better results have been reported with combination procedures (e.g., photodynamic therapy and retinoids).

Deleterious effect of radiation therapy on epidermodysplasia verruciformis patients. de Oliveira WR, da Cruz Silva LL, Neto CF, et al. *J Cutan Med Surg* 2015; 19: 416–21.

Radiotherapy might be associated with progression of SCC in EV patients, and it is recommended that this method of treatment be avoided in this patient population.

Re-evaluation of epidermodysplasia verruciformis: reconciling more than 90 years of debate. Przybyszewska J, Zlotogorski A, Ramot Y. *J Am Acad Dermatol* 2017; 76(6): 1161–75.

The different characteristics of seemingly clinically similar disorders are highlighted between EV, acquired EV, and generalized verrucosis.

First-Line Therapies

• Sun avoidance/protection	E
• Cryotherapy with liquid nitrogen	E
• Topical retinoic acid 0.05%–0.1% cream for benign, flat, cosmetically troublesome lesions	E
• Shave excision of flat lesions	E
• Surgical excision of malignant lesions	E

Second-Line Therapies

• Interferon- α with retinoids (acitretin)	E
• Systemic isotretinoin	E
• Imiquimod 5% cream	E
• Topical 15% glycolic acid lotion	C
• Topical squaric acid dibutylester 2% solution (SADBE)	E
• Oral zinc sulfate	E
• Topical 1% cidofovir cream	E

Treatment of epidermodysplasia verruciformis with a combination of acitretin and interferon alfa-2a. Anadolu R, Oskay T, Erdem C, et al. *J Am Acad Dermatol* 2001; 45: 296–9.

A patient treated with oral acitretin 50 mg daily and systemic interferon- α_{2a} 3 million IU was subcutaneously injected three times weekly for 6 months. Improvement was followed by relapse after discontinuation of treatment, and the same regimen was reintroduced. The interferon was eventually discontinued after 4 months and the acitretin was reduced to 25 mg for 3 months, then ultimately stopped. Improvement was maintained during the subsequent 12-month follow-up. Used as monotherapy, interferon- α has minimal benefit and is not recommended.

Systemic low-dose isotretinoin maintains remission status in epidermodysplasia verruciformis. Rallis E, Papatheodorou G, Bimpakis E, et al. *J Eur Acad Dermatol Venereol* 2008; 22: 523–5.

In this case isotretinoin 0.8 mg/kg/day for 6 months produced complete clearance, with relapse 4 months after discontinuation of medication. Maintenance treatment with 20 mg/day resulted in sustained remission. EV in this case was associated with HPV-3 – that is, a more benign variant responsive to therapy.

Treatment of a patient with epidermodysplasia verruciformis carrying novel EVER2 mutation with imiquimod. Berthelot C, Dickerson MC, Rady P, et al. *J Am Acad Dermatol* 2007; 56: 882–6.

An EV patient with homozygous gene mutation of the *EVER2* gene with a 10-year history of flat warts underwent treatment with wide, local excision of large SCC on the chest and topical 5% imiquimod 5 days weekly for 3 months to multiple SCCs on face with significant improvement.

Acquired epidermodysplasia verruciformis syndrome in HIV-infected pediatric patients: prospective treatment trial with topical glycolic acid and human papillomavirus genotype characterization. Moore RL, de Schaezen V, Joseph M, et al. *Arch Dermatol* 2012; 148: 128–30.

Topical 15% glycolic acid lotion had a good effect in HIV-infected children; the therapy was regarded as safe and efficacious.

Epidermodysplasia verruciformis: successful treatment with squaric acid dibutylester. Kehdy J, Erickson C, Rady P, et al. *Cutis* 2015; 96: 114–8.

A case of 25-year history of refractory EV that was successfully treated with topical SADBE contact sensitizer agent. SADBE has been used over the years for the treatment of a variety of skin diseases, including alopecia areata and refractory cutaneous warts.

Efficacy of oral zinc therapy in epidermodysplasia verruciformis with squamous cell carcinoma. Sharma S, Barman KD, Sarkar R, et al. *Ind Derm Online J* 2014; 5: 55–8.

A 24-year-old patient with EV was treated with oral zinc sulfate (550 mg/kg/day) with a satisfactory result (clearance of wart-like lesions on the face and upper and lower extremities by 30%–40%). The squamous cell carcinoma of the right hand was removed surgically.

New human papillomavirus (HPV) types involved in epidermodysplasia verruciformis (EV) in 3 HIV-infected patients: response to topical cidofovir. Darwich E, Darwich L, Klaustermeier J, et al. *J Am Acad Dermatol* 2011; 65(2): e43–5.

Two out of three HIV patients with recalcitrant EV-like lesions were treated with topical 1% cidofovir cream for 4–9 weeks with

resolution. Notably, patients who responded were only carriers of a novel genotype HPV-36 and had the most common HLA-II haplotypes associated with EV.

Third-Line Therapies		
• Photodynamic therapy		E
• CO ₂ laser for malignant and premalignant lesions		E
• Skin autografts		E

Photodynamic therapy for human papillomavirus-related diseases in dermatology. Szeimies RM. Med Laser Appl 2003; 18: 107–16.

Topical PDT using 20% 5-aminolevulinic acid was reported to yield excellent results in a case of EV associated with HPV-5, 8, 36, and other strains. Twelve months after PDT the lesions started to reappear but resolved after repeated treatments. The authors suggest annually repeated PDT is safe and will help control EV lesions.

CO₂ laser treatment of warts in immunosuppressed patients. Lauchli S, Kempf W, Dragieva G, et al. Dermatology 2003; 206: 148–52.

Alternative therapies for recalcitrant HPV-induced cutaneous warts in EV may include CO₂ laser or neodymium laser. Laser therapy of recalcitrant warts proved to be efficacious in both immunosuppressed and immunocompetent individuals.

Skin autografts in epidermodysplasia verruciformis: human papillomavirus-associated cutaneous changes need over 20 years for malignant conversion. Majewski S, Jablonska S. Cancer Res 1997; 57: 4214–6.

For very widespread, constantly developing new lesions not responding to any therapy, the only effective method is removal of the most involved skin area (usually on the forehead) and its replacement with skin from non-exposed inner aspects of the arms.

Epidermolysis bullosa

Tobias Welponer, Johann W. Bauer, Martin Laimer



Epidermolysis bullosa (EB) comprises a group of rare, genetically inherited mechanobullous skin disorders. Underlying mutations impair the structural and functional integrity of the epidermis and dermoepidermal basement membrane zone (BMZ) of skin and mucous membranes. The clinical hallmarks include increased mucocutaneous fragility with trauma-induced blistering, erosions, and scarring (see figure). Based upon the level of blister formation within the BMZ, EB is subclassified into four major types: simplex (intraepidermal), junctional (lamina lucida), dystrophic (dermal), and Kindler EB (mixed). Considerable genetic heterogeneity as well as secondary epigenetic, biochemical, and environmental factors constitute for the wide phenotypical variety of the disease. The index genes involved are also expressed in other epithelialized (gastrointestinal, respiratory, urogenital tract) or mesenchymal (skeletal muscle) organs rendering particularly the more severe EB variants a systemic disease with high morbidity and mortality.

MANAGEMENT STRATEGY

Currently no curative treatment options are available in clinical practice. As such, management of EB primarily consists of avoidance of provoking factors, supportive care, and symptomatic therapies (i.e., skin and wound care; avoidance of wound infection; nutritional support; management of extracutaneous manifestations, itch, and pain). Developing individualized care plans for each patient is crucial due to the high geno- and phenotypical

interpatient variance as well as to address changing individual needs and preferences to increase therapy adherence. Milder variants of EB, like localized simplex or mild dystrophic forms, mostly do not require close monitoring and can be seen once a year. Patients suffering from severe forms of EB (severe dystrophic, junctional, and generalized simplex forms) need close monitoring at least every 3–6 months and require a multidisciplinary approach of care.

Skin care and avoidance of trauma are keys to avoid painful blister formation and erosions.

Avoidance of trauma to healthy skin is a difficult task when dealing with everyday life, especially during infancy and childhood. It is crucial not to limit physiological needs and movement patterns, as this would alter the development of bones, tendons, and muscles, causing a non-physiological posture that needs intensive physical therapy or even surgical interventions.

Cleansing: bathing in pure water can be painful for patients with larger wounds. Adding salt to the bathtub approximates isotonic conditions; reduces bacterial colonization, pain, and body odor as well as skin exudate; and facilitates removal of wound dressings.

Moisturizing: regular skin care with soft and non-sticking emollients containing, for example, dexpanthenol, zinc, or glycerine, as well as taking oil baths, increases skin smoothness and improves structural integrity while reducing vulnerability of the skin.

Dressings: non-adherent, flexible, polyurethane foam pads (e.g., Mepilex Transfer, Mepilex Lite) applied on skin areas prone to pressure and shearing forces (knees, elbows, wrists, feet) establish an artificial barrier that absorbs mechanical stress and simultaneously maintains a moist wound bed supporting the healing process. Based on our clinical experience, these wound dressings can easily be removed and reapplied to intact skin or wounds, without inflicting additional trauma.

Individualized *wound care* is essential to restore the barrier function of the skin and to prevent infections, as well as to reduce pain. Wounds need to be assessed on a daily basis by the caregiver or patient considering localization, course, and characteristics (size, exudate, bacterial colonization, infection, and pain) in order to choose an appropriate wound dressing.

Blisters have to be punctured with a sterile needle to prevent further extension. Wounds are cleansed with non-cytotoxic solutions (e.g., 0.9% saline solutions, 0.1% chlorhexidine, 0.1% polyhexanide). In order to promote healing, *avital tissue* needs to be debrided, preferably using non-physical methods (e.g., hydrogels, calcium alginate, tensid-containing polyurethane foams).

Bacterial colonization as well as *infections* primarily caused by *Staphylococcus* spp., *Streptococcus* spp., or *Pseudomonas aeruginosa* have to be treated with topical antibiotics, antimicrobials, or antiseptics (e.g., 2% fusidic acid, 2% mupirocin, 1% silver sulfadiazine, 2–4% chlorhexidine). Topical antibiotics need to be rotated every 2–6 weeks to prevent resistance. Bathing in antiseptic agents (e.g., 100 mL bleach in a bathtub) is very useful to control critically colonized wounds and microbial burden. If cutaneous infections are unresponsive to topical treatment or signs of systemic infections occur, antibiogram-guided systemic therapy has to be initiated. Granulating wounds without signs of infection can be covered with paraffin- or white petrolatum-impregnated gauzes and dry lesions with hydrogels. Non-stick and non-adherent silicone dressings (e.g., UrgoTul, Adaptic, Mepitel) or foams (e.g., Mepilex) minimize traumatization when removing the dressings.

Tissue-engineered *skin grafts* derived from neonatal foreskin or allogeneic composite cultured skin (e.g., Apligraf, OrCel) can promote wound healing in non-infected wounds unresponsive to conservative therapies and for which malignancy has been ruled out.

Management of *itch and pain* is a very important issue in EB due to their chronic course and huge impact on quality of life. Conservative and supportive as well as psychological, therapeutic options should be fully exploited before implementing a pharmacological analgesic treatment. While classical antihistamines do not work sufficiently in EB, the anti-IL-4R α monoclonal antibody dupilumab anecdotally proved some preliminary efficacy. Likewise, differential diagnoses (e.g., contact dermatitis) and other causes of pain and itch should be determined (and repeated at intervals). Special diligence needs to be attributed to the change of wound dressings as a significant measure in pain reduction. If pharmaceutical treatment is necessary, it should adhere to the ladder approach of the World Health Organization and include topical analgesics, if applicable.

Improving nutritional intake – due to structural issues alongside mucosal involvement within the oro-esophageal-gastrointestinal tract, as well as a chronic hypercatabolic state, there is reduced intake and increased nutrient loss caused by an impaired skin and intestinal barrier, especially in dystrophic and junctional EB. Failure to thrive necessitates intake of high caloric formulas. Nasogastric tubes and gastrostomy may be considered in severe cases. Patients with low levels of micronutrients (e.g., iron, albumin, zinc, calcium, selenium, or vitamin D) suffer from poor wound healing, growth deficit, osteoporosis, or anemia, which might increase the risk of severe cardiomyopathies. Supplementation, especially of iron, albumin, vitamin D, and zinc, prevents, diminishes, or delays complications.

Primary and secondary *extracutaneous involvement* especially occurs in the severe forms of EB. Common complications involve ocular, oral, and dental lesions, as well as esophageal or genitourinary strictures and mitten deformities, which often require surgical treatment.

Patients with junctional (JEB) and recessive dystrophic EB (RDEB) are at high risk for developing aggressive mucocutaneous *squamous cell carcinomas* (SCCs). Suspicious skin areas (chronic, non-healing ulcers with excessive pain and rapid growth; hypergranulating tissue; raised borders; hyperkeratotic areas in a wound) should be biopsied or excised for histological examination. Differentiation of malignant lesions from pseudoepitheliomatous hyperplasia or granulation tissue may sometimes be challenging. In case of proven malignancy, regular controls as well as clinical and radiographic (e.g., CT, PET-CT, MRI) follow-up every 3–6 months are necessary due to the aggressive course of these tumors.

In light of the serious morbidity and mortality of EB, therapeutic options are highly needed. Such strategies include genome editing, as well as gene-, protein- and cell-based therapies, which are currently under development.

Specific Investigations

- Rule out differential diagnoses of EB
- Skin biopsy for immunofluorescence microscopy
- Skin biopsy for transmission electron microscopy
- Whole blood in ethylenediamine tetra-acetic acid (EDTA) for genomic DNA extraction and mutational analysis

Clinical practice guidelines for laboratory diagnosis of epidermolysis bullosa. Has C, Liu L, Bolling MC, et al. Br J Dermatol 2020; 182: 574–592.

In patients presenting with skin fragility and blistering, a traumatic, metabolic, hematologic, infectious, drug-induced, and autoimmune etiology has to be ruled out. If history and clinical features are indicative for EB, a skin biopsy from a newly developed blister and peripheral blood sampling should be taken for immunofluorescence mapping and direct genetic testing (Sanger sequencing,

next-generation sequencing), respectively. Thus irregular protein expression, cleavage level, and pathogenic sequence variants can be identified. Immunofluorescence investigation allows a fast and feasible initial diagnostic work-up. Simultaneously, genetic testing should be performed for full molecular characterization to deliver a final diagnosis (and rationale for approaches of molecular therapy). Although rarely necessary, transmission electron microscopy might be helpful in select cases to identify skin cleavage level and ultrastructural anomalies to confirm or refine results obtained from immunofluorescence mapping.

First-Line Therapies

• Wound care and management of extracutaneous manifestations	B
• Treatment of SCC	D
• Management of pain and pruritus	B
• Meeting nutritional requirements	B
• Psychosocial support	B
• Occupational therapy	B

A consensus approach to wound care in epidermolysis bullosa. Pope E, Lara-Corrales I, Mellerio J, et al. J Am Acad Dermatol 2012; 67: 904–17.

Skin and wound care is the backbone of treatment of EB patients. This consensus recommendation guideline for wound care is based on the best evidence available established by EB experts. It takes into account EB (sub-) type, wound localization, and characteristics, as well as patient age, nutritional status, hemoglobin levels, limitations of daily activities, pain, and itch to establish an individualized treatment plan for each patient to improve wound healing and prevent complications like antibiotic resistance by, for example, rotating topical antibiotics. Providing education and support to patients, parents, and treatment circles is obligatory to increase adherence to treatment.

Management of cutaneous squamous cell carcinoma in patients with epidermolysis bullosa: best clinical practice guidelines. Mellerio JE, Robertson SJ, Bernardis C, et al. Br J Dermatol 2016; 174: 56–67.

Severe EB types, especially JEB and RDEB, are associated with the development of aggressive mucocutaneous SCCs, which constitute significant morbidity and mortality and may arise early even in premature patients. These tumors develop at sites of chronic skin blistering, wounds, and scars, which makes clinical detection challenging. Given the low number of patients, no prospective clinical trials are available comparing treatment options. Wide local excision is currently the treatment of choice. Adjuvant or neoadjuvant radio- and/or chemotherapy might be useful for unresectable tumors or at a metastatic stage. Case reports on epidermal growth factor receptor antagonists, PD-1 inhibitors, and tyrosine kinase inhibitors show some favorable results in metastatic disease. Due to the aggressive course of these SCCs, efforts should be directed toward palliative care when tumor progress is inevitable.

Pain care for patients with epidermolysis bullosa: best care practice guidelines. Goldschneider KR, Good J, Harrop E, et al. BMC Med 2014; 12: 178.

Management of pain and pruritus is of special importance in EB as it poses major limitations on quality of life. This guideline grades recommendations regarding safety and harm, health benefit to patient, burden of adherence, and cost-effectiveness, as well as impact on morbidity, mortality, or quality of life. Differentiating acute and chronic pain, as well as pain characteristics,

localization, and origin impact therapeutic decisions. Pain management comprises treatment of the underlying cause, cognitive behavioral therapy, and environmental comfort measures, supportive measures, and pharmacologic therapy taking into account complications of chronic intake. The guideline also attributes special topics and offers recommendations for infants and end-of-life pain care. Management of itch consists in environmental and behavioral interventions, antihistamines, centrally acting medications, and antidepressants.

Nutritional aspects of children and adolescents with epidermolysis bullosa: literature review. Zidorio AP, Dutra ES, Leao DO, et al. *An Bras Dermatol* 2015; 90: 217–23.

Gastrointestinal problems in EB lead to severe nutritional deficits, among which esophageal stenosis hinders swallowing and thus further aggravates nutrient deficits without appropriate intervention. A dietary plan for EB patients takes into consideration evaluation of interfering factors regarding food intake and absorption, biochemical assessment, EB-intrinsic hypercatabolic state, and assessment of nutritional intake compared to healthy individuals. To meet energy requirements for EB patients it is proposed to approach 100%–150% of the estimated energy requirement of sex-, age-, and height-matched healthy individuals.

Natural history of growth and anaemia in children with epidermolysis bullosa: a retrospective cohort study. Reimer A, Hess M, Schwieger-Briel A, et al. *Br J Dermatol* 2019.

This paper demonstrates that nutritional compromise with growth failure and anemia occurs early in RDEB and may therefore require interventions as of the first year or two of life.

Psychosocial recommendations for the care of children and adults with epidermolysis bullosa and their family: evidence based guidelines. Martin K, Geuens S, Asche JK, et al. *Orphanet J Rare Dis* 2019; 14: 133.

The manifold and often severe complications of EB have a big impact on psychosocial life. People and families living with EB need psychological guidance with the aim to improve quality of life and psychosocial wellbeing and to help them cope with the condition. Pain and physical limitations have a big impact on mental health and therefore should be prioritized in the clinical treatment. Psychosocial techniques can support and extend guideline-adherent pain management.

Occupational therapy for epidermolysis bullosa: clinical practice guidelines. Chan JM, Weisman A, King A, et al. *Orphanet J Rare Dis* 2019; 14: 129.

Chronic wounding and inflammation in EB patients induce sustained tissue-remodeling and contractures, which limit activities of daily living. Occupational therapy supports patients to maximize their functional abilities and improve quality of life.

Second-Line Therapies

- Downregulation of IL-1 β in generalized severe epidermolysis bullosa simplex **C**
- Inhibition of phosphodiesterase-4 in generalized severe epidermolysis bullosa simplex **E**
- Induced premature termination codon read-through **C**
- Dapsone as antiinflammatory agent in EB simplex **E**

Diacerein orphan drug development for epidermolysis bullosa simplex: a phase 2/3 randomized, placebo-controlled, double-blind clinical trial. Wally V, Hovnanian A, Ly J, et al. *J Am Acad Dermatol* 2018; 78: 892–901. e897.

Targeting trauma-induced inflammatory pathways, 17 patients suffering from generalized EB simplex who were treated with topical diacerein, an IL-1 β inhibitor, for 6 weeks showed a significant reduction of blisters by more than 70% without any adverse events in the treatment arm.

Epidermolysis bullosa simplex generalized severe induces a T helper 17 response and is improved by apremilast treatment. Castela E, Tulic MK, Rozieres A, et al. *Br J Dermatol* 2019; 180: 357–64.

Treatment with the phosphodiesterase-4 inhibitor apremilast approved for the treatment of psoriasis resulted in an improvement of skin blistering and good tolerance in three adult patients with generalized EB simplex.

Successful dapsone therapy in inherited epidermolysis bullosa. Gibson M, Rogers CL, Murrell DF. *J Eur Acad Dermatol Venereol* 2020; doi: 10.1111/jdv.16301.

One patient with generalized EB simplex receiving 100 mg dapsone daily showed a rapid reduction in number and size of blisters. A second patient with intermediate JEB and end-stage kidney disease received 25 mg dapsone up to three times weekly. After 10 months of treatment, his Quality of Life in EB score and the activity score in the EB Disease Activity and Scarring Index (EBDASI) improved, while the damage score in the EBDASI remained unaffected.

Gentamicin induces functional type VII collagen in recessive dystrophic epidermolysis bullosa patients. Woodley DT, Cogan J, Hou Y, et al. *J Clin Invest* 2017; 127: 3028–38.

Five RDEB patients harboring nonsense mutations received topical gentamicin 0.1% ointment or placebo three times daily for 2 weeks and intradermal injections with 8 mg of gentamicin or placebo for 2 days. Gentamicin treatment restored type VII collagen as well as anchoring fibrils and was associated with a trend toward improved wound closure and a reduction in blister formation.

Third-Line Therapies

- Granulocyte colony-stimulating factor **C**
- Gene replacement **E**
- Transplantation of revertant mosaic skin **E**
- Bone marrow transplantation **C**
- Injection of wild-type allogeneic fibroblasts **C**
- Injections of autologous, gene-corrected fibroblasts **C**
- Allogeneic mesenchymal stromal cell therapy **D**

Overview of the management of epidermolysis bullosa. Murrell DF. 2020; UpToDate; <https://www.uptodate.com> (Accessed 2020 June 6).

Different molecular therapy approaches for EB are currently under investigation involving gene replacement via cDNA delivery, revertant mosaicism, bone marrow transplantation, injection of wild-type allogeneic or autologous gene-corrected fibroblasts, allogeneic mesenchymal stromal cell therapy, and systemic granulocyte colony-stimulating factors. All of the named therapies are at an experimental stage and require further evaluation regarding feasibility, clinical safety, and effectiveness. Moderate overall formal quality of clinical evidence reflects significant methodological limitations to research in rare disease populations.

Epidermolysis bullosa acquisita

Lawrence S. Chan



Courtesy Iris Aronson

Epidermolysis bullosa acquisita (EBA) is an uncommon, chronic, autoimmune blistering disease affecting the skin and mucous membranes. The disorder affects patients of any age, and the skin lesions occur commonly at trauma-prone skin areas (in the non-inflammatory mechanobullous scarring subset) or widespread skin areas (in the generalized inflammatory non-scarring subset). Although IgG (or rarely IgA or IgM) class autoantibodies targeting the skin basement membrane component type VII collagen (anchoring fibrils) are major contributing factors, minor physical trauma also plays an important role in the blister development.

MANAGEMENT STRATEGY

EBA, particularly the non-inflammatory mechanobullous subset, is characteristically very refractory to conventional medical therapies. For an immune-mediated blistering disease associated with autoantibodies that target skin components, the obviously logical approach is to suppress the immune responses, thereby reducing the production and effect of the autoantibodies to their target skin component type VII collagen. Unfortunately, currently there is no target-specific medication available. Thus the presently available non-target-specific immunosuppressive medications not only suppress the immune responses against type VII collagen but also reduce the patient's immune defense to pathogens, leading to a relative immunodeficiency. Therefore, when treating patients with this disease, every effort should be made to use antiinflammatory instead of immunosuppressant agents, to use the lowest possible doses of immunosuppressant for the shortest time frame, and to replace immunosuppressant with antiinflammatory medications whenever feasible. Because of its rarity, well-controlled clinical trials have not been performed for EBA. The therapeutic guidelines in this chapter are derived mainly

from case reports of small groups or single patients. A commonly used start-up regimen consists of a *systemic corticosteroid combined with either mycophenolate mofetil or dapsone or both* as a corticosteroid-sparing agent. For adult patients without major medical problems, a combination of oral prednisone (1 mg/kg daily), mycophenolate mofetil (1–2 g daily), and dapsone (100–200 mg daily) can be initiated.

Other medications also reported to be beneficial for EBA are *colchicine* (1–2 mg daily); *ciclosporin* (5–9 mg/kg daily); *intravenous immunoglobulin (IVIG)* treatment (400 mg/kg daily); and *extracorporeal photochemotherapy*. Most recently, a monoclonal antibody against B-cell-specific target CD20, *rituximab* (usual dose 375 mg/m² body surface area, multiple doses), has been reported to be effective in several cases.

In addition, patients with EBA should *avoid physical trauma* as much as possible. Patients should be informed to *care for open wounds promptly* and to recognize local skin infection and *seek medical attention when infection occurs*.

Specific Investigations

- Skin biopsy and serum for direct and indirect immunofluorescence, respectively, to detect in vivo bound and circulating IgG (or IgA, IgM) class skin basement membrane-specific autoantibodies
- Transmission immune-EM, FOAM analysis, or serration pattern analysis
- Serum for enzyme-linked immunosorbent assay (ELISA) to detect IgG (or IgA, IgM) class type VII collagen-specific autoantibodies
- Gastrointestinal workup for possible inflammatory bowel disease

Epidermolysis bullosa acquisita: ultrastructural and immunologic studies. Yaoita H, Briggaman RA, Lawley TJ, et al. *J Invest Dermatol* 1981; 76: 288–92.

Identification of the skin basement-membrane autoantigen in epidermolysis bullosa acquisita. Woodley DT, Briggaman RA, O'Keefe EJ, et al. *N Engl J Med* 1984; 310: 1007–13.

Direct immunofluorescence typically detects linear IgG deposits at the dermoepidermal junction in all patients. Indirect immunofluorescence detects IgG circulating autoantibodies bound to the dermal side of salt-separated normal skin substrate in approximately 50% of patients.

Development of an ELISA for rapid detection of antitype VII collagen autoantibodies in epidermolysis bullosa acquisita. Chen M, Chan LS, Cai X, et al. *J Invest Dermatol* 1997; 108: 68–72.

ELISA using recombinant protein of the non-collagenous (NC1) domain of human type VII collagen is the most sensitive and specific method for detecting IgG class circulating autoantibodies in patients.

Consensus on EBA diagnostic criteria International Bullous Diseases Group – Consensus on Diagnostic Criteria for Epidermolysis Bullosa Acquisita. Prost-Squarcioni C, Caux F, Schmidt E, et al. *Br J Dermatol* 2018; 179(1): 30–41. doi: 10.1111/bjd.16138 [Epub 2018 May 8].

In case circulating autoantibodies are not detected by indirect immunofluorescence (IIF) or ELISA methods, special techniques including transmission immune-EM, fluorescent overlay antigen

mapping, or serration pattern analysis of direct IF are helpful in delineating the location of autoantibody target.

IgA-mediated epidermolysis bullosa acquisita: two cases and review of the literature. Vodegel RM, de Jong MC, Pas HH, et al. *J Am Acad Dermatol* 2002; 47: 919–25.

In rare incidences, IgA class rather than IgG class autoantibodies were found to target the type VII collagen, resulting in a clinical phenotype indistinguishable from the classic IgG-mediated disease. IgA-mediated disease, however, is less likely to form scars and is more responsive to dapsone treatment.

IgM-type epidermolysis bullosa acquisita. Omeland SH, Gniadecki R. *Br J Dermatol* 2015; 173: 1566–8.

This is a very rare case where the targeting autoantibodies appear to be the IgM class.

Epidermolysis bullosa acquisita and inflammatory bowel disease. Raab B, Fretzin DE, Bronson DM, et al. *JAMA* 1983; 250: 1746–8.

Inflammatory bowel disease, particularly Crohn disease, is strongly associated with EBA. All patients should be questioned for symptoms of inflammatory bowel disease. If symptoms are present, a comprehensive gastrointestinal workup is indicated.

The epidermolysis bullosa acquisita antigen (type VII collagen) is present in human colon and patients with Crohn's disease have autoantibodies to type VII collagen. Chen M, O'Toole EA, Sanghavi J, et al. *J Invest Dermatol* 2002; 118: 1059–64.

The presence of type VII collagen in the gut and autoantibodies to type VII collagen in patients with inflammatory bowel disease without skin manifestations supports an inflammation link between the gut and the skin.

Black patients of African descent and HLA-DRB1*15:03 frequency overrepresented in epidermolysis bullosa acquisita. Zumelzu C, Le Roux-Villet C, Loiseau P, et al. *J Invest Dermatol* 2011; 131: 2386–93.

A higher percentage of patients affected by EBA are Black patients of African descent and that the human leukocyte antigen HLA-DRB1*15:03 allele may contribute to this disease development.

Congenital epidermolysis bullosa acquisita: vertical transfer of maternal autoantibody from mother to infant. Abrams ML, Smidt A, Benjamin L, et al. *Arch Dermatol* 2011; 147: 337–41.

Although EBA rarely occurs in children, it has never been reported in an infant until 2011. This infant case should raise the awareness of maternally transferred EBA by physicians when they encounter blistering disease in a neonate.

Physicians need to recognize the possibility of maternal transfer of autoantibodies and the transient nature of the blisters (with no need for systemic treatment). This case of passive transfer of disease further demonstrates the pathogenic role of the autoantibodies, as was illustrated in a passive transfer animal model of EBA.

In utero development of epidermolysis bullosa acquisita. Dewan AK, Braue J, Danford B, et al. *Pediatr Dermatol* 2019; 36: e46–7.

This is the first reported case of in utero development of an active EBA. Physicians should consider infant-onset EBA in their differential diagnoses of neonatal blistering diseases.

First-Line Therapies

• Systemic corticosteroids	D
• Mycophenolate mofetil	E
• Dapsone	D

Epidermolysis bullosa acquisita – a pemphigoid-like disease. Gammon WR, Briggaman RA, Woodley DT, et al. *J Am Acad Dermatol* 1984; 11: 820–32.

Five patients with the generalized inflammatory subset of disease responded at least partially to prednisone (40–120 mg daily), with or without the addition of immunosuppressive azathioprine 100 mg daily.

Epidermolysis bullosa acquisita. Prost-Squarcioni C, Caux F. In: Murrell DF, ed. *Blistering Diseases: Clinical Features, Pathogenesis, Treatment*. Berlin: Springer-Verlag, 2015; 405–412.

The use of systemic glucocorticosteroids (GCDs) is controversial in EBA.

Childhood IgA-mediated epidermolysis bullosa acquisita responding to mycophenolate mofetil as a corticosteroid-sparing agent. Tran MM, Anhalt GJ, Barrett T, et al. *J Am Acad Dermatol* 2006; 54: 734–6.

Mycophenolate mofetil (700 mg/day) was added to the regimen of prednisolone (25 mg/day) and dapsone (25 mg/day) when the disease flared upon reduction of prednisolone dose in this 2-year-old patient affected by an IgA-mediated EBA. With the addition of mycophenolate mofetil, the systemic corticosteroid was totally tapered off over a 9-month period.

Mycophenolate mofetil in epidermolysis bullosa acquisita. Kowalick L, Suckow S, Zuiegler H, et al. *Dermatology* 2003; 207: 332–4.

Mycophenolate mofetil (1 g twice daily) was used successfully in conjunction with plasmapheresis as a corticosteroid-sparing agent in one patient with EBA not controlled by azathioprine (150 mg daily) and prednisolone (60 mg daily). The clinical improvement was associated with a reduction in autoantibody titers.

Bullous pemphigoid and epidermolysis bullosa acquisita: presentation, prognosis, and immunotherapy in 11 children. Edwards S, Wakelin SH, Wojnarowska F, et al. *Pediatr Dermatol* 1998; 15: 184–90.

A survey of five childhood-onset cases showed good clinical responses to combined corticosteroids and dapsone, as well as a good long-term prognosis.

Epidermolysis bullosa acquisita responsive to dapsone therapy. Hughes AP, Callen JP. *J Cutan Med Surg* 2001; 5: 397–9.

One patient who failed to respond to prednisone (40 mg daily) plus tetracycline and niacinamide achieved complete control of blistering activities after 2 months on dapsone 150 mg daily.

Second-Line Therapies

• Intravenous immunoglobulin	D
• Rituximab	D

Successful adjuvant treatment of recalcitrant epidermolysis bullosa acquisita with anti-CD20 antibody rituximab. Schmidt E, Benoit S, Brocker E-B, et al. *Arch Dermatol* 2006; 142: 147–50.

The patient, who had both skin and oral mucosal involvement, was not controlled with prednisolone (up to 250 mg/day), dapsone (150 mg/day), and subsequently azathioprine (up to 175 mg/day) and colchicine (2.5 mg/day). The regimen was changed to rituximab weekly infusions (375 mg/m² body surface area) for 4 consecutive weeks, with continuous use of azathioprine (175 mg/day) and colchicine (2.5 mg/day) and reducing doses of prednisolone. The patient's lesions completely healed in 11 weeks post-rituximab infusion, allowing the tapering of systemic steroid, colchicine, and azathioprine. Fourteen weeks after the discontinuation of colchicine and prednisolone, the patient remained in clinical remission. No complication was reported except an event of deep vein thrombosis.

A successful therapeutic trial of rituximab in the treatment of a patient with recalcitrant, high-titer epidermolysis bullosa acquisita. Crichlow SM, Mortimer NJ, Harman KE. *Br J Dermatol* 2006; 156: 194–6.

A patient with both oral mucosal and skin lesions and a high titer of IgG autoantibodies to skin basement membrane zone (titer up to 1:3200) was treated with conventional therapeutic agents (prednisolone up to 60 mg/day, mycophenolate mofetil 2 g/day, and subsequently IVIG infusions (2 g/kg body weight/month)) without much success. Moreover, the patient could not tolerate azathioprine (due to liver toxicity) or ciclosporin (due to nephrotoxicity and hypertension). In the meantime, the patient's conditions were worsening, with an increasing autoantibody titer and involvement of the esophagus. Therefore, weekly rituximab infusions (375 mg/m² body surface area) were then given to the patient along with mycophenolate mofetil (2 g/day) and prednisolone (30 mg/day). The patient had slow but progressive improvement of the lesions, and all were healed 5 months after starting rituximab. One year after the rituximab treatment the patient was still in partial remission, suffering only occasional trauma-induced blisters, and the autoantibody titer fell to 1:10.

Epidermolysis bullosa acquisita following bullous pemphigoid, successfully treated with anti-CD20 monoclonal antibody rituximab. Wallet-Faber N, Franck N, Matteux F, et al. *Dermatology* 2007; 215: 252–5.

An interesting patient who initially developed bullous pemphigoid but who upon subsequent flare manifested a generalized skin and mucosal (oral and genital) blistering disease that was confirmed as EBA by target antigen identification. The initial success of treatment (combined prednisone 1.5 mg/kg/day and azathioprine 100 mg/day) did not last, as the reduction of prednisone resulted in rapid worsening of the condition, further complicated by a life-threatening *Legionella pneumophila* infection. Furthermore, the patient could not tolerate mycophenolate mofetil. Therefore, rituximab (375 mg/m² body surface area) was initiated on a weekly interval for 4 consecutive weeks, resulting in dramatic improvement of the patient's condition. At 10 months' follow-up post-rituximab initiation the patient had only a few visible blisters.

Treatment-resistant classical epidermolysis bullosa acquisita responding to rituximab. Sadler E, Schafleitner B, Lanschuetzer C, et al. *Br J Dermatol* 2007; 157: 417–9.

A patient with both skin and multiple mucosal (oral, esophageal, and laryngeal) lesions who failed to respond to multiple conventional immunosuppressive medications subsequently responded to rituximab. Over a 6-year period the patient failed to show complete clinical response to methylprednisolone (up to 5 mg/kg/day), azathioprine (up to 2.5 mg/kg body weight),

ciclosporin (up to 9 mg/kg/day), mycophenolate mofetil (up to 30 mg/kg/day), cyclophosphamide (500 mg/m² body surface area IV, followed by 1 mg/kg/day orally), colchicine (up to 1.5 mg/day), IVIG (up to 2.5 g/kg body weight/cycle), gold (1 mg/kg/week IV, followed by IM and oral preparations), and daclizumab (1 mg/kg body weight, six infusions over 3 weeks). Therefore, a regimen of a reduced dose of rituximab (144 mg/m² infusion per week for 5 weeks) along with azathioprine (2 mg/kg/day) was given; the patient tolerated the treatment without any side effects or infections. A remarkable improvement was noticed 4 weeks after the initiation of rituximab treatment, and all medications were subsequently discontinued. Two years after all medications were tapered, the patient's disease activity remained very low.

Clinical response of severe mechanobullous epidermolysis bullosa acquisita to combined treatment with immunoadsorption and rituximab (anti-CD20 monoclonal antibodies). Niedermeier A, Eming R, Pfitze M, et al. *Arch Dermatol* 2007; 143: 192–8.

Two patients affected by the mechanobullous type of EBA were treated with combined immunoadsorption (daily treatment for 8 consecutive days) and rituximab (375 mg/m² body surface area/week for a total of 4 weeks). Mycophenolate mofetil (1–3 g/day) continued during this period. In both patients, treatment with multiple medications, including ciclosporin, azathioprine, dapsone, dexamethasone pulse, and cyclophosphamide pulse, was unsuccessful. One patient achieved near-complete clinical resolution, but the other could only obtain stable disease status. This report illustrates the treatment-resistant nature of EBA.

Severe, refractory epidermolysis bullosa acquisita complicated by an oesophageal stricture responding to intravenous immune globulin. Harman KE, Whittam LR, Wakelin SH, et al. *Br J Dermatol* 1998; 139: 1126–7.

The patient had the non-inflammatory mechanobullous subset of disease and esophageal stricture and was refractory to prednisone (up to 80 mg daily), dapsone (100 mg daily), cyclophosphamide (150 mg daily), and azathioprine (3 mg/kg daily). The patient was treated with courses of IVIG (0.4 g/kg daily) on 5 consecutive days at 4- to 6-week intervals as a monotherapy, resulting in a dramatic fall in the circulating titers of antibasement membrane IgG autoantibodies, reduction of new blister formation, and disappearance of dysphagia. Not all patients reported in the literature responded to this treatment. The major disadvantage of this regimen is the high cost.

Treatment of epidermolysis bullosa acquisita with intravenous immunoglobulin in patients non-responsive to conventional therapy: clinical outcome and post-treatment long-term follow-up. Ahmed AR, Gürkan HM. *J Eur Acad Dermatol Venereol* 2012; 26: 1074–83.

In this report the authors examined 10 EBA patients (mean age 57.4 years), who received 16–31 cycles (2 g/kg/cycle) of IVIG (mean 23.1 cycles) for 30–52 months (mean 38.8 months), with all other medications tapered off in 5–9 months (mean 7.2 months) and IVIG as monotherapy thereafter. All treated patients had satisfactory improvement. At the time of follow-up, occurring 29–123 months posttreatment (mean 53.9 months), they revealed no disease recurrence. No serious side effects were noted.

Meta-analysis of the clinical and immunopathological characteristics and treatment outcomes in epidermolysis bullosa acquisita. Iwata H, Vorobyev A, Koga H, et al. *Orphanet J Rare Dis* 2018; 13: 153.

In this 2018 meta-analysis on 1159 cases of EBA, the study researchers concluded that EBA is a difficult disease to treat and that IVIG and rituximab are the only two medications associated with complete remission by Chi-square analysis.

Epidermolysis bullosa acquisita: the 2019 update. Koga H, Prost-Squarcioni C, Iwata H, et al. *Front Med (Lausanne)* 2019; 5: 362.

In this 2019 update, the authors concluded that IVIG and rituximab are the two most promising therapeutics currently available.

Third-Line Therapies	
• Colchicine	D
• Ciclosporin	D
• Minocycline	E

Colchicine for epidermolysis bullosa acquisita. Cunningham BB, Kirchmann TT, Woodley DT. *J Am Acad Dermatol* 1996; 34: 781–4.

Four patients with the non-inflammatory mechanobullous subset of disease, some refractory to prednisone treatment, were treated with oral colchicine (1–2 mg daily), with or without additional cyclophosphamide (50 mg daily). In all patients there was substantial clinical improvement in the reduction of skin fragility and spontaneous blister formation. An initial dose of 0.4–0.6 mg

daily is recommended, with an increase by 0.6 mg daily each week until diarrhea develops. The patients are instructed to take the highest tolerable doses. Other than diarrhea, the long-term administration of colchicine (up to 4 years) was well tolerated. However, the side effect of diarrhea makes it difficult for those patients who already have associated inflammatory bowel disease.

Oral cyclosporine in the treatment of inflammatory and noninflammatory cases. A clinical and immunopathologic analysis. Gupta AK, Ellis CN, Nickoloff BJ, et al. *Arch Dermatol* 1990; 126: 339–50.

Two patients with EBA (subset not defined) were treated with oral ciclosporin (6 mg/kg daily) for a total of 8 weeks. These patients experienced a gradual reduction in the frequency of new blister and erosion formation. The known renal toxicity of ciclosporin makes it an unsuitable long-term regimen.

Inflammatory epidermolysis bullosa acquisita effectively treated with minocycline. Kawase K, Oshitani Y, Mizutani Y, et al. *Acta Derm Venereol* 2014; 94: 615–6.

In this report, a patient with generalized inflammatory subtype of the disease was effectively controlled with an antibiotic with antiinflammatory function.

Erosive pustular dermatosis

Bhavnit K. Bhatia, Jenny E. Murase



Erosive pustular dermatosis (EPD) is a rare condition characterized by pustular, erosive, and crusted lesions in areas of alopecia that tend to be atrophic, actinically damaged, or subject to local iatrogenic or external trauma. The condition primarily affects the elderly and is located on the scalp but has also been documented to occur on the legs. EPD lesions tend to be chronic, progressive, and difficult to treat. Laboratory and histopathologic findings are not diagnostic.

MANAGEMENT STRATEGY

Traditionally, *potent topical corticosteroids* have been used in EPD with a generally positive but variable response within a few months of use. Due to steroid-related cutaneous atrophy and residual scarring, *tacrolimus 0.1% ointment*, *calcipotriol cream*, *oral and topical zinc*, *topical dapsone*, and *photodynamic therapy* (PDT) have been introduced as alternative therapies. *Retinoids and oral corticosteroids* have also shown some promise when used in conjunction with topical antibiotics, topical corticosteroids, topical tacrolimus, oral dapsone, and oral zinc therapy. Individual case reports exist for other *immunosuppressants*, *silicone gel*, and *fractional 2940-nm laser*. Topical and systemic antibiotics and antifungals are essentially ineffective.

First-Line Therapy

- High-potency topical corticosteroids

D

Erosive pustular dermatosis of the scalp: clinical, trichoscopic, and histopathologic features of 20 cases. Starace M, Loi C, Bruni F, et al. *J Am Acad Dermatol* 2017; 76(6): 1109–14.

Fourteen of 17 patients responded to clobetasol 0.05% ointment. Two responded to prednisone 25 mg daily tapered over 20 days. All three patients treated with topical tacrolimus responded. Mean duration of treatment before clinical efficacy was 5 months.

Erosive pustular dermatosis of the scalp. Pye RJ, Peachey RD, Burton JL. *Br J Dermatol* 1979; 100: 559–66.

Six cases are presented in the first description of erosive pustular dermatosis of the scalp (EPDS) in the literature. Five of the six cases resolved after potent topical steroids, often used with neomycin or nystatin.

Second-Line Therapies

• Photodynamic therapy	D
• Topical 25% powdered zinc oxide	D
• Topical 5% dapsone gel	E
• Topical 0.1% tacrolimus ointment	E

Aminolevulinic acid photodynamic therapy in the treatment of erosive pustular dermatosis of the scalp: a case series. Yang CS, Kuhn H, Cohen LM, et al. *JAMA Dermatol* 2016; 152: 694–7.

Eight patients with EPDS underwent curettage followed by aminolevulinic acid photodynamic therapy 1–2 weeks later, with complete resolution of lesions in six patients. The remaining two patients had complete resolution after a second cycle of curettage and PDT.

Although this case series shows good results after PDT, the literature also notes that PDT is a risk factor for developing EPD.

Topical zinc oxide: an effective treatment option for erosive pustular dermatosis of the leg. Di Altobrando A, Patrizi A, Vara G, et al. *Br J Dermatol* 2020; 182(2): 495–7.

In 51 patients with leg EPD, 23 patients were treated with topical corticosteroids alone, compared with 28 patients treated with topical corticosteroids for 10 days and transitioned to 25% powdered zinc oxide. Treatment was successful in all patients; however, 10/23 patients in the corticosteroid-only group relapsed, compared with 4/28 in the latter group.

Erosive pustular dermatosis of the scalp: a review with a focus on dapsone therapy. Broussard KC, Berger TG, Rosenblum M, et al. *J Am Acad Dermatol* 2012; 66: 680–6.

Four patients with recalcitrant EPD responded to topical 5% dapsone in an average of 3 months after previously failing topical, intralesional, and oral steroids, antibiotics, silver sulfadiazine cream, topical tacrolimus, salicylic acid, and ultraviolet phototherapy.

Erosive pustular dermatosis of the scalp: treatment with topical tacrolimus. Laffitte E, Kaya G, Piguet V, et al. *Arch Dermatol* 2003; 139: 712–4.

In two patients, topical 0.1% tacrolimus ointment resulted in marked improvement within 2 weeks, with complete resolution and recovery of skin atrophy within 6–8 months.

Multiple case reports exist for topical tacrolimus ointment in the literature. The majority are as monotherapy, few as maintenance therapy after successful short-term treatment with topical steroids, and rare reports in conjunction with oral steroids.

Third-Line Therapies

• Oral dapsone	E
• Oral steroids	E
• Oral zinc	E
• Oral retinoids	E
• Oral tofacitinib	E
• Oral ciclosporin	E
• Topical silicone gel	E
• Topical calcipotriol cream	E
• Fractional 2940-nm laser	E

Disseminated erosive pustular dermatosis also involving the mucosa: successful treatment with oral dapsone. Feramisco JD, George T, Schulz SE, et al. *Acta Derm Venereol* 2012; 92: 91–2.

A patient presented after failing antifungal creams, antiseptic solutions, oral antibiotics, glucocorticoids, oral zinc replacement, and oral fluconazole. Significant improvement was observed in a few days and complete pustule resolution in 6 weeks on oral dapsone 50 mg three times daily with vitamin C 1000 mg daily.

Erosive pustular dermatosis of the scalp successfully treated with oral prednisone and topical tacrolimus. Zahdi MR, Seidel GB, Soares VC, et al. *An Bras Dermatol* 2013; 88: 796–8.

The patient initially experienced significant improvement with prednisone 40 mg daily; however, they had increased purulent discharge when it was tapered. When prednisone was restarted with 0.1% topical tacrolimus, lesions healed completely after 10 weeks, and prednisone was successfully tapered.

Cases for successful treatment with oral steroids are often in combination with oral zinc, topical steroids, or topical tacrolimus.

Erosive pustular dermatosis of the scalp successfully treated with oral zinc sulfate. Ikeda M, Arata J, Isaka H. *Br J Dermatol* 1982; 106: 742–3.

A patient's pustules disappeared after 90 mg zinc sulfate daily for 5 days. The dose was increased to 180 mg daily thereafter, and the patient remained pustule free.

The majority of cases for oral zinc report success when used in combination with topical or oral steroids.

Erosive pustular dermatosis of the scalp responding to acitretin. Darwich E, Muñoz-Santos C, Mascaró JM Jr. *Arch Dermatol* 2011; 147: 252–3.

After failing minocycline, betamethasone 17-valerate, and fusidic acid cream, a patient was started on acitretin 50 mg daily and topical 0.1% tacrolimus ointment. Tacrolimus was discontinued after 10 days due to burning. The lesions healed completely after 3 months.

Oral tofacitinib treatment of erosive pustular dermatosis of the scalp. Leung N, Eldik H, Ramirez MR, et al. *JAMA Dermatol* 2019; 155(6): 752–4.

A patient with poorly controlled rheumatoid arthritis experienced significant improvement after 4 weeks of oral tofacitinib 5 mg twice daily. She had previous limited response to clobetasol, topical tacrolimus, mupirocin, and intralesional Kenalog.

Familial erosive pustular dermatosis of the scalp and legs successfully treated with ciclosporin. Di Lernia V, Ricci C. *Clin Exp Dermatol* 2016; 41(3): 334–5.

Combination ciclosporin 3 mg/kg/day and topical clobetasol resulted in rapid improvement of scalp EPD. Ciclosporin had to be discontinued due to adverse effects, and relapses on the scalp and leg were controlled with clobetasol.

Erosive pustular dermatosis successfully treated with a novel silicone gel. Uva L, Aphale AN, Kehdy J, Benedetto AV. *Int J Dermatol* 2016; 55(1): 89–91.

An elderly male underwent extensive debridement of EPD lesions and Mohs micrographic surgery of a recurrent squamous cell carcinoma on the scalp. A semi-occlusive, gas-permeable, topical silicone gel wound dressing was applied to all granulating wounds, with 98% reepithelialization after five months.

Erosive pustular dermatosis of the scalp successfully treated with calcipotriol cream. Boffa MJ. *Br J Dermatol* 2003; 148: 593–5.

Topical calcipotriol twice daily was started in a patient with significant cutaneous atrophy. Calcipotriol was discontinued 2 months later, after complete resolution, and some hair regrowth was seen at 3 months and 9 months posttreatment.

Successful use of a fractional 2940-nm laser in treating chronic, severe erosive pustular dermatosis of the scalp. Grubbs HE, Robb CW. *JAAD Case Rep* 2019; 5(2): 188–90.

A patient had an excellent response to 19 treatments with fractional 2940-nm laser over 20 months, in combination with topical and oral dapsone and topical tacrolimus. She had previously failed treatment with topical corticosteroids, mycophenolate mofetil, and azathioprine.

Erythema annulare centrifugum

Bryan E. Anderson, Matthew F. Helm



Courtesy of Joslyn Kirby.

BACKGROUND

Erythema annulare centrifugum (EAC) is a gyrate erythema characterized by minimally pruritic, polycyclic, erythematous patches or plaques that may expand up to 2–3 mm/day and clear centrally. There are two forms: the far more common superficial form has a trailing scale at the inner borders of the erythema, whereas the deep form has erythematous induration with minimal to no scale. EAC has a mean duration of 2.8 years, and treatment is often difficult. EAC has been seen to persist for decades.

DIAGNOSIS/MANAGEMENT STRATEGY

EAC represents a hypersensitivity reaction to a myriad of conditions; therefore, a search for and treatment of an underlying disease is the primary management strategy. Most often an underlying cause is not found.

A concurrent skin infection is the most common underlying association. Fungal, bacterial, viral, mycobacterial, and parasitic pathogens have been reported. Typically, the infection is cutaneous and is at a distant location from the EAC eruption. Dermato-phytosis is implicated in up to 48%. Thus, the skin, especially the feet, groin, and nails, should be carefully examined for tinea. Anecdotal reports of other associated skin infections include molluscum contagiosum, herpesvirus infection, and *Pthirus pubis* infestation. Less commonly, the infection is internal with intestinal *Giardia* or *Candida*. Latent Epstein-Barr virus infection, human immunodeficiency virus (HIV) infection, chronic viral hepatitis, appendicitis, tonsillitis, secondary syphilis, urinary tract *Escherichia coli*, and nematode infestations have been anecdotally

reported. Although EAC is typically associated with an active infection, it has also been reported to occur after reactivation of herpes zoster virus in corresponding dermatomes.

Rarely, EAC may be associated with either benign or malignant hematologic and solid neoplasms. This paraneoplastic erythema annulare centrifugum eruption (PEACE) is thought to result from hypersensitivity to tumor proteins released by these neoplasms. However, in the absence of strong clinical suspicion, an extensive search for malignancy is not recommended. If neoplasia is identified, EAC activity correlates with tumor response to treatment.

Medications may be associated with EAC – anecdotal reports include acetazolamide, amitriptyline, ampicillin, azacitidine, boceprevir, chloroquine, cimetidine, cyclopenthi-azide, cotrimoxazole, etizolam, finasteride, gold, hydrochlorothiazide, hydroxy-chloroquine, ibuprofen, iron, Neutradonna (aluminum silicate and belladonna), oxprenolol, pegylated interferon- α_{2a} plus riba-virin, piroxicam, rituximab, salicylates, sorafenib, spironolactone, thioacetazone, and ustekinumab. Early reports of antimalarials as a cause of EAC may be debated: what was considered EAC in these reports may actually have been unrecognized forms of subacute cutaneous lupus erythematosus. Sipuleucel-T immunotherapy of autologous antigen presenting cells for prostate cancer has been associated with EAC. EAC may also be caused by hypersensitivity to other ingested agents, such as blue cheese *Penicillium*.

Other conditions associated with EAC include thyroid disease, liver disease, hypereosinophilic syndrome, sarcoidosis, surgical trauma, linear IgA dermatosis, and autoimmune disease such as relapsing polychondritis, rheumatoid arthritis, pemphigus vulgaris, hemolytic anemia, polyglandular autoimmune disease, autoimmune hepatitis, Budd-Chiari syndrome, and pregnancy. One form of EAC, described as *autoimmune progesterone dermatitis* (see [Chapter 20](#)), can be reproduced by intradermal and patch testing to progesterone and may involve Th1-type cytokines. Another form of EAC may occur annually and seasonally over 2–40 years and may be associated with hereditary lactate dehydrogenase deficiency. EAC may even be familial: there has been one report involving identical twins. Rarely, EAC may be a form of contact dermatitis: there is a single report of contact-induced EAC attributed to a hypersensitivity reaction from topical nickel and cobalt exposure.

Once the underlying condition is treated, EAC usually resolves spontaneously. Frequently, however, the cause is elusive, and treatment becomes empiric and temporizing. Spontaneous remission is also possible, making assessments of therapy difficult. *Topical steroids* may provide symptomatic relief and may improve its appearance. In one report of EAC with unknown etiology, all lesions cleared with *topical calcipotriol* treatment. *Topical tacrolimus* can be helpful as well. In another case, EAC remitted after the patient was treated with *oral metronidazole* given for rosacea. A trial of empiric antimicrobials may be helpful to eradicate an underlying, clinically undetected infection – a case series has shown significant improvement with *oral erythromycin* treatment. If these more conservative treatments fail, the patient's perceived need for treatment should be reassessed. Stronger treatments may be more harmful than the condition itself. Systemic glucocorticoids can usually suppress EAC, but it commonly recurs after the course is completed, and they cannot be routinely recommended. If EAC is very disabling to the patient, other *systemic immunomodulators* may need to be considered. One patient responded very well to *etanercept* therapy.

EAC should be distinguished from the following clinical mimickers: tinea corporis, granuloma annulare, sarcoidosis, mycosis fungoides, psoriasis, pityriasis rosea, tinea versicolor, cutaneous lupus, annular erythema of Sjögren syndrome, granuloma faciale, necrolytic migratory erythema, bullous pemphigoid, secondary

syphilis, Hansen disease, annular urticarial and fixed drug reactions, hypereosinophilic dermatitis, annular erythema of infancy, and other reactive erythemas such as erythema multiforme, erythema gyratum repens, erythema migrans, neutrophilic figurate erythema, palpable migratory arciform erythema, erythema marginatum, and even inflammatory metastatic breast carcinoma. Skin biopsy clarifies the diagnosis in these situations.

Specific Investigations

- Biopsy for histologic examination
 - Superficial type: focal spongiosis, superficial perivascular lymphocytic infiltrate
 - Deep type: superficial and deep perivascular lymphohistiocytic infiltrate
- Full skin examination for potential skin infections
- Potassium hydroxide (KOH) test or culture of suspected EAC lesion and any sites of potential dermatophyte infection
- Wood light examination
- Consider intradermal trichophyton or candidal skin injection and tuberculin test to test for underlying infection
- Review medication list
- Systemic workup: complete blood count (CBC), liver function tests (LFTs), urinalysis (UA), chest X-ray initial screen; if warranted, antinuclear antibodies (ANAs), thyroid-stimulating hormone (TSH), HIV, syphilis serology, malignancy workup including serum protein electrophoresis/urine protein electrophoresis (SPEP/UPEP) with immunofixation

Erythema annulare centrifugum and intestinal *Candida albicans* infection – coincidence or connection? Schmid MH, Wollenber A, Sander CA, et al. *Acta Derm Venereol* 1997; 77: 93–4.

Intradermal trichophyton and candidal skin injection tests may demonstrate a local cutaneous hypersensitivity. These tests may help confirm this reaction pattern and support a trial of empiric antifungals despite an inability to locate the site of a pathogen.

Erythema annulare centrifugum: a review of 24 cases with special reference to its association with underlying disease. Mahood JM. *Clin Exp Dermatol* 1983; 8: 383–7.

A basic workup for internal disease may include a CBC, LFTs, UA, and chest radiograph.

Erythema annulare centrifugum: results of a clinicopathologic study of 73 patients. Weyers W, Diaz-Cascajo C, Weyers I. *Am J Dermatopathol* 2003; 25: 451–62.

Clinicopathologic analysis of 66 cases of erythema annulare centrifugum. Kim KJ, Chang SE, Choi JH, et al. *J Dermatol* 2002; 29: 61–7.

Erythema annulare centrifugum in a HIV-positive patient. Gonzalez-Vela MC, Gonzalez-Lopez MA, Val-Bernal JF, et al. *Int J Dermatol* 2006; 45: 1423–5.

Unusual huge erythema annulare centrifugum presentation of second syphilis. Liu ZH, Chen JF. *QJM* 2014; 107: 231–2.

Erythema annulare centrifugum induced by generalized *Phthirus pubis* infestation. Bessis D, Chraïbi H, Guillot B, et al. *Br J Dermatol* 2003; 149: 1291.

Erythema annulare centrifugum. A case due to tuberculosis. Burkhart CG. *Int J Dermatol* 1982; 21: 538–9.

Erythema annulare centrifugum and *Escherichia coli* urinary infection. Borbujo J, de Miguel C, Lopez A, et al. *Lancet* 1996; 347: 897–8.

Erythema annulare centrifugum following herpes zoster infection: Wolf's isotopic response? Lee HW, Lee DK, Rhee DY, et al. *Br J Dermatol* 2005; 153: 1241–3.

Erythema annulare centrifugum revealing chronic lymphocytic leukemia. Stokkermans-Dubois J, Beylot-Barry M, Vergier B, et al. *Br J Dermatol* 2007; 157: 1045–7.

Erythema annulare centrifugum associated with mantle B-cell non-Hodgkin's lymphoma. Carlesimo M, Fidanza L, Mari E, et al. *Acta Derm Venereol* 2009; 89: 319–20.

Erythema annulare centrifugum: a rare skin finding of autoimmune hepatitis. Aygun C, Kocaman O, Gurbuz Y, et al. *Gastroenterol Res* 2010; 3: 96–8.

Pemphigus vulgaris presenting as erythema annulare centrifugum. Aguilar-Duran S, Deroide F, Mee J, et al. *Clin Exp Dermatol* 2015; 40: 466–7.

Erythema annulare centrifugum-like mycosis fungoides. Ceyhan AM, Akkaya VB, Chen W, et al. *Aust J Dermatol* 2010; 52: e11–3.

Erythema annulare centrifugum following pancreatobiliary surgery. Thami GP, Sachdeva A, Kaur S, et al. *J Dermatol* 2002; 29: 347–9.

Linear IgA dermatosis presenting with erythema annulare centrifugum lesions: report of three cases in adults. Dippel E, Orfanos CE, Zouboulis CHC. *J Eur Acad Dermatol Venereol* 2000; 15: 167–70.

Erythema annulare centrifugum and relapsing polychondritis. Dippel E, Orfanos CE, Zouboulis C. *Ann Dermatol Venereol* 2000; 127: 735–9.

Erythema annulare centrifugum in a patient with polyglandular autoimmune disease type 1. Garty B. *Cutis* 1998; 62: 231–2.

Pregnancy as a possible etiologic factor in erythema annulare centrifugum. Dogan G. *Am J Clin Dermatol* 2009; 10: 33–5.

Autoimmune progesterone dermatitis manifested as erythema annulare centrifugum: confirmation of progesterone sensitivity by in vitro interferon-gamma release. Halevy S, Cohen AD, Lunenfeld E, et al. *J Am Acad Dermatol* 2002; 47: 311–3.

Contact erythema annulare centrifugum. Sambucety PS, Agapito PG, Preto MAR. *Contact Dermatitis* 2006; 55: 309–10.

First-Line Therapies

• Treatment of underlying condition	E
• Discontinue potential causative medications	E
• Topical corticosteroids	E
• Ultraviolet light therapy	E
• Oral erythromycin	D
• Oral fluconazole	D
• Oral azithromycin	C

An observational study of the efficacy of azithromycin in erythema annulare centrifugum. Sardana K, Chugh S, Mahajan K. Clin Exp Dermatol 2018; 43: 296–9.

Clinical trial of 10 patients given oral azithromycin 250 mg once daily until clinical resolution and followed for relapse. Eight responded with no relapse during the monitoring period.

Erythromycin as a safe and effective treatment option for erythema annulare centrifugum. Chuang FC, Lin SH, Wu WM. Indian J Dermatol 2015; 60: 519.

Case series of eight subjects with EAC. Subjects were given erythromycin stearate 1000 mg per day for 2 weeks. All subjects showed reduction in lesion size and erythema at 2 weeks. Upon completion of the treatment course, three patients had recurrent disease. Retreatment with erythromycin was effective.

Pediatric erythema annulare centrifugum treated with oral fluconazole: a retrospective series. Kruse LL, Kenner-Bell BM, Mancini AJ. Pediatr Dermatol 2016; 33: 501–6.

Case series of five subjects with EAC. Patients were empirically treated with fluconazole 3–6 mg/kg/day (maximum dose of 200 mg/day) for 4–6 weeks. All showed improvement with three clearing entirely.

Erythema annulare centrifugum secondary to treatment with finasteride. Al Hammadi A, Asai Y, Patt MI, et al. J Drugs Dermatol 2007; 6: 460–3.

Erythema annulare centrifugum: an unusual case due to hydroxychloroquine sulfate. Hudson LD. Cutis 1985; 36: 129–30.

Erythema annulare centrifugum in the era of triple therapy with boceprevir plus pegylated interferon α -2b and ribavirin for hepatitis C virus infection. di Meo N, Stinco G, Fadel M, et al. J Cutan Med Surg 2015; 19: 203–4.

EAC has been associated with numerous medications. Elimination of the suspected agent may be curative.

Erythema annulare centrifugum and Hodgkin's disease: association with disease activity. Leimert JT, Corder MP, Skibba CA, et al. Arch Intern Med 1979; 139: 486–7.

Erythema annulare centrifugum responding to natural ultraviolet light. Coronel-Perez IM, Morillo-Andújar M. Actas Dermosifiliogr 2010; 101: 177–8.

Two patients, ages 22 and 27 years, each with more than 8 years of EAC, failed treatment with topical corticosteroids.

After years of sunlight avoidance, one patient cleared, and the other had significant improvement with summer sunlight exposure.

Second-Line Therapies

• Empiric antimicrobials	E
• Topical or systemic antipruritics	E
• Topical tacrolimus	E

Annular erythema responding to tacrolimus ointment. Rao NG, Pariser RJ. J Drugs Dermatol 2003; 2: 421–4.

Two patients with annular erythema of unclear etiology treated selected lesions with topical tacrolimus 0.1% ointment twice daily. Those lesions that were treated resolved within 2–6 weeks, whereas other untreated lesions did not respond until they, too, were treated with tacrolimus.

This suggests that tacrolimus, and not spontaneous remission, was responsible for the improvement.

Third-Line Therapies

• Systemic corticosteroids	E
• Immunomodulatory agents	E
• Topical calcipotriol	E
• Metronidazole	E

Erythema annulare centrifugum. Seidel DR, Burgdorf WHC. In: Demis DJ, et al., eds. Clinical Dermatology. Lippincott Williams & Wilkins, Philadelphia, 1999; Ch 7–5: 1–4.

Calcipotriol for erythema annulare centrifugum. Gniadecki R. Br J Dermatol 2002; 146: 317–9.

A 73-year-old woman had EAC of unknown cause that was resistant to topical and systemic steroids, antifungals, and psoralen and ultraviolet light (PUVA) treatment. It cleared completely after 3 months of topical, once-daily calcipotriol.

Erythema annulare centrifugum successfully treated with metronidazole. De Aloe G, Rubegni P, Risulo M, et al. Clin Exp Dermatol 2005; 30: 583–4.

A 38-year-old man with EAC failed oral antibiotics and antifungals, as well as topical calcipotriol. Only systemic steroids provided temporary improvement of his skin lesions. Because the patient had rosacea, oral metronidazole 400 mg daily was prescribed for 6 weeks, with resolution of EAC.

A novel therapeutic approach to erythema annulare centrifugum. Minni J, Sarro R. J Am Acad Dermatol 2006; 54: S134–5.

In a personal communication, one patient with extensive EAC was reported to clear with etanercept 25 mg twice-weekly injections. After 4 weeks of treatment the patient was 95% clear, and complete remission was achieved after continued therapy. After 6 months the treatment was discontinued and EAC recurred. The lesions responded again to a repeat treatment regimen.

Erythema dyschromicum perstans

Robert F. Duffy, Warren R. Heymann



Erythema dyschromicum perstans (EDP) is an acquired, generalized dermal hypermelanosis of unknown etiology. Clinically it presents as asymptomatic, ashen-gray-blue macules of varying sizes, most commonly on the trunk and proximal extremities. Variable components include erythema and papulation. It has been reported most frequently in dark-skinned Latin American people, although all racial groups can be affected. EDP has similarities to lichen planus pigmentosus and the 'ashy dermatosis' of Ramirez (which many consider to be synonymous with EDP), although the precise relationship of these conditions remains uncertain.

MANAGEMENT STRATEGY

Histology reveals vacuolar degeneration of the basal layer associated with pigmentary incontinence. Dermal vessels are surrounded with an infiltrate of lymphocytes and histiocytes, and many melanophages are present.

EDP may need to be differentiated from the late stage of pinta. Dark-field examination and serologic tests for syphilis should be carried out to exclude this treponematoses in suspected cases. Idiopathic eruptive macular pigmentation is a similar condition. Histology demonstrates that the pigment is located in the basal layer of the epidermis and the lichenoid inflammation characteristic of EDP is not present.

Although EDP may persist for many years, there have been reports of spontaneous resolution, making a conservative approach reasonable. Treatment is based on anecdotal evidence. Data suggests the use of *tacrolimus ointment*, either as monotherapy or in

combination with other treatment modalities (i.e., *topical steroids, light therapy, or laser*), as effective. Some systemic treatments (*steroids, isotretinoin, dapsone, and clofazimine*) have also shown efficacy.

Specific Investigation

- Biopsy

First-Line Therapies

• No therapy	D
• Topical corticosteroid	E
• Topical tacrolimus	E

Erythema dyschromicum perstans in children: a report of 14 cases. Torrelo A, Zaballos P, Colmenero I, et al. *J Eur Acad Dermatol Venereol* 2005; 19: 422–6.

No treatment was used. In six of these cases the eruption cleared or improved during follow-up ranging from 1 to 5 years.

Erythema dyschromicum perstans: identical to ashy dermatosis or not? Numata T, Harada K, Tsuboi R, et al. *Case Rep Dermatol* 2015; 7: 146–50.

The erythema responded to a topical steroid.

Second-Line Therapies

• Erbium-doped fractionated laser and topical tacrolimus	E
• Narrowband ultraviolet B (NB-UVB) therapy and topical steroids and tacrolimus	E

Improvement of erythema dyschromicum perstans using a combination of the 1,550-nm erbium-doped fractionated laser and topical tacrolimus ointment. Wolfshohl JA, Geddes ERC, Stout AB, et al. *Lasers Surg Med* 2017; 49: 60–2.

One patient had 75% improvement with five treatment sessions on 4–6-week intervals of erbium-doped fractionated laser with a 15 mm spot size, a fluence range between 5–9 mJ/microscopic treatment zone, a treatment level 5 corresponding to 14% coverage, and a total of eight passes with total energy ranging from 4.65–4.91 kJ. This was combined with concurrent daily then every other day application of tacrolimus.

Erythema dyschromicum perstans: a case report and systematic review of histologic presentation and treatment. Leung N, Oliveira M, Selim MA, et al. *Int J Women's Dermatol* 2018; 4: 216–22.

One patient experienced a significant decrease in hyperpigmentation following 2 months of NB-UVB starting at 300 mJ three-times weekly increased by 10–15% per session with continued use of clobetasol and tacrolimus.

Third-Line Therapies

• Isotretinoin	E
• Dapsone 100 mg/day for 3 months	E
• Clofazimine 100 mg/day for 3 months	D

Erythema dyschromicum perstans response to isotretinoin. Wang F, Zhao YK, Wang Z, et al. *JAMA Dermatol* 2016; 152: 841–2.

A 41-year-old man with EDP demonstrated 90% improvement within 4 months of isotretinoin (20 mg daily). Periodic recurrences responded to doses as low as 10 mg daily during 7 years of follow-up.

Erythema dyschromaticum perstans: response to dapsone therapy. Bahadir S, Cobanoglu U, Cimsit G, et al. *Int J Dermatol* 2004; 43(3): 220–2.

A 16-year-old boy with widespread EDP was treated with dapsone 100 mg daily for 3 months with lesion disappearance, pigmentation decrease, and cessation of new lesion formation.

Erythema dyschromaticum perstans in phototype II women: three unusual clinical cases studied with electron microscopy. Persechino S, Caperchi C, Cortesi G, et al. *Eur J Dermatol* 2011; 21: 261–2.

Three cases demonstrated marked decrease in pigmentation on treatment with dapsone 100 mg daily for 3 months.

Involvement of cell adhesion and activation molecules in the pathogenesis of erythema dyschromaticum perstans (ashy dermatitis). The effect of clofazimine therapy. Baranda L, Torres-Alvarez B, Cortes-Franco R, et al. *Arch Dermatol* 1997; 133: 325–9.

A prospective clinical and immunohistochemical study indicating that clofazimine reduces the inflammatory response in EDP. Four out of six patients treated with clofazimine 100 mg/day showed marked improvement after 3 months of treatment.

Erythema elevatum diutinum

Sidra S. Khan, Ian H. Coulson



Erythema elevatum diutinum (EED) is a rare neutrophilic dermatosis consisting of violaceous, brown or red papules, plaques, nodules, and occasionally vesicobullous lesions over the extensor surfaces of the joints and buttocks, genitalia, trunk, and face. Early lesions tend to be soft and erythematous. Advanced lesions tend to be nodular and firm, secondary to fibrosis. EED is thought to be a form of immune complex-mediated leukocytoclastic vasculitis, although its etiology remains unclear. Infections (including HIV and streptococcal), hematologic abnormalities, inflammatory bowel disease, celiac disease, verrucous carcinoma, systemic lupus erythematosus, primary Sjögren syndrome, ophthalmic disorders (peripheral keratitis), and pulmonary lymphoepithelioma-like carcinoma (possibly as part of a paraneoplastic syndrome) have been associated. Drug-induced EED may result from interferon- β , erythropoietin, antituberculosis chemotherapy, and cisplatin exposure.

Differential diagnoses of early lesions of EED include extrafacial granuloma faciale, Sweet syndrome, rheumatoid neutrophilic dermatitis or palisaded neutrophilic and granulomatous, dermatitis, and advanced lesions include rheumatoid nodules and multicentric reticulohistiocytosis.

MANAGEMENT STRATEGY

EED is a chronic disease that may persist for several years or decades and typically proves challenging to treat.

After management of any underlying disease, *dapsone* 100 mg daily remains the initial treatment of choice. The response may

be partial and dose dependent. Both intralesional and systemic corticosteroids (prednisolone 30–40 mg daily) have produced favorable responses.

Sulfonamides (sulfamethoxypyridazine 500 mg once daily and sulfapyridine 0.5–1 g three times daily), *nicotinamide/niacinamide* 100 mg three times daily, *colchicine* 0.5 mg twice daily with 0.5 mg three times daily for 3–4 days to abate minor disease flares, and *chloroquine* 300 mg daily have produced resolution of lesions.

Specific Investigations

- Full blood count
- Full metabolic panel
- Immunoglobulins and serum electrophoresis/immunofixation electrophoresis
- Antinuclear antibody (ANA)
- Antineutrophil cytoplasmic antibodies (ANCA)
- Anti-dsDNA antibody
- Antiphospholipid antibodies
- Celiac disease screen
- Hepatitis B and C serology
- HIV test
- Chest radiograph
- Urinalysis
- Histology
- Skin biopsy

Erythema elevatum diutinum: clinical, histopathologic, and immunohistochemical characteristics of six patients. Wahl CE, Bouldin MB, Gibson LE. *Am J Dermatopathol* 2005; 27: 397–400.

The vascular endothelium of EED stains positive for CD31, CD34, VEGF, and factor VIII, and negative for factor XIIIa, TGF β , and LANA. This pattern does not distinguish it from similar-appearing lesions. Therefore, the chronic and recurrent nature of EED is the primary means of distinguishing it from entities that are clinically and histologically similar.

Erythema elevatum diutinum and IgA paraproteinaemia: “a preclinical iceberg”. Chowdhury MMU, Inaloz HS, Motley RJ, et al. *Int J Dermatol* 2002; 41: 368–70.

The technique of immunofixation electrophoresis is more sensitive than immunoelectrophoresis. This uses a combination of zone electrophoresis and immunoprecipitation with specific antisera to detect monoclonal immunoglobulins or light chains at very low concentrations in serum and urine. This is useful in EED because patients may have associated paraproteinemias, which, in some cases, may undergo malignant transformation.

The authors note that in monoclonal disorders there is extensive asymptomatic tumor proliferation and possible malignant transformation in 20% of patients during long-term follow-up. It was recommended that there should be lengthy follow-up and monitoring for patients with both EED and IgA paraproteinemia because of the risk of progression to IgA myeloma.

Is IgA antineutrophil cytoplasmic antibody a marker for patients with erythema elevatum diutinum? A further three cases demonstrating this association. Crichlow SM, Alexandroff AB, Simpson RC, et al. *Br J Dermatol* 2011; 164: 675–7.

Two studies evaluating the prevalence of ANCAs in EED. IgA ANCAs were present in all patients with EED.

Erythema elevatum diutinum and HIV infection: a report of five cases. Muratori S, Carrera C, Gorani A, et al. *Br J Dermatol* 1999; 141: 335–8.

The largest case series of patients with EED and HIV infection. Streptococcal infection seemed to trigger exacerbations in four of five patients. EED can stimulate Kaposi sarcoma and bacillary angiomatosis, which can be challenging in the context of an HIV-seropositive patient. Histopathologic confirmation of the diagnosis is therefore advocated.

Erythema elevatum diutinum associated with peripheral ulcerative keratitis. Vaiyavatjamai P, Wattanakrai P. *J Eur Acad Dermatol Venereol* 2011; 25: 741–2.

Progressive keratolysis with pseudopterygium associated with erythema elevatum diutinum. Lekhanont K, Patarakittam T, Mantachote K, et al. *Ophthalmology* 2011; 118: 927–33.

Erythema elevatum diutinum with verrucous carcinoma: a rare association. Nair SR, Viswanath V, Sonavane AD, et al. *Indian J Dermatol Venereol Leprol* 2010; 76: 420–2.

Erythema elevatum diutinum as a paraneoplastic syndrome in a patient with pulmonary lymphoepithelioma-like carcinoma. Liu T-C, Chen I-S, Lin T-K, et al. *Lung Cancer* 2009; 63: 151–3.

Erythema elevatum diutinum presenting with a giant annular pattern. Di Giacomo TB, Marinho RT, Nico MMS. *Int J Dermatol* 2009; 48: 290–2.

Erythema elevatum diutinum associated with pyoderma gangrenosum in an HIV-positive patient. Maksimovic L, Duriez P, Lascaux-Cametz A-S, et al. *Ann Dermatol Venereol* 2010; 137: 386–90.

Erythema elevatum diutinum in systemic lupus erythematosus. Chan Y, Mok CC, Tang WYM. *Rheumatol Int* 2011; 31: 259–62.

These citations indicate the range of pathologies associated with EED.

First-Line Therapies

- Dapsone D
- Dapsone plus antiretrovirals in HIV-associated disease E
- Dapsone plus another agent (e.g., corticosteroids, antibiotics) D

Erythema elevatum diutinum: a case report and review of literature. Doktor V, Hadi A, Hadi A, et al. *Int J Dermatol* 2019; 58: 408–15.

This case report of EED also includes a thorough literature review and summary of 133 cases of EED between 1990 and 2014. Twenty-one cases were associated with HIV and 47 with paraproteinemias (IgA paraproteinemia making up 57.45%, thus making it the most common subtype). Of the 40 cases with associated autoimmune conditions, rheumatoid arthritis was the most common ($n = 10$). Treatment options vary from case to case and it is important to treat associated conditions. Within the review, 75 patients were treated with dapsone (50–100 mg once daily). Thirty-six achieved a complete treatment response, 24 achieved a partial response and seven achieved no response.

Other treatments included topical or systemic steroids and/or colchicine.

Alternative procedure to allow continuation of dapsone therapy despite serious adverse reaction in a case of dapsone-sensitive erythema elevatum diutinum. Seneschal J, Guillet S, Ezzedine K, et al. *Dermatology (Basel)* 2012; 224: 115–9.

This patient responded well to dapsone but developed drug reaction with eosinophilia and systemic symptoms (DRESS), confirmed in vitro by the presence of circulating dapsone-specific T cells. As treatment alternatives to dapsone are limited, it is recommended that dapsone hypersensitivity syndrome is confirmed using interferon assay and modified lymphocyte transformation tests. After confirmation, a dapsone tolerance induction protocol may be administered over a period of days in order to obtain tolerance, thus allowing continuation of dapsone.

Nodular lesions of erythema elevatum diutinum in patients infected with the human immunodeficiency virus. LeBoit PE, Cockerell CJ. *J Am Acad Dermatol* 1993; 28: 919–22.

A clinicopathologic study of four patients with HIV infection who had unusual nodular lesions of EED. None of the patients responded to treatment with oral dapsone, and the authors commented that this observed lack of response may reflect the preponderance of fibrosis rather than neutrophils in these advanced lesions.

Second-Line Therapies

- Sulfonamides D
- Colchicine D
- Oral steroids D
- Niacinamide and tetracycline E
- Chloroquine E
- Methotrexate E
- Dapsone with ciclosporin E

Erythema elevatum diutinum: a case successfully treated with colchicine. Henriksson R, Hofer PA, Hörnqvist R. *Clin Exp Dermatol* 1989; 14: 451–3.

A case report of a 68-year-old man with EED refractory to treatment with oral dapsone who responded well to treatment with colchicine 0.5 mg twice daily over 6 weeks. Minor flares were abated temporarily, increasing colchicine to 0.5 mg three times a day for 3–4 days, without provoking diarrhea.

Complete resolution of erythema elevatum diutinum using oral sulfasalazine. Chen ML, Chlopik A, Hoang MP. *Dermatol Online* 2017; 23(10):13030/qt8267v8v9.

A 35-year old female with EED initially responded very well to dapsone but stopped this after 7 months when she became pregnant (category C), whereupon her symptoms recurred. She was subsequently treated with oral sulfasalazine (category B) and reported completed resolution of symptoms. Although no difference in safety is explicitly proven between dapsone and sulfasalazine during pregnancy, some physicians and patients feel more comfortable with the latter.

Erythema elevatum diutinum treated with niacinamide and tetracycline. Kohler IK, Lorincz AL. *Arch Dermatol* 1980; 116: 693–5.

A 60-year-old woman with EED that cleared completely after 4 weeks of treatment with oral niacinamide 100 mg three times

daily and oral tetracycline hydrochloride 250 mg four times daily. After this, oral niacinamide alone was sufficient for disease suppression.

Successful combination therapy with dapsone and cyclosporine for erythema elevatum diutinum with unusual appearance. Takahashi H, Fukami Y, Honma M, et al. *J Dermatol* 2012; 39: 486–7.

In this case of EED with an unusual distribution on the soles, fingers, trunk, and feet accompanied with ulcerations, the patient initially failed to respond to oral dapsone 75 mg daily but improved with the addition of ciclosporin 4 mg/kg/day.

Third-Line Therapies	
• Topical dapsone 5%	E
• Localized surgical excision (nodular EED)	E
• Cyclophosphamide	E
• Plasma exchange ± thalidomide	E
• Reduction in cyclosporin dose	E
• Transdermal nicotine patches	E
• Methylprednisolone	E
• Colectomy	E
• Gluten-free diet	E
• Phenformin	E

Novel use of topical dapsone 5% gel for erythema elevatum diutinum: safer and effective. Frieling GW, William NL, Lim SJ. *J Drugs Dermatol* 2013; 12: 481–4.

This case report showed some improvement in erythema and flattening of lesions of EED using dapsone 5% gel for 1 week before start of oral dapsone therapy.

Other topical treatments, including topical corticosteroids and intralesional steroid injections, have shown variable results in a few case reports.

Successful surgical treatment of advanced erythema elevatum diutinum. Rinard JR, Mahabir RC, Greene JE, et al. *Can J Plast Surg* 2010; 18: 28–30.

In this case report, a patient with late-stage nodular EED, in whom medical treatment was contraindicated, was treated with continued surgical excisions of recurrent nodules with symptomatic relief.

Fibrotic nodules often respond poorly to dapsone; surgical excision may help.

Erythema elevatum diutinum in a patient with relapsing polycondritis. Bernard P, Bedane C, Delrous JL, et al. *J Am Acad Dermatol* 1992; 26: 312–5.

A 69-year-old man with a history of relapsing polycondritis developed EED, which responded to treatment with oral cyclophosphamide 100 mg daily and prednisolone 20 mg daily. Cyclophosphamide was discontinued after 2 months, and the prednisolone was subsequently tapered to 15 mg daily.

Erythema elevatum diutinum associated with IgA paraproteinemia successfully controlled with intermittent plasma exchange. Chow RK, Benny WB, Coupe RL, et al. *Arch Dermatol* 1996; 132: 1360–4.

Intermittent plasma exchange has been reported to successfully control EED associated with IgA paraproteinemia.

Case of erythema elevatum diutinum associated with IgA paraproteinemia successfully controlled with thalidomide and plasma exchange. Manni E, Cervadoro E, Papineschi F. *Ther Apher Dial* 2015; 19: 195.

An 83-year-old woman with EED treated with dapsone for a year was found to have an IgA kappa paraproteinemia consistent with monoclonal gammopathy of undetermined significance and commenced on treatment with plasma exchange, 3-weekly sessions down to 1-weekly sessions. Commenced thalidomide on week 13, with 200 mg/day and 100 mg/day alternatively and plasma exchange reduced to one exchange every 2 weeks. Thalidomide was then continued as monotherapy followed by a treatment regimen with periods of plasma exchange ± thalidomide, which led to improvement of skin lesions and stabilization of raised IgA values.

Erythema elevatum diutinum after liver transplantation: disappearance of the lesions associated with a reduction in cyclosporine dosage. Hernández-Cano N, De Lucas R, Lázaro TE, et al. *Pediatr Dermatol* 1998; 15: 411–2.

Lesions of EED resolved after a reduction in ciclosporin dosage in a 10-year-old patient who had previously received a cadaveric hepatic allograft because of Alagille disease.

Erythema elevatum diutinum manifesting as a penile ulcer. Yoshii N, Kanekura T, Higashi Y, et al. *Clin Exp Dermatol* 2007; 32: 211–3.

A 74-year-old man with EED lesions on his limbs responded well to the nicotine patches that released 6.25 mg nicotine applied every 24 hours. The penile lesions remained recalcitrant to the nicotine patches as well as dapsone, requiring treatment with methylprednisolone (40 mg/day).

Erythema elevatum diutinum: an unusual association with ulcerative colitis. Buahene K, Hudson M, Mowat A, et al. *Clin Exp Dermatol* 1991; 16: 204–6.

A 58-year-old woman developed EED during severe acute exacerbation of ulcerative colitis, which resolved after colectomy.

Erythema elevatum diutinum in association with coeliac disease. Tasanen K, Raudasoja R, Kallioinen M, et al. *Br J Dermatol* 1997; 136: 624–7.

A 47-year-old woman who presented with typical EED and previously undiagnosed celiac disease. Treatment with dapsone was partially effective, but complete healing of the EED lesions was achieved only after the introduction of a strict gluten-free diet. Maintenance treatment with a gluten-free diet only was required.

Erythema elevatum diutinum: cutaneous vasculitis, impaired clot lysis, and response to phenformin. Schumacher HR, Carroll E, Taylor F, et al. *J Rheumatol* 1977; 4: 103–12.

A variety of treatments were tried with no success in this case report, but phenformin 50 mg three times daily produced marked improvement for periods of 11 and 16 months on two occasions.

Phenformin is a biguanide antidiabetic drug that has been withdrawn in many countries due to high risk of lactic acidosis.

Erythema multiforme

Jean Revuz



Erythema multiforme (EM) is a distinct cutaneous reaction pattern to a variety of stimuli, predominantly herpes simplex virus (HSV) infection, occurring mostly in young adults. It usually runs a self-limiting course but has a tendency to recur. It is defined by the presence of 'typical' three-zone target lesions, with a usual acral distribution. The presence of mucosal involvement at more than one site distinguishes EM major from EM minor. A specific variant has mucosal lesions only, without skin involvement. EM major can be distinguished from Stevens–Johnson syndrome, which lacks typical targetoid lesions and an acral location, but rather presents with irregular macules or atypical targets and a truncal location; regardless, these two diseases are still frequently confused. EM is frequently misdiagnosed as other entities such as urticarial dermatoses and, more rarely, in cases of cutaneous lupus, vasculitis, erythema annulare, and drug eruptions. Paraneoplastic pemphigus may mimic EM major.

MANAGEMENT STRATEGY

In 30%–50% of cases the etiology of EM is unknown. The most commonly recognized precipitant is HSV infection; both types I and II HSV-specific DNA has been isolated from lesional tissue in 60%–70% of cases. HSV particles are found in the circulating precursors of epidermal Langerhans cells. A variety of other viral infections (orf, varicella zoster virus [VZV], Epstein–Barr virus [EBV], cytomegalovirus [CMV], human immunodeficiency virus [HIV], hepatitis B vaccination), bacterial infections (mainly *Mycoplasma pneumoniae* but also tularemia), and fungal infections (predominantly histoplasmosis) have been implicated. An extensive list of drugs has been reported to trigger EM, but most cases,

if not all, are the result of confusion with Stevens–Johnson syndrome. Rare cases may be attributed to contact allergy.

Acute episodes of EM need only *symptomatic treatment* in most cases. Recurrent EM, which may severely affect quality of life, has a well-recognized *preventive treatment* in case of HSV infection but may be highly recalcitrant when no cause is identified. A persistent continuous variety of EM has been reported with antidesmoplakin antibodies, which do not testify pemphigus.

There are no double-blind or open trials of treatments for acute episodes of EM. Most cases, particularly EM minor, run a self-limiting course. Symptomatic measures include *oral antihistamines* and *mild-to-moderate-potency* to reduce pruritus. Underlying conditions, mainly *Mycoplasma pneumoniae* infection, should be treated. Recurrent EM (>6 attacks per year) may respond to long-term *anti-HSV drugs*. In resistant cases a variety of other therapies can be helpful (see later).

Mucosal manifestations of EM major are a source of morbidity. The most common sites affected are the buccal mucosa and lips. Symptomatic measures include *mouthwashes*, a *soft diet*, *topical anesthetics*, and *topical corticosteroids* (e.g., 0.1% triamcinolone acetonide paste). Budesonide or beclomethasone inhalers (one puff three to four times daily) provide an alternative method of delivering local corticosteroid to the inflamed mucosal surfaces. Short courses of high-dose *oral prednisolone* may be needed for severe oral disease. Strict eye care to reduce secondary infection and scarring includes *saline washes* for removal of crusts, *local antibiotics*, and frequent *debridement of tarsal and bulbar conjunctival adhesions*.

Specific Investigation

- Histology/immunofluorescence

EM is a clinical diagnosis. Histology, with direct immunofluorescence, can be useful in atypical cases to exclude other bullous diseases that present with oral manifestations, such as pemphigus vulgaris or cicatricial pemphigoid.

Investigations directed at determining the underlying trigger factors include culture or serologic testing for HSV or other infections, especially *M. pneumoniae*, as indicated by clinical findings.

First-Line Therapies

• Antivirals (aciclovir, valaciclovir, ganciclovir)	A
• Macrolide antibiotics for <i>Mycoplasma pneumoniae</i> -induced EM major	C

Recurrent erythema multiforme: clinical features and treatment in a large series of patients. Schofield JK, Tatnall FM, Leigh IM. Br J Dermatol 1993; 128: 542–5.

A review of 65 patients with recurrent EM: 71% had episodes triggered by HSV infection. Treatment with standard doses of aciclovir for HSV was relatively disappointing; continuous aciclovir 400 mg twice daily for 6 months was more effective, with remission in some responders. Some patients responded to dapsone, antimalarials, azathioprine (10 of 11), and human immunoglobulin.

A double-blind, placebo-controlled trial of continuous aciclovir therapy in recurrent erythema multiforme. Tatnall FM, Schofield JK, et al. Br J Dermatol 1995; 132: 267–70.

Aciclovir 400 mg twice daily for 6 months suppressed EM in seven of 11 patients (including one with apparently idiopathic EM). Two patients went into complete remission.

A therapeutic trial of aciclovir is justified even when clinical evidence of HSV is lacking. Aciclovir 400 mg twice daily can be administered for 6 months to 2 years because it has a good long-term safety profile. It is ineffective in an acute episode once the herpetic lesion or EM eruption has developed. Recurrence is usual after stopping the drug.

Clinical and histologic features of *Mycoplasma pneumoniae*-related erythema multiforme: a single-center series of 33 cases compared with 100 cases induced by other causes. Amode R, Ingen-Housz-Oro S, Ortonne N, et al. J Am Acad Dermatol 2018; 79: 110–7.

MP-induced EM have more mucous membrane lesions, more atypical targets, and more respiratory tract sequelae; they have to be treated by macrolide antibiotics.

Recurrent erythema multiforme: clinical characteristics, etiologic associations, and treatment in a series of 48 patients at Mayo Clinic, 2000 to 2007. Wetter DA, Davis MD. J Am Acad Dermatol 2010; 62: 45–53.

Of 48 patients, HSV was responsible in 11 (23%); the cause remained unknown in 28 (58%). Systemic corticosteroids were used in most patients. Sixteen of 33 patients receiving continuous antiviral treatment had either partial or complete disease suppression. Mycophenolate mofetil provided partial or complete response in six of eight patients.

Second-Line Therapies

• Dapsone	C
• Azathioprine	C
• Thalidomide & lenalidomide	B
• Potassium iodide	C
Oral EM	
• Topical corticosteroid	B
• Levamisole	B
• Systemic corticosteroid	D

Characteristics of the oral lesions in patients with cutaneous recurrent erythema multiforme. Farthing PM, Maragou P, Coates M, et al. J Oral Pathol Med 1995; 24: 9–13.

In this series of 82 patients with typical cutaneous EM, 70% had oral mucosal involvement. Five patients with resistant disease were controlled with azathioprine 100–150 mg daily.

Azathioprine therapy in the management of persistent erythema multiforme. Jones RR. Br J Dermatol 1981; 105: 465–7.

Azathioprine 100–150 mg daily was effective in two patients and permitted reduction of the corticosteroid dosage.

Treatment by thalidomide of chronic multiforme erythema: its recurrent and continuous variants. A retrospective study of 26 patients. Cherouati K, Claudy A, Souteyrand P, et al. Ann Dermatol Venereol 1996; 123: 375–7 [in French].

Thalidomide reduces the duration of episodes of recurrent EM by 11 days on average; it is dramatically effective in the exceptional continuous variant. Remission can be maintained with low-dose (25–50 mg daily) thalidomide.

Lenalidomide as an alternative to thalidomide for treatment of recurrent erythema multiforme. Drahy F, Ingen-Housz-Oro S, Grootenboer-Mignot S, et al. JAMA Dermatol 2018; 154: 487–9.

Three patients were successfully treated with this analog of thalidomide with fewer side effects.

Potassium iodide in erythema nodosum and other erythematous dermatoses. Horio T, Danno K, Okamoto H, et al. J Am Acad Dermatol 1983; 9: 77–81.

Fourteen of 16 subjects with EM (six related to HSV infection) responded within 1 week to 300 mg potassium iodide three times daily. Gastrointestinal and cutaneous side effects can occur with this treatment.

Erythema multiforme – response to corticosteroid. Ting HC, Adam BA. Dermatologica 1984; 169: 175–8.

Thirteen patients with EM minor treated with systemic corticosteroids were compared with 12 patients who were treated without. Apart from a shorter duration of fever, the corticosteroid-treated group did not respond better than the non-corticosteroid-treated group.

There is no reason to treat EM minor with steroids. This drug may still be useful in EM major.

Open preliminary clinical trial of clobetasol propionate ointment in adhesive paste for treatment of chronic oral vesiculo-erosive diseases. Lozada-Nur F, Huang MZ, Zhou GA. Oral Surg Oral Med Oral Pathol 1991; 71: 283–7.

Clobetasol propionate 0.05% ointment mixed 1:1 with Orabase paste two to three times daily was helpful in four patients with chronic oral EM.

Erythema multiforme: diagnosis, clinical manifestations and treatment in a retrospective study of 22 patients. Sanchis JM, Bagán JV, Gavalda C, et al. J Oral Pathol Med 2010; 39: 747–52.

Systemic corticosteroids are effective in controlling the outbreaks; their use as maintenance therapy is not clearly indicated.

Recurrent oral erythema multiforme. Clinical experience with 11 patients. Bean SE, Quezada RK. JAMA 1983; 249: 2810–2.

In this retrospective study, patients with severe, recurrent oral EM involvement were treated with prednisolone 40–60 mg daily, subsequently tapered over 2–3 weeks. This reduced the time taken for oral erosions to heal but did not influence recurrences.

Some authorities, however, believe that use of corticosteroids in EM increases the frequency and chronicity of attacks.

Third-Line Therapies

• Antimalarials	D
• Human immunoglobulin	D
• Interferon- α	E
• Rituximab	D
• Tamoxifen	E
• Zinc sulfate	E
• Cimetidine	E
• Ciclosporin	E
• Pulsed methylprednisolone	E
• Apremilast	E
• Tofacitinib	E
• Anti-TNF drugs	E

Recurrent erythema multiforme: clinical features and treatment in a large series of patients. Schofield JK, Tatnall FM, Leigh IM. Br J Dermatol 1993; 128: 542–5.

The use of normal human immunoglobulins and antimalarials was reported in a few patients in this study. Intramuscular human immunoglobulin 750g once a month caused suppression of EM in 11 of 13 patients. One responder remained in remission after therapy was discontinued. There was a 50% success rate with antimalarials (both hydroxychloroquine and mepacrine) used in four patients.

Severe erythema multiforme responding to interferon alfa. Geraminejad P, Walling HW, Voigt MD, et al. J Am Acad Dermatol 2006; 54: S18–21.

A patient with recurrent EM associated with hepatitis C had been in complete remission for 6 years after treatment with IFN- α . A new recurrence was successfully treated with IFN- α in the absence of recurring hepatitis C virus infection.

Interferon may be a first-line treatment for patients with hepatitis C.

Rituximab, a new treatment for difficult to treat chronic erythema multiforme major. Five cases. Hirsch G, Ingen-Housz-Oro S, Fite C, et al. J Eur Acad Dermatol Venereol 2016; 30: 1140–3.

Chronic continuous or relapsing EM resistant to several drugs, including aciclovir corticosteroids, and thalidomide; four had complete remission.

Progesterone-induced erythema multiforme. Wojnarowska F, Greaves MW, Peachey RD, et al. J Roy Soc Med 1985; 78: 407–8.

EM linked to the luteal phase of the menstrual cycle was controlled with tamoxifen.

Topical treatment of recurrent herpes simplex and postherpetic erythema multiforme with low concentrations of zinc sulphate solution. Brody I. Br J Dermatol 1981; 104: 191–4.

Treatment of the skin at the site of the herpetic infection with zinc sulfate solution prevented relapse of postherpetic EM over a 2-year period of observation in one patient. For the oral mucous membrane, 0.01%–0.025% zinc sulfate solution was used.

Ciclosporin therapy for bullous erythema multiforme. Wilkel CS, McDonald CJ. Arch Dermatol 1990; 126: 397–8.

High-dose ciclosporin (5–10 mg/kg daily) suppressed an atypical bullous eruption with histologic features of EM.

Apremilast for treatment of recurrent erythema multiforme. Chen T, Levitt J, Geller L. Dermatol Online J. 2017; 15: 23(1): 13030/qt15s432gx.

Recalcitrant mucous membrane lesions of three patients were cleared by 30–60 mg daily.

Idiopathic erythema multiforme: evidence of underlying Janus kinase–signal transducer and activator of transcription activation and successful treatment with tofacitinib. Damsky W, King BA. JAAD Case Rep 2016; 2: 502–4.

Case report of success in a recalcitrant chronic EM.

Treatment of recurrent erythema multiforme with adalimumab as monotherapy. Baillis B, Maize JC Sr. JAAD Case Rep 2017; 3: 95–7.

A severe relapsing EM major associated with HSV was not controlled by aciclovir and systemic steroids. Adalimumab 40 mg every 2 weeks for 6 months cleared the disease but there was a flare at 6 months after the drug was no longer administered.

Erythema nodosum

Bridget E. Shields, Amy Forrestel, Misha Rosenbach



Erythema nodosum (EN) is an inflammatory septal panniculitis that presents as tender, erythematous nodules and plaques distributed symmetrically on the extensor surfaces of the lower extremities. EN is thought to be a delayed-type hypersensitivity reaction and may be isolated and idiopathic, or, more commonly, a sign of an underlying systemic disease (outlined later). Individual lesions frequently resolve within 2–6 weeks, but persistent lesions and intermittent disease recurrence may occur. EN is often accompanied by systemic symptoms such as fever, fatigue, arthritis, cough, and gastrointestinal complaints.

MANAGEMENT STRATEGIES

Management of EN first requires investigation for an underlying etiology, including a detailed history, review of systems, and targeted evaluation. Numerous etiologies have been implicated, including chronic inflammatory states, infections, reactions to medications or hormones, and malignancies. Even after extensive evaluation, many cases are classified as idiopathic.

Many infectious agents have been associated with EN. Bacterial and protozoan causes include: *Streptococcus* (most common), *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Yersinia enterocolitica*, *Salmonella enteritidis*, *Giardia lamblia*, *Shigella*, *Klebsiella* spp., tuberculosis, brucellosis, psittacosis, cat scratch disease, chancroid, tularemia, rickettsiosis, leptospirosis, and *Campylobacter*. Viral causes include hepatitis B, hepatitis C, human immunodeficiency virus, and herpes simplex virus. Fungal triggers include blastomycosis, sporotrichosis, coccidioidomycosis, histoplasmosis, nocardiosis, and fungal kerions.

Chronic inflammatory conditions associated with EN include sarcoidosis (most common), inflammatory bowel disease (IBD), Behçet disease, Sweet syndrome, pyoderma faciale, and diverticulitis.

Medication-induced EN has been reported with use of oral contraceptives (most common) and other female hormone therapies, antibiotics (specifically penicillins and sulfonamides), iodides, bromides, quinolones, lidocaine injections, aromatase inhibitors, all-trans retinoic acid, propylthiouracil, granulocyte colony-stimulating factor, echinacea supplements, glatiramer acetate, valproate, non-steroidal antiinflammatory drugs (NSAIDs), thalidomide, and dapsone. Targeted chemotherapeutic agents such as BRAF and MEK inhibitors, and more recently the checkpoint inhibitor class of agents, have been described to cause an EN-like panniculitis. Multiple vaccines have been suggested as well, albeit in very small numbers – and the health benefits of vaccines outweigh the rare potential for this type of reaction.

Malignancies such as leukemias, lymphomas, myelodysplastic syndrome, and parathyroid carcinoma have rarely been implicated in triggering EN.

Skin biopsy is generally not necessary if the history and physical examination are suggestive of EN. Biopsies are typically performed in atypical cases, persistent or treatment-refractory cases, or cases where there is a broad differential diagnosis and a biopsy may help exclude alternative etiologies. Pathology classically demonstrates subcutaneous septal inflammation with limited extension into surrounding fat lobules. Inflammation may be acute or chronic, and can include histiocytes, foreign body giant cells, neutrophils, and eosinophils. Multinucleated giant cells ('Miescher granulomas') are occasionally seen. Other findings can include septal fibrosis and radial arrays of macrophages around blood vessels. If there is a concern for infectious panniculitis, tissue may be sent for culture and stains.

If identified, treatment or elimination of the underlying trigger will often lead to spontaneous remission of EN. This is the primary treatment strategy and should be emphasized in all cases; if there is an EN-triggering disease, it should be treated, and if there is an EN-associated medication, it should be discontinued. This may not be recommended in cases of molecular-targeted therapy.

Treatment of primary EN consists of bed rest, leg elevation, compression, NSAIDs, and potassium iodide. Naproxen and indomethacin have the most evidence in the treatment of EN, but aspirin, celecoxib, diclofenac, and ibuprofen have all been utilized. A reasonable starting dose of indomethacin is 50mg three times daily. Note that NSAIDs have also been reported as potential EN-inducing drugs, and in such cases treatment with NSAIDs is not advised. Potassium iodide is generally well tolerated, effective, and non-immunosuppressive but may not be widely available. Typical dosing is with a supersaturated solution of potassium iodide (SSKI) starting at 1–2 drops three times daily and gradually titrating up to 5 drops (often dissolved in orange juice to increase tolerability of taste) taken three times per day. One drop of SSKI contains approximately 50mg of iodide. SSKI tablets in 65mg and 130mg concentrations are also available. Side effects include hypothyroidism and hyperkalemia; rarely, concentrated iodide can induce a neutrophilic eruption (iododerma). SSKI should be used with caution in patients with dermatitis herpetiformis as it can flare the disease. Thyroid-stimulating hormone should be monitored monthly while on treatment.

In patients who fail these treatments, alternative therapies can be considered. *Prednisone* is highly effective and may be used in particularly refractory, widespread, or symptomatic patients to gain rapid control. Infection and malignancy should be ruled out before initiation. *Colchicine*, *hydroxychloroquine*, *dapsone*, and some immunomodulatory and immunosuppressive agents have anecdotal reports of efficacy.

Notably, while tumor necrosis factor (TNF)-alpha inhibitors have been efficacious in treating EN (especially in patients with underlying IBD), they have also been paradoxically associated with the development of EN.

Specific Investigations to Consider (not all are necessary in all patients)

- Complete blood count (with differential), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)
- Anti-streptolysin O (ASO) titer or anti-deoxyribonuclease B (anti-DNase B) titer, throat culture
- Urinalysis and urine pregnancy test
- Chest radiograph
- Purified protein derivative (PPD) standard tuberculosis skin test or interferon gamma release assay
- Skin biopsy

Erythema nodosum: a review. Soderstrom RM, Krull EA. *Cutis* 1978; 21: 806–10.

Streptococcal infection was the most common etiology, and sarcoidosis is the most common disease associated with EN.

All patients should have a chest radiograph, ASO titer, throat culture, and PPD/testing for latent tuberculosis.

Erythema nodosum: an evaluation of 100 cases. Mert A, Kumbasar H, Ozaras R, et al. *Clin Exp Rheumatol* 2007; 25: 563–70.

The results showed a 6:1 female predominance; 53% idiopathic and 11% streptococcal infections, 10% tuberculosis, 10% sarcoidosis, 6% Behçet, 5% drug reactions, 3% IBD, and 2% pregnancy.

First-Line Therapies

• NSAIDs	E
• Potassium iodide	B

Suppression of erythema nodosum by indomethacin. Ubogye Z, Persellin RH. *Acta Derm Venereol* 1982; 62: 265–7.

Three patients with EN secondary to streptococcal pharyngitis refractory to erythromycin, penicillin, and aspirin improved with indomethacin 100–150 mg for 2 weeks.

Chronic erythema nodosum treated with indomethacin. Barr WG, Robinson JA. *Ann Intern Med* 1981; 95: 659.

Idiopathic EN in a 32-year-old woman refractory to aspirin resolved with indomethacin 25 mg three times daily for 1 month.

Control of chronic erythema nodosum with naproxen. Lehman CW. *Cutis* 1980; 26: 66–7.

A 28-year-old woman with recurrent EN refractory to phenylbutazone and aspirin was treated with naproxen 250 mg orally twice daily for 1 month, with cessation of symptoms within 96 hours and clearing in 14 days. Relapsed with therapy cessation but recleared when naproxen restarted.

Potassium iodide in erythema nodosum and other erythematous dermatoses. Horio T, Danno K, Okamoto H, et al. *J Am Acad Dermatol* 1983; 9: 77–81.

Twelve of 16 patients treated with potassium iodide improved within a few days, with complete resolution in 10–14 days. Six had recurrent attacks, with resolution upon repeat dosing with

potassium iodide. Better outcomes were obtained with earlier treatment initiation.

Potassium iodide may be a reasonable choice for those patients who cannot tolerate NSAIDs or corticosteroids.

Treatment of erythema nodosum and nodular vasculitis with potassium iodide. Schultz EJ, Whiting DA. *Br J Dermatol* 1976; 94: 75–8.

Twenty-four of 28 patients with EN improved within 48 hours and resolved within 2 weeks with 300–900 mg daily of potassium iodide.

Potassium iodide in dermatology. A 19th century drug for the 21st century: uses, pharmacology, adverse effects, and contraindications. Sterling JB, Heymann WR. *J Am Acad Dermatol* 2000; 43: 691–7.

An excellent review article.

Second-Line Therapies

• Colchicine	D
• Hydroxychloroquine	E
• Prednisone	E

Traitement de l'érythème noueux par la colchicine. De Coninck P, Baclet JL, Di Bernardo C, et al. *Presse Med* 1984; 13: 680.

Five women were treated with colchicine (2 mg daily for 3 days, then 1 mg daily for 2–4 weeks) and improved within 72 hours. None recurred after treatment cessation.

Erythema nodosum treated with colchicine. Wallace S. *JAMA* 1967; 202: 144.

One patient with EN was successfully treated with colchicine.

A double-blind trial of colchicine in Behçet's syndrome. Yurdakul S, Mat C, Tüzün Y, et al. *Arthritis Rheum* 2001; 44: 2686–92.

Two-year randomized, double-blind, placebo-controlled study of 116 patients with Behçet syndrome. There were significantly fewer new attacks of EN among female patients on colchicine (1–2 mg/day) versus placebo. At trial end, 79% of female patients in the colchicine arm remained EN free compared with 39% of females in the placebo arm ($p=0.004$ by log-rank test). Additionally, the mean number of EN lesions was significantly less in the colchicine arm compared with placebo among the women (1.4 ± 3.9 versus 6.0 ± 14.9 , respectively; $p=0.002$).

Hydroxychloroquine in the treatment of chronic erythema nodosum. Alloway JA, Franks LK. *Br J Dermatol* 1995; 132: 661–70.

A 38-year-old woman with a 24-year history of EN with almost monthly flares refractory to aspirin and indomethacin was treated with hydroxychloroquine 200 mg orally twice daily. Within 3 months she had a dramatic reduction in lesions and remained stable for at least 6 months.

Hydroxychloroquine and chronic erythema nodosum. Jarrett P, Goodfield MJD. *Br J Dermatol* 1996; 134: 373.

A 52-year-old with idiopathic EN refractory to NSAIDs and prednisone improved with hydroxychloroquine 200 mg orally twice a day and prednisone 15 mg four times a day for 8 weeks. Prednisone was stopped, and 8 weeks later the

hydroxychloroquine dose was cut by half, but the patient experienced a flare, and the original dose was restarted. After 3 more months the hydroxychloroquine was stopped, although intermittent dosing was required.

Third-Line Therapies

• Dapsone	E
• Erythromycin	E
• Mycophenolate mofetil	E
• Etanercept	E
• Adalimumab	E
• Infliximab	E
• Prophylactic penicillin	E
• Vitamin B ₁₂ (if levels low)	E
• Tetracycline	E

Acne fulminans and erythema nodosum during isotretinoin therapy responding to dapsone. Tan B, Lear J, Smith A. Clin Exp Dermatol 1997; 22: 26–7.

Acne fulminans and EN that occurred in a patient 3 weeks after starting isotretinoin responded to dapsone without oral prednisone.

Dapsone for treatment of erythema nodosum. Song JS, Halim K, Vleugels RA, et al. Dermatol Online J 2016; 22.

Three patients with recurrent EN recalcitrant to standard therapies. Addition of dapsone resulted in resolution of EN in all three patients.

Extracorporeal monocyte granulocytapheresis was effective for a patient of erythema nodosum concomitant with ulcerative colitis. Fukunaga K, Sawada K, Fukuda Y, et al. Ther Apher Dial 2003; 7: 122–6.

A patient with ulcerative colitis and EN refractory to high-dose corticosteroids improved after monocyte granulocytapheresis once a week for 5 weeks. He was also on 5-aminosalicylic acid.

Severe erythema nodosum due to Behçet's disease responsive to erythromycin. Kaya TI, Tursen U, Baz K, et al. J Dermatol Treat 2003; 14: 124–7.

A patient with refractory Behçet disease and EN responded to coincidental treatment with erythromycin for erythrasma.

Use of mycophenolate mofetil in erythema nodosum. Boyd AS. J Am Acad Dermatol 2002; 47: 968–9.

A patient taking estrogen replacement with EN refractory to discontinuing hormone therapy and azathioprine cleared with mycophenolate mofetil 750 mg twice a day and remained clear after a slow taper.

Dermatologic manifestations of Crohn disease in children: response to infliximab. Kugathasan S, Miranda A, Nocton J, et al. J Pediatr Gastroenterol Nutr 2003; 37: 150–4.

One child with Crohn disease and resistant EN cleared with infliximab 5 mg/kg and was maintained on 6-mercaptopurine.

Treatment of chronic erythema nodosum with infliximab. Clayton TH, Walker BP, Stables GI. Clin Exp Dermatol 2006; 31: 823–4.

A 26-year-old woman with IBD and EN improved with infliximab.

Sweet's syndrome and erythema nodosum associated with Crohn's disease treated by infliximab. Vanbiervliet G, Anty R, Schneider S, et al. Gastroenterol Clin Biol 2002; 26: 295–7.

Patient with underlying Crohn disease who developed concurrent Sweet syndrome and EN, both of which resolved with infliximab.

Etanercept treatment of erythema nodosum. Boyd AS. Skinmed 2007; 6: 197–9.

One patient with a 5-year history of recalcitrant EN was treated with etanercept 25 mg subcutaneously twice. She was clear after 4 months. After 6 months the etanercept dose was reduced to 25 mg subcutaneously weekly.

Refractory chronic erythema nodosum successfully treated with adalimumab. Ortego-Centeno N, Callejas-Rubio JL, Sanchez-Cano D, et al. J Eur Acad Dermatol Venereol 2007; 21: 408–10.

A 79-year-old patient with chronic recalcitrant EN cleared with adalimumab 40 mg subcutaneously every 2 weeks and was clear after 7 months of follow-up.

Adalimumab for the treatment of Japanese patients with intestinal Behçet's disease. Tanida S, Inoue N, Kobayashi K, et al. Clin Gastroenterol Hepatol 2015; 13: 940–8. e3.

Twenty patients with active intestinal Behçet disease refractory to corticosteroids and/or immunomodulator therapies were given 160 mg adalimumab, 80 mg 2 weeks later, then 40 mg every other week for 52 weeks. Eighty-eight percent of the patients with EN cleared.

A case of fistulizing Crohn's disease and erythema nodosum managed with adalimumab. Quin A, Kane S, Ulitsky O. Nat Clin Pract Gastroenterol Hepatol 2008; 5: 278–81.

A 20-year-old female with EN and perianal fistula with sigmoid colitis with complete resolution following initiation of adalimumab 160 mg dose subcutaneously, followed by 80 mg at week 2, then 40 mg every other week.

Prophylaxis of recurrent erythema nodosum with penicillin. Bhalla M, Thami GP. Dermatology 2007; 215: 363–4.

Three patients with recurrent EN were cleared with monthly doses of intramuscular benzathine penicillin 2.4 million units. One patient had high ASO titers, and the other two had idiopathic biopsy-proven EN. All patients remained clear at 6 months.

The use of benzathine penicillin in streptococcal erythema nodosum: may it reduce recurrence? Aouam A, Hafsa M, Kooli K, et al. Presse Med 2019; 48: 1180–2.

Retrospective cohort study including 77 patients hospitalized with streptococcal EN. Patients with cutaneous nodules on the extensor lower legs consistent with EN who suffered preceding upper respiratory tract infection and elevated anti-streptolysin O antibody were enrolled. Following complete resolution of their acute EN, group A (24 patients) received antibiotic prophylaxis with intramuscular injection of benzathine penicillin G, 1.2 million IU (if <80 kg) and 2.4 million IU (if >80 kg) every 15 days. The comparison group B (53 patients) received no antibiotics. EN recurred in one patient in group A (4.1%) and in 16 patients in group B (30.2%). Rate of recurrence was significantly higher in the control group than the prophylactic group, $p=0.01$. Hazard ratio showed that prophylactic antibiotics with benzathine penicillin following an episode of streptococcal-induced EN reduced the risk of recurrence by 90% [HR 0.1, 95% CI 0.01–0.8].

Successful treatment of chronic erythema nodosum with vitamin B₁₂. Volkov I, Rudoy I, Press Y. J Am Board Fam Pract 2005; 18: 567–9.

One patient had EN resolve after being treated for a low serum B₁₂ level with twice-weekly injections of 1000 mcg of B₁₂.

Response of recalcitrant erythema nodosum to tetracyclines. Davis MD. J Am Acad Dermatol 2011; 64: 1211–2.

One patient with a renal transplant and recalcitrant EN resolved after 1 month of minocycline 100 mg twice daily. Minocycline was

discontinued because of hyperpigmentation. EN recurred within a week and resolved again with tetracycline 500 mg twice a day.

Role of tetracycline in recalcitrant erythema nodosum. Rohatgi S, Basavaraj KH, Ashwini PK, et al. Indian Dermatol Online J 2014; 5: 314–5.

A 40-year-old male with chronic recurrent EN cleared after 2 weeks of tetracycline 500 mg four times daily. The patient was switched to doxycycline and the EN recurred, so tetracycline was restarted with sustained complete regression for 6 months.

Erythrasma

Melissa C. Barkham, Brendan Khong



In its most typical form, erythrasma is characterized by well-defined, reddish-brown, flexural plaques that show fine scaling and no tendency to central clearing. It may also present with maceration of the toe webs.

The responsible organism, *Corynebacterium minutissimum*, is an inhabitant of normal human skin. Factors that predispose to clinically apparent infection include diabetes mellitus, obesity, human immunodeficiency virus (HIV), old age, and a humid environment.

MANAGEMENT STRATEGY

Erythrasma is often a trivial infection, but therapy may be requested because of the cosmetic appearance or because of pruritus. Coinfection with dermatophyte fungi or *Candida albicans* is common and may influence the choice of treatment.

Fusidic acid cream is the topical treatment of choice where no concomitant yeast or fungal infection is found. It is both effective and well tolerated. Despite the apparent efficacy of fusidic acid cream alone, a combination of oral and topical treatment for extensive or stubborn toe web infections might be more effective.

Topical imidazoles (miconazole, clotrimazole) are well tolerated and also effective against concomitant fungal or yeast infection.

There has been recent evidence for topical mupirocin 2% ointment as a treatment. However, more studies and comparison to placebo is required to evaluate its efficacy.

When the disease is extensive or when compliance with topical therapy is unlikely, oral antibiotics such as *single-dose clarithromycin* or *oral erythromycin* should be considered.

A combination of oral and topical treatment may be required for stubborn infections, particularly of the toe webs.

Specific Investigations

- Examination under Wood light
- Potassium hydroxide (KOH) preparation of skin scrapings

Rapid confirmation of the diagnosis is achieved by examination of the skin under Wood (long-wave ultraviolet) light. The characteristic coral-red fluorescence observed is due to the production of coproporphyrin III by the organism. Fluorescence may not be seen if the patient has bathed immediately before examination. Culture is unreliable because the organism does not always grow satisfactorily. Microscopy of skin scrapings is performed to seek evidence of concomitant infection, such as the presence of fungal hyphae or yeasts.

First-Line Therapies

• Fusidic acid cream	A
• Miconazole cream	C
• Clotrimazole cream	C
• Mupirocin 2% ointment	D
• Clindamycin lotion or solution	E

A comparison between the effectiveness of erythromycin, single dose clarithromycin and topical fusidic acid in the treatment of erythrasma. Avci O, Tanyildizi T, Kuskü E. *J Dermatolog Treatment* 2013; 24: 70–4.

Of the 151 patients included in this study, around two-thirds had toe web infections. A complete response (defined as no fluorescence) was observed in 30/31 patients treated with 2% fusidic acid cream twice daily for 14 days in this double-blind, placebo-controlled trial. The response was superior to oral clarithromycin (20/30), oral erythromycin (16/30), placebo cream (4/30), and placebo tablets (1/30). The authors acknowledged the limitations of the grading system of fluorescence used to assess response. They mention that the higher efficacy of fusidic acid cream over oral antibiotics might well be due to the removal of coproporphyrin III from the stratum corneum during topical applications.

A clinical double-blind trial of topical miconazole and clotrimazole against superficial fungal infections and erythrasma. Clayton YM, Knight AG. *Clin Exp Dermatol* 1976; 1: 225–32.

This was a comparison of the two preparations in dermatophyte infection, but 11 patients with erythrasma were also studied: six treated with miconazole, five with clotrimazole, both twice daily. All patients in both groups were free of infection at 4 weeks.

Topical treatment for erythrasma. Cochran RJ, Rosen T, Landers T. *Int J Dermatol* 1981; 20: 562–4.

Two cases cleared with two or three times' daily application of 2% aqueous clindamycin solution for 1 week. No recurrence was noted 6 weeks later.

Erythrasma: a report of nine men successfully managed with mupirocin 2% ointment monotherapy. Greywal T, Cohen PR. *Dermatol Online J* 2017; 23(5): 13030/qt9zh116s1.

A series of nine cases cleared with twice daily application of mupirocin 2% ointment within 2–4 weeks of therapy. There was no report of treatment-associated folliculitis. Mupirocin 2% ointment was not compared with placebo and clearance was measured by non-fluorescence under Wood lamp examination. No recurrence was noted during follow-up appointments. More studies are required.

Second-Line Therapies

• Single-dose clarithromycin	B
• Erythromycin	C

Erythrasma treated with single-dose clarithromycin. Wharton JR, Wilson PL, Kincannon JM. Arch Dermatol 1998; 134: 671–2.

Three patients treated with a single 1-g dose of clarithromycin showed no sign of residual disease at 2 weeks. Compliance is likely to be good with this regimen.

Interdigital Pedal Erythrasma treated with one-time dose of oral clarithromycin 1 g: Two case reports. Khan MJ. Clin Case Rep 2020; 8: 672–674.

Interdigital pedal erythrasma was successfully treated with a one-time dose of oral clarithromycin 1 g. This is ideal for patients who failed topical therapy or have mechanical or psychosocial

restrictions. Treatment provides better compliance, less gastric side effects, and lower treatment costs than oral alternatives.

Systemic or local treatment of erythrasma? A comparison between erythromycin tablets and Fucidin cream in general practice. Hamann K, Thorn P. Scand J Prim Health Care 1991; 9: 35–9.

This double-blind trial compared 14 days' treatment with erythromycin 500 mg twice daily, 2% fusidic acid cream twice daily, and placebo. Four weeks after treatment, 18 of 21 patients with erythromycin and 23 of 25 with fusidic acid cream were cured. Both were better than placebo.

Erythroderma

Arun C. Inamadar, Ragunatha Shivanna



Erythroderma (ED) is a skin reaction pattern presenting as an extreme state of anatomical and physiological dysfunction characterized by extensive erythema and scaling involving more than 90% of the body surface area.

Several skin disorders may evolve into erythroderma (Table 78.1): exacerbation of preexisting dermatoses (e.g., psoriasis, eczema, atopic dermatitis, pityriasis rubra pilaris, and pemphigus foliaceus), drug eruption, and cutaneous lymphomas (mycosis fungoides, Sézary syndrome, adult T-cell leukemia/lymphoma) are some of the common causes. Many cases remain idiopathic despite extensive search for the cause and in-depth laboratory investigations.

ED is associated with significant morbidity and mortality in addition to the variable prognosis inherent to underlying etiology.

MANAGEMENT STRATEGY

The precise diagnosis of erythroderma is essential for proper management and better therapeutic outcome. Erythroderma has a gradual and insidious onset except for drug-induced cases. Psoriasis is the most frequent cause of ED.

ED is a dermatological emergency necessitating immediate therapeutic intervention. The diagnosis of underlying cause of erythroderma and early recognition of consequences of erythroderma is crucial in reducing associated morbidity and mortality. The consequences of the erythroderma differ depending upon the etiology: vesiculobullous diseases like pemphigus foliaceus can end in acute skin failure and inflammatory disease (psoriasis, AD) and other disorders of keratinization (PRP) will culminate

in ED with a chronic course leading to chronic skin failure. The consequences of ED are due to failure of primary functions of the skin such as loss of an effective mechanical barrier, loss of thermoregulation from increased fluid loss via evaporation or exudation, and loss of protein due to the increased proliferative and metabolic activity with the risk of high-output cardiac failure. All these effects are greatest at the extremes of age.

The diagnostic clues can be uncovered by a detailed history, including comprehensive drug history comprising all over-the-counter and herbal remedies and thorough clinical examination. Table 78.2 lists the cutaneous examination clues for the diagnosis of diseases causing erythroderma. Drugs implicated in erythroderma described in the literature are anticonvulsants, antibiotics, non-steroidal antiinflammatory drugs, and even herbal medicines.

The clinicopathologic correlation is difficult because non-specific features of erythroderma may mask the specific features of an underlying dermatosis. Direct immunofluorescence studies may be of diagnostic utility in cases of erythroderma secondary to pemphigus foliaceus, bullous pemphigoid, graft-versus-host disease, and connective tissue disorders. Histopathology should be carried out as soon as possible and should be repeated in different areas and different stages of erythroderma. Immunohistochemistry techniques allow a better evaluation of the skin infiltrates, especially in cutaneous T-cell lymphoma (CTCL). Table 78.3 lists the investigations to be done and clinical parameters to be evaluated.

Initial management of all types of erythroderma is similar, even without an etiologic diagnosis. The main goal of management of erythroderma is restoring the functions of skin, and careful monitoring and prevention of infectious, metabolic, and systemic complications.

The first step is *discontinuation of any unnecessary medications* and appropriate workup. Bed rest and sedation should be advised when necessary. A sedative *antihistamine* such as *hydroxyzine hydrochloride* 25 mg twice daily is useful. *Regulating environmental temperature* is crucial since patients with this condition lose homeostatic body functions that prevent cooling or overheating. Ideally, room temperature must be kept at 30–32°C in order to slow catabolism and reduce the loss of calories through the skin. Skin barrier function can be improved with *colloid baths, wet compresses, along with emollient creams and low-potency topical corticosteroids*. Therapy must also include *nutrition*, preferably enteral nutrition, as it has also a protective effect on the intestinal mucosa and decreases bacterial colonization. Usually the number of calories required is 1500–2000 kcal/day. *Fluid balance* is a main focus in the management of ED. Once the percentage of the involved skin is established, *Ringer lactate (RL) infusion* of 1–2 mL/kg/% of involved skin must be started during the first 24 h.

A marked loss of exfoliated scales occurs that may reach 20–30 g/day. This contributes to the hypoalbuminemia commonly observed in ED. *Albumin* is recommended only if albumin serum level is <2.5 mg/dL. *Nutritional supplementation* is indicated if there is clinical evidence of pedal edema, or if biochemical values support for low serum protein, low serum proteins and reversal of albumin/globulin ratio are evident.

Wet wrap therapy (WWT) is an extremely effective treatment for acute erythrodermic eczema.

Bleach bath and antibiotics are advised if there is evidence of secondary infection. Routine use of antibiotics is contraindicated but there are specific indications for the use of antibiotics in ED, such as an increased number of bacteria cultured from the skin with selection of a single strain, sudden drop in temperature, deterioration in the patient's condition, and symptoms of infections pertaining to a particular system.

Table 78.1 Causes of erythroderma

1	Inflammation	• Psoriasis • Pityriasis rubra pilaris • Lichen planus • Eczemas
2	Infection and infestation	• Staphylococcal scalded skin syndrome • Toxic shock syndrome • Congenital cutaneous candidiasis • Dermatophytoses • Crusted scabies
3	Infiltration	• Sézary syndrome • Mycosis fungoides • Diffuse cutaneous mastocytosis • Internal malignancy
4	Ingestion	• Drugs • Alternative medicines • Systemic contact dermatitis
5	Inherited	• Ichthyosiform disorders • Primary immunodeficiency disorders • Metabolic disorders
6	Immunological	• Graft-versus-host disease • Dermatomyositis • Subacute cutaneous lupus erythematosus • Sarcoidosis
7	Idiopathic	No known etiological agent

From Inamadar AC, Rangunatha S. The rash that becomes an erythroderma. Clin Dermatol 2019;37(2):88–98, with permission from Elsevier.

The use of more specific pharmaceutical intervention requires careful consideration as directed by the etiology of the ED. Immunosuppressive drugs may be considered to be contraindicated if malignancy is suspected (particularly cutaneous lymphoma or paraneoplastic ED). When a firm diagnosis cannot be made, treatment may have to be directed at the most likely cause, based on the clinical and histologic features.

The rash that becomes an erythroderma. Inamadar AC, Rangunatha S. Clin Dermatol 2019; 37: 88–98.

A stepwise approach ensures completeness of clinical evaluation. The initial clinical presentation, cutaneous examination findings, and systemic clues reveal important information regarding the diagnosis, course, and prognosis of erythroderma. *The article is a very comprehensive account of rashes that progress to erythroderma.*

Acute skin failure: concept, causes, consequences and care. Inamadar AC, Palit A. Indian J Dermatol Venereol Leprol 2005; 71: 379–85.

The concept of skin failure is new to non-dermatologist clinicians and sketchy among many dermatologists. Here the pathomechanism of skin failure has been analyzed and a guideline for monitoring has been provided.

A practical approach to the diagnosis and treatment of adult erythroderma. Cuellar-Barboza A, Ocampo-Candiani J, Herz-Ruelas. Actas Dermosifiliogr 2018; 109: 777–90.

Table 78.2 Cutaneous examination clues for the diagnosis of diseases causing erythroderma

Sl no.	Cutaneous examination clues	Disease
1	Preexisting plaques, involvement of periumbilical area (infants), typical nail changes	Psoriasis
2	Preexisting eczematous/ lichenified flexural lesions, prurigo, sparing of diaper area (infants)	Atopic dermatitis
3	Black dots or follicular hyperkeratotic papules on proximal phalanx of fingers, islands of sparing of skin, 'orange' palmoplantar keratoderma	Pityriasis rubra pilaris
4	Annular and polycyclic erythematous plaques	Subacute cutaneous lupus erythematosus, dermatophytosis
5	Facial edema, purpuric rash on dependent areas	Drug reactions
6	Sparing of skin folds (deckchair sign) in elderly men	Papuloerythroderma of Ofuji
7	Macerated and malodorous intertriginous area, positive Nikolsky sign	Pemphigus foliaceus
8	Tenderness of skin, perioral radiating scale-crusts, positive Nikolsky sign	Staphylococcal scalded skin syndrome
9	Linear and swirled pattern of hyperkeratosis/ hyperpigmentation	Conradi–Hünemann–Happle syndrome
10	Scalp involvement with or without alopecia	Omenn syndrome
11	Erythema without scaling, Darier sign, doughy skin, flushing	Diffuse cutaneous mastocytosis
12	Marked periorificial eczematous lesions	Holocarboxylase synthetase deficiency
13	Multiple confetti-like normal skin	Reticulate ichthyosiform erythroderma (ichthyosis with confetti)
14	Leonine facies	Cutaneous T-cell lymphoma, chronic actinic dermatitis
15	Heliotrope rash, Gottron papules/sign, poikiloderma	Dermatomyositis

From Inamadar AC, Rangunatha S. The rash that becomes an erythroderma. Clin Dermatol 2019;37(2):88–98, with permission from Elsevier.

Table 78.3 Specific investigations

Baseline or routine investigations	Etiology directed/specific	Imaging studies	Clinical parameters
- Complete blood count - Liver function tests - Serial skin biopsies to histology - Total IgE - HIV serology - Potassium hydroxide preparation and fungal culture	- Blood culture - Screening for connective tissue disease - Immunodeficiency screen - Immunophenotyping of lymphocytes by flow cytometry - Sézary cell count in peripheral blood smear - T-cell receptor (TCR) gene rearrangement analysis by polymerase chain reaction (PCR) in the blood - High-throughput sequencing of T-cell receptor β gene - Lactate dehydrogenase - Protein electrophoresis - HTLV 1/2 serology - Skin biopsy to TCR gene rearrangement analysis - Lymph node excisional biopsy (if ≥ 1.5 cm or if abnormal characteristics are found, e.g., firm, irregular, clustered, or fixed) - Serum thymus and activation-regulated chemokines (TARC) levels	- Baseline chest X-ray (if acute respiratory distress syndrome [ARDS], later for comparison) - Computed tomography of thorax, abdomen, and pelvis (staging of CTCL, idiopathic erythroderma to search for internal malignancies)	- Pulse rate, respiratory rate - Temperature, level of consciousness - Urine output - Gastric emptying

The authors present a practical review of the etiology, diagnosis, and treatment of ED.

Diagnosing erythrodermic cutaneous T-cell lymphoma. Russell-Jones R. Br J Dermatol 2005; 153: 1–5.

A very useful review with an algorithm to help differentiate between erythroderma due to CTCL and ‘reactive’ causes of erythroderma. The author proposed three key procedures to determine the correct diagnosis for patients with chronic erythroderma of unknown etiology: biopsy of lesional skin; analysis of peripheral blood; and lymph node biopsy. Each sample should be analyzed for morphology, immunophenotype, and the presence of a T-cell clone.

Erythroderma with circulating atypical T-cells, likely Sézary syndrome. Ugonabo N, Kim R, Chen L, et al. Dermatol Online J 2019; 25: 10.

The authors present an erythrodermic patient with repeated biopsies demonstrating a spongiotic process that was found to have circulating, atypical T cells concerning for underlying erythrodermic T-cell leukemia, most closely related to Sézary syndrome. *The importance of serial biopsy is stressed.*

High-throughput sequencing of the T cell receptor β gene identifies aggressive early-stage mycosis fungoides. de Masson A, O’Malley JT, Elco CP, et al. Sci Transl Med 2018; 10(440).

Tumor clone frequency greater than 25% predicts aggressive course for CTCL. In patients with questionable histology, this test accurately diagnoses CTCL.

Ichthyosiform erythroderma revealing a severe combined immunodeficiency. [Article in French]. Ghariani Fetoui N,

Bousofara L, Hmida D, et al. Ann Dermatol Venereol 2020; 147: 131–4.

Neonatal erythroderma must be considered a warning sign of primary immunodeficiency requiring immediate immunological phenotyping as well as genetic testing for a definitive diagnosis.

Familial ‘benign’ pemphigus? Erythroderma and fatal outcome. Tansini PB, Boff AL, Weber MB, et al. An Bras Dermatol 2020; 95: 75–7.

The authors report an unusual case of generalized Hailey–Hailey disease with erythroderma and fatal outcome.

Erythroderma as first manifestation of squamous cell lung cancer: rare case report. Arandes-Marcocci J, Iglesias-Sancho M, Setó-Torrent N, et al. An Bras Dermatol 2020; 95: 67–70.

This case report demonstrates the need to search for a neoplasm in patients presenting with erythroderma, particularly in the presence of accompanying debilitating symptoms.

Drug induced exfoliative dermatitis: state of the art. Yacoub M-R, Berti A, Campochiaro C, et al. Clin Mol Allergy 2016; 14: 9

This is a very comprehensive review with in-depth discussion on prophylactic, supportive, and complications therapy of drug-induced exfoliative dermatitis (ED).

Lichenoid drug reaction due to anti-tubercular therapy presenting as erythroderma. Katara A, Arora P, Sardana K, et al. Dermatol Ther 2020; 33: e13169.

Lichenoid drug eruption (LDR) presenting as erythroderma is very rare. The authors report a case of exfoliative dermatitis secondary to LDR, which developed after 5 months of antitubercular therapy.

Norwegian scabies presenting as erythroderma in HIV: a case report. Paparizos V, Vasalou V, Velissariou E, et al. *Infez Med* 2019; 27: 332–5.

Crusted scabies is a rare and extreme manifestation of scabies that is observed mainly among immunosuppressed patients. Authors describe the case of a 55-year-old patient with a history of HIV infection and injection drug use. There should be a high degree of suspicion for this disease in patients with AIDS, even when the lesions do not have the classical appearance.

Paraneoplastic erythroderma: unusual presentation secondary to diffuse large B cell lymphoma. Lim PN, Fox CP, Pammi M, et al. *BMJ Case Rep* 2019; 12: e228412.

Paraneoplastic dermatoses can manifest as the first clinical sign of underlying malignancy, heralding a cancer diagnosis.

Bullous erythroderma: novel association of pityriasis rubra pilaris with bullous pemphigoid. Genovese G, Muratori S, Berti E, et al. *Clin Exp Dermatol* 2019; 44: 73–5.

Clinicians should be aware that concurrence of PRP and bullous erythroderma is a differential diagnosis to consider in patients with blistering erythroderma.

Erythroderma as a manifestation of leprosy. Baldissera RL, Shwetz GA, Fillus Neto J, et al. *An Bras Dermatol* 2019; 94: 89–92.

This report demonstrates that chronic multibacillary leprosy can manifest as erythroderma and thus should be included in the differential diagnosis.

Imatinib mesylate induced erythroderma. Lunge S, Bhise R. *J Assoc Physicians India* 2018; 66: 79–80.

Exfoliative dermatitis has been reported with imatinib in a 55-year-old female who initially presented with a maculopapular rash and developed erythroderma on continuation of the drug.

Pityriasis rubra pilaris-like erythroderma secondary to phosphoinositide 3-kinase inhibition. Dewan AK, Sowerby L, Jadeja S, et al. *Clin Exp Dermatol* 2018; 43: 890–4.

Phosphoinositide 3-kinase (PI3K) inhibitors are a class of small-molecule inhibitors approved for the treatment of certain leukemia and lymphomas.

Three patients on PI3K inhibitors for treatment of malignancy developed diffuse erythroderma and keratoderma. Clinical and histopathological findings were consistent with pityriasis rubra pilaris (PRP)-like reactions.

First-Line Therapies

• Bed rest	C
• Emollients	C
• Wet wrap technique (WWT)	D

Wet wrap dressings as a rescue therapy option for erythrodermic psoriasis. Navrotsky BRE, Nihi FM, Camilleri MJ, et al. *An Bras Dermatol* 2018; 93: 598–600.

Wet wrap dressings provide an ancillary treatment option for erythrodermic patients. Seven patients with erythrodermic psoriasis who responded promptly to WWT prior to the initiation of systemic treatment are reported.

Second-Line Therapies

• Topical steroids	C
• Psoralen and UVA therapy (PUVA)	C
• Oral corticosteroids/systemic steroids	C
• Reti-PUVA	E

Therapeutic options and prognosis of chronic idiopathic erythroderma in older adults. Ohga Y, Bolortuya B, Imafuku S. *Dermatol Ther* 2019; 32: e12977.

The authors have reported that chronic idiopathic erythroderma (CIE) that lasts for more than 3 months without specific cause occurs almost exclusively in older men. Twenty cases were identified, of which CIE was treated with oral corticosteroids, oral ciclosporin A (CsA), ultraviolet (UV) therapy, or a combination of these therapies. Low-dose oral CsA (50–100 mg/day) was the most effective treatment, which resulted in cures in four cases. UV therapy also effectively cured two subjects, and oral corticosteroids cured one patient. In patients that were treated with oral CsA or corticosteroids, the terminations of the treatments within 2–3 months resulted in relapses in multiple patients. Maintenance of the treatments for a certain period may be necessary in cases that involve treatments with these orally administered drugs.

Burns can be difficult to distinguish from erythroderma, making phototherapy problematic.

Third-Line Therapies

• Ciclosporin	B
• Other immunosuppressive drugs: methotrexate	B
• Systemic retinoids	E
• Biologics for psoriasis	B
• Topical lovastatin and cholesterol	E
• Topical simvastatin	E
• Apremilast	E
• Topical hypochlorite	E
• Extracorporeal photopheresis	C
• Bexarotene	D
• Rituximab	E
• Mogamulizumab/etoposide	E
• Lovastatin and cholesterol lotion	E

A systematic review of treatment strategies for erythrodermic psoriasis. Reynolds KA, Pithadia DJ, Lee EB, et al. *J Dermatol Treat* 2019 Nov 4 [Epub ahead of print].

This systematic review of the literature reveals a variety of immunomodulatory (ciclosporin, oral retinoids) and biologic therapies (secukinumab, ustekinumab, guselkumab, ixekizumab, and brodalumab) as effective molecules for treating erythrodermic psoriasis (EP).

Papuloerythroderma of Ofuji responding to treatment with ciclosporin. Sommer S, Henderson CA. *Clin Exp Dermatol* 2000; 25: 293–5.

A patient with papuloerythroderma of Ofuji responded to systemic steroids, but remission was not maintained on reduction of the dose. Ciclosporin was added, which led to rapid clearing of the skin, and remission was maintained after discontinuation of treatment.

Efficacy and safety of biologics in erythrodermic psoriasis: a multicenter, retrospective study. Viguier M, Pagés C, Aubin F, et al. *Br J Dermatol* 2012; 167: 417–23.

This study addresses the efficacy and safety of biologics (infliximab, adalimumab, etanercept, ustekinumab, and efalizumab) in 28 patients. Overall, 42% of patients with EP reached a 75% improvement of skin severity 10–14 weeks after starting biologics. Safety is mostly affected by infectious complications with skin origin.

Efficacy and safety of brodalumab in patients with generalized pustular psoriasis and psoriatic erythroderma: results from a 52-week, open-label study. Yamasaki K, Nakagawa H, Kubo Y, et al. *Br J Dermatol* 2017; 176: 741–51.

Improvement or remission was observed in 18 cases of psoriatic erythroderma over the course of this 52-week study.

Infliximab as sole or combined therapy, induces rapid clearing of erythrodermic psoriasis. Takahashi MDE, Castro LG, Romiti R. *Br J Dermatol* 2007; 157: 828–31.

This is an open-label, single-center study of seven patients with EP. One patient was treated with infliximab 5 mg/kg at weeks 0, 4, and 6 and methotrexate 15 mg/week. Four patients were treated with infliximab (same regimen as before) and acitretin 0.3–0.6 mg/kg. All five patients reported excellent outcome at week 6 after the third infusion.

Treatment of erythrodermic psoriasis with etanercept. Esposito M, Mazzotta A. *Br J Dermatol* 2006; 155: 156–9.

An open-label study of 10 patients with EP. Etanercept was administered as a 25-mg subcutaneous injection twice weekly; six achieved Psoriasis Area and Severity Index (PASI) 75 and two achieved PASI 50 at week 24. These improvements were noted as early as week 12 of the study.

Ustekinumab treatment of pityriasis rubra pilaris: a report of five cases. Napolitano M, Lembo L, Fania L, et al. *J Dermatol* 2018; 45: 202–6.

After three injections of ustekinumab, complete remission of skin lesions was achieved in four out of five cases and a significant clinical improvement was shown in one case. Ustekinumab may be a possible first-line treatment for PRP patients who are refractory to conventional therapies.

A case of erythrodermic psoriasis successfully treated with ixekizumab. Megna M, Gallo L, Balato N, et al. *Dermatol Ther* 2019; 32: e12825.

Ixekizumab, a fully human antiinterleukin (IL)-17A monoclonal antibody, is approved for moderate-to-severe plaque psoriasis, while its use in EP is off label. Authors report the case of a 66-year-old Caucasian female with EP successfully treated with ixekizumab.

Successful treatment of Netherton syndrome with ustekinumab in a 15-year-old girl. Volc S, Maier L, Gritsch A, et al. *Br J Dermatol* 2020 Jan 24 [Epub ahead of print].

Treatment of Netherton syndrome has always been challenging, but evidence is accumulating that an IL-17-dominant inflammatory response is found in orphan ichthyoses and that the inflammation may be targeted efficiently by ustekinumab, anti-TNF, and anti-IL-12/23 antibodies.

Secukinumab emerges as a rapidly effective therapy for pityriasis rubra pilaris. Bonomo L, Levitt JO. *Cutis* 2018; 101: 367–9.

The authors report two new cases of severe refractory PRP that responded rapidly to treatment with secukinumab, the IL-17A antagonist.

Complete resolution of erythrodermic psoriasis with first-line apremilast monotherapy. Krishnamoorthy G, Kotecha A, Pimentel J. *BMJ Case Rep* 2019; 12: e226959.

The authors report complete and longstanding resolution of EP with first-line apremilast monotherapy. Apremilast may be an effective option with comparatively minor side effects for EP.

Topical hypochlorite and skin acidification improves erythroderma of Omenn syndrome. Wat M, Olicker A, Meyerson H, et al. *Pediatrics* 2018; 141 (Suppl 5): S408–11.

This case reveals for the first time that dilute topical hypochlorite and skin pH restoration holds promise to control severe dermatitis associated with immunodeficiency and inflammatory syndromes with minimal side effects.

Extracorporeal photopheresis in Sézary syndrome: hematologic parameters as predictors of response. Evans AV, Wood BP, Scarisbrick JJ, et al. *Blood* 2001; 98: 1298–301.

Twenty-three patients with Sézary syndrome who received monthly (up to 1 year) extracorporeal photopheresis (ECP) as the sole therapy showed that 57% achieved a reduction in erythema of more than 25% from baseline.

Bexarotene therapy for mycosis fungoides and Sézary syndrome. Abbott RA, Whittaker SJ, Morris SL, et al. *Br J Dermatol* 2009; 160: 1299–307.

This retrospective study of 66 patients demonstrates that bexarotene is well tolerated in most patients and responses are well seen in almost half of patients with all disease stages. Two patients with erythroderma achieved complete response with bexarotene (one subsequently received reduced-intensity stem cell transplant and the other remains on bexarotene).

Non-endemic erythrodermic pemphigus foliaceus: a case with delayed diagnosis and response to rituximab. Patsatsi A, Kyriakou A, Douma S, et al. *J Dtsch Dermatol Ges* 2019; 17: 537–9.

Successful treatment of erythrodermic mycosis fungoides with mogamulizumab followed by etoposide monotherapy. Fujimura T, Tanita K, Sato Y, et al. *Case Rep Oncol* 2018; 11: 29–32.

In this report, the authors present a case of erythrodermic mycosis fungoides successfully treated with mogamulizumab followed by etoposide monotherapy.

CHILD syndrome: successful treatment of skin lesions with topical lovastatin and cholesterol lotion. Sandoval KR, Machado MCR, Oliveira ZNP, et al. *An Bras Dermatol* 2019; 94: 341–3.

The authors report a 2-month-old child treated with a topical solution containing cholesterol and lovastatin, with complete clearance of her CHILD nevus.

Erythrokeratodermas

Gabriele Richard



Courtesy of Dr Margarita Larralde, Buenos Aires, Argentina.

Erythrokeratodermas (EK) are a clinically and genetically heterogeneous group of rare inherited disorders of cornification characterized by two distinct morphologic features: localized hyperkeratosis and erythema. The best characterized form of EK is *erythrokeratoderma variabilis et progressiva* (EKVP). The hallmark of EKVP is the seemingly independent occurrence of transient, figurate erythematous patches and relatively fixed, sharply outlined hyperkeratotic plaques in a symmetrical distribution on the face and buttocks, and over extensor surfaces of the extremities. These hyperkeratotic plaques tend to increase in number and size before either stabilizing, regressing, or, rarely, disappearing later in life. Diffuse palmoplantar keratoderma (PPK) transgressing to the dorsal hands and feet is a common feature. EKVP is an autosomal dominant (ad) or, very rarely, autosomal recessive (ar) disorder caused by pathogenic sequence variants in one of the connexin genes, *GJB3* (connexin 31), *GJB4* (connexin 30.3), and *GJA1* (connexin 43) expressed in human epidermis, which result in disturbed gap junction intercellular communication or augmented hemichannel function.

Progressive symmetric erythrokeratoderma (PSEK) has been used to describe the presence of well-demarcated, localized-to-widespread hyperkeratotic plaques with underlying erythema in symmetrical distribution with diffuse PPK but without fleeting erythema. Nevertheless, genetic studies have revealed that 'PSEK' encompasses different forms of EK, each with distinct clinical features and molecular causes, and may be part of the EKVP spectrum. EK can be also a feature of other rare genetic syndromes, such as keratitis-ichthyosis-deafness syndrome;

loricrin keratoderma, mental retardation, enteropathy, deafness, peripheral neuropathy, ichthyosis, and keratoderma (MEDNIK) syndrome; severe dermatitis, multiple allergies, and metabolic wasting (SAM) syndrome; erythrokeratoderma-cardiomyopathy (EKC) syndrome; Chanarin-Dorfman syndrome; or *PNPLA1*-related autosomal recessive congenital ichthyosis.

Key features of *Olmsted syndrome* (ad/ar) are striking erythematous, sharply outlined, hyperkeratotic plaques with periorificial predilection on face, buttocks, groin, and abdomen; severe pruritus; and very painful, mutilating PPK impeding ambulation and reducing quality of life. Alopecia, nail dystrophy, propensity to cutaneous infections, follicular keratosis, and hyperhidrosis are less frequent features. The disorder can be caused by pathogenic gain-of-function variants in the *TRPV3* and *TRPM4* genes leading to constitutive activation of cation channels in the skin. Less common are variants in the *PERP* gene, encoding a component of desmosomes and other cell junctions, or in the X-linked *MBTPS2* gene, which produces a zinc metalloprotease essential for cholesterol homeostasis and endoplasmic reticulum stress response.

PSEK with or without thrombocytopenia (ar) results from defective acylceramide biosynthesis in the skin and bone marrow due to biallelic variants in the *KDSR* gene. The spectrum of severity is broad, including Harlequin or collodion presentation at birth and extensive erythrokeratoderma. Sharply demarcated, bright red, thick, verrucous or scaling plaques or streaks on the cheeks and chin, and in periorificial locations, as well as PPK, are characteristic. Half of reported individuals developed in infancy persistent and sometimes progressive thrombocytopenia, resulting in easy bruising or bleedings.

Erythrokeratoderma-spinocerebellar ataxia (type Giroux-Barbeau; SCA34) is a very rare form of ataxia (ad) originally described in a large French-Canadian family, which manifests during childhood with features of EKVP on hands, feet, and limbs. While skin findings disappear in the third decade of life, patients develop gait ataxia due to progressive cerebellar atrophy in the fourth and fifth decades. The causative genetic defects for SCA34 with or without EK involve the elongase gene *ELOVL4*, which encodes an enzyme for the elongation of very long-chain fatty acids and formation of complex lipids in the epidermis, retina, and central nervous system.

MANAGEMENT STRATEGY

Erythrokeratodermas (EK) are heritable, chronic disorders that often require lifelong treatment. Management depends on the location, severity, and extent of hyperkeratosis, which may vary over time and from patient to patient. The spectrum may range from fixed hyperkeratotic plaques over the knees and elbows to generalized hyperkeratosis with accentuated skin markings and peeling, or thickened plates with a spiny, hystrix-like appearance. Palmoplantar keratoderma (PPK) is a common feature and often debilitating due to pain from fissures, deep cracks, or digital ischemia when circular constriction bands form, and can limit ambulation and working with the hands.

The *topical management* of EK remains a therapeutic cornerstone, although it can be disappointing in some cases. Topical treatment of mild, localized hyperkeratosis is symptomatic and focuses on hydration, lubrication, and keratolysis. Whereas, in some patients, *emollients* such as petrolatum twice daily may suffice, most patients require topical treatment with *keratolytic agents*. Lactic acid (6%–12%) and urea applied once or twice daily in combination with emollients are effective, although their use may be limited, especially in children, because of irritation. Other α -hydroxy acids, salicylic acid (2%–6%), propylene glycol,

glycolic acid, vitamin D analogs (calcipotriol), or combinations of these are alternative treatment options. Topical treatment with *retinoids* and derivatives has been successful in some patients (especially with EKVP) but ineffective in others. Regimens with synthetic retinoids, such as short-contact topical tazarotene therapy combined with moisturizers, seem promising in EKVP. PPK may also benefit from soaking, mechanical removal, or surgical parings of excessive hyperkeratosis. In addition, avoidance of trauma to the skin, such as sudden temperature changes, friction, and mechanical irritation, may be beneficial.

Systemic retinoids are the treatment of choice in EK with extensive or generalized skin involvement. Although highly effective in EKVP, the therapeutic response in other EKs is less satisfactory and consistent, especially in Olmsted syndrome. The effects of acitretin or etretinate are superior to those of systemic isotretinoin. It seems advantageous to start at low doses of acitretin for 3–6 weeks and then to gradually increase the dose until the desired therapeutic effect is achieved. The minimal effective maintenance dose for EKVP is usually lower than for patients with other forms of EK or ichthyosis. Both morphologic components respond well to retinoid treatment, resulting in rapid, dramatic improvement or clearing of hyperkeratosis and significant moderation or resolution of erythema. Nevertheless, using retinoids should always be considered carefully, as chronic therapy is required for continuing results, and long-term side effects, especially in children, may ensue. Intermittent cycles of systemic retinoid treatment may be considered to balance between beneficial therapeutic and adverse effects.

In contrast to EKVP, topical and systemic treatment of Olmsted syndrome is challenging. Oral retinoids (acitretin, etretinate), corticosteroids, methotrexate, or surgical parings achieve only poor-to-moderate relief. Anecdotal *systemic rapamycin* (sirolimus), an mTOR pathway inhibitor, was effective in a few patients, reducing erythema, periorificial hyperkeratotic plaques, and pain, while PPK showed modest or no improvements. Pain medications (opioids, topical lidocaine, cold applications) were temporarily effective in managing chronic pain. One adult and two case series totaling seven children with Olmsted syndrome due to *TRPV3* mutations demonstrated rapid response and sustained improvement of debilitating PPK, flexural contractions, pruritus, pain, and other associated symptoms with oral *EGFR tyrosine kinase inhibitor erlotinib hydrochloride*. This treatment approach is based on a gain-of-function effect of pathogenic *TRPV3* variants, which in vitro and in transgenic mice leads to augmented activation of transient receptor potential cation channels in keratinocytes and may induce transactivation of EGFR with activation of the downstream mTOR pathway. No significant adverse effects have been reported; moderate hair loss and other minor side effects were tolerable or manageable with dose adjustments. Nevertheless, long-term treatment with EGFR inhibitors might be necessary in these patients, and requires careful monitoring and dose adjustments based on tolerability and side effects.

Anecdotally, *PUVA therapy* alone or combined with acitretin (Re-PUVA) has been beneficial in the treatment of PSEK, while narrowband UVB (NB-UVB) therapy has been effective for a patient with EKVP. Few patients have been reported with clearing of skin lesions under oral treatment with low-dose vitamin A or a polyaromatic retinoid (arotinoid ethylester).

The variable erythema in EKVP or residual periorificial lesions in Olmsted syndrome and KSDR-related PSEK often result in cosmetic concerns, which can be limited by masking uncovered skin with makeup and camouflage. Serious discomfort due to burning and pruritus at erythematous lesions can be therapeutically challenging. If systemic aromatic retinoid therapy alone fails to

reduce or suppress erythema and the associated burning and itching sensations, symptomatic relief has been achieved in anecdotal cases with systemic therapy using sedating *H₁-antihistamines*.

Specific Investigations

- Family history
- Histopathology

Erythrokeratoderma variabilis et progressiva. Ishida-Yamamoto A. *J Dermatol* 2016; 43: 280–5.

Review of clinical and histological features, treatment and underlying pathomechanisms of connexin-related EKVP. Connexin disorders of the skin. Richard G. *Clin Dermatol* 2005; 23: 23–32.

Summary of the clinical features and molecular genetics of EKVP due to causative variants in the connexin genes *GJB3* (Cx31) and *GJB4* (Cx30.3), as well as of other connexin disorders associated with *GJB2* (Cx26), *GJB6* (Cx30), and *GJA1* (Cx43).

The missense mutation G12D in connexin 30.3 can cause both erythrokeratoderma variabilis of Mendes da Costa and progressive symmetric erythrokeratoderma of Gottron. Van Steensel MAM, Oranje AP, van der Schroeff JG, et al. *Am J Med Genet Part A* 2008; 149A: 657–61.

Mutation analysis in five Dutch patients, two with PSEK and three with erythrokeratoderma variabilis (EKV), revealed the same G12D mutation in *GJB4* (Cx30.3) on the same ancestral haplotype, indicating that G12D is a Dutch founder mutation presenting with features of either EKV or PSEK. Systemic treatment of an adult male patient with PSEK with 20–40 mg etretinate during the wintertime reportedly resulted in satisfactory symptomatic relief. The name *erythrokeratoderma variabilis et progressiva* (EKVP) was introduced to indicate the clinical variability of this disorder.

Olmsted syndrome: clinical, molecular and therapeutic aspects. Duchatelet S, Hovnanian A. *Orphanet J Rare Dis* 2015; 10: 33. Thorough review of 73 published cases of Olmsted syndrome.

First-Line Therapies

• Emollients	D
• Topical keratolytics	D
• Topical retinoids	D
• Topical calcipotriol	E

Erythrokeratoderma variabilis successfully treated with topical tazarotene. Yoo S, Simzar S, Han K, et al. *Pediatr Dermatol* 2006; 23: 382–5.

Topical short-contact (15 min) treatment with tazarotene (0.05% gel) once a day followed by the topical corticosteroid (fluocinolone oil) application on moist skin and hydrophilic ointments resulted in complete remission of hyperkeratotic plaques and erythematous patches in a 16-month-old child with EKVP within 1 month. Emollients were continued during quiescent periods, and the aforementioned regimen during flares.

Tazarotene is a topical, receptor-selective retinoid.

Erythrokeratoderma variabilis. Report of 3 clinical cases and evaluation of the topical retinoic acid treatment. Lacerda

E, Costa MH, de Brito Caldeira J. *Med Cutan Ibero Lat Am* 1975; 3: 281–7.

Topical retinoic acid (0.1% cream) treatment of three EKVP patients substantially reduced hyperkeratosis. Discontinuation resulted in prompt relapse.

Progressive symmetrische erythrokeratoderme Darier-Gottron. Ott H, Lehmann S, Poblete-Guitierrez P, et al. *Hautarzt* 2004; 10: 994–6.

A 5-year-old boy with PSEK and severe PPK with flexural contractures on both hands was treated with topical steroids of various strength and urea without lasting improvement. Topical tretinoin 0.03% cream combined with hydrophilic ointments and physical therapy resulted in significant and lasting skin improvement and regression of contractures after a few weeks.

Progressive symmetric erythrokeratoderma: report of an Indian family. Gupta LK, Saini P, Khare AK, et al. *Int J Dermatol* 2014; 53: e317–9.

The proband of a multigenerational family with a clinical diagnosis of PSEK showed no appreciable improvement when treated with topical emollients, urea, and salicylic acid ointment, nor with acitretin 25 mg/day for 3 months.

Progressive symmetric erythrokeratoderma – response to topical calcipotriol. Bilgin I, Bozdağ KE, Uysal S, et al. *J Dermatol Case Rep* 2011; 5: 50–2.

A female with EK plaques in flexural regions and PPK was treated with 0.5 mg/kg/day isotretinoin for 2 months without improvement. Topical calcipotriol ointment applied twice daily yielded marked improvement of hyperkeratosis within 2 weeks.

Progressive symmetrical erythrokeratoderma on the face: a rare condition and successful treatment with calcipotriol. Tarkci N, Goencue K, Yueksel T, et al. *JAAD Case Rep* 2016; 2: 70–1.

A 7-year-old boy with sharply demarcated EK plaques on the face and elbows since 1 year of age showed complete resolution after twice daily topical application of calcipotriol ointment without adjuvant steroids or emollients for 1 month. Treatment was stopped without relapse in 4 months follow-up.

Second-Line Therapies

• Acitretin	C
• Isotretinoin	D
• EGFR inhibitors	D

Clinical and genetic heterogeneity of erythrokeratoderma variabilis. Common JEA, O'Toole EA, Leigh IM, et al. *J Invest Dermatol* 2005; 125: 920–7.

Four of six EKVP patients had a good-to-excellent response to 0.125–0.25 mg/kg/day oral acitretin. Two patients cleared completely, one on 20 mg acitretin daily. The remaining patients had residual hyperkeratosis, especially on the legs.

Erythrokeratoderma variabilis caused by a recessive mutation in GJB3. Fuchs-Telem D, Pessach Y, Mevorah B, et al. *Clin Exp Dermatol* 2011; 36: 406–11.

Third report of a consanguineous EKVP family due to biallelic mutations in *GJB3* (Cx31). A 14-year-old boy showed dramatic improvement followed by complete resolution of hyperkeratosis with low-dose treatment (25 mg four times a week)

with acitretin. The migratory erythematous patches, however, remained.

Both low-dose arotinoid ethylester and acitretin are effective in the treatment of familial erythrokeratoderma variabilis. Zhang L, Hong Y, Zheng S, et al. *Dermatol Ther* 2014; 27: 240–3.

Skin lesions in two siblings with EKVP cleared within 2 weeks/2 months with systemic therapy with either 0.03 mg/day arotinoid ethylester or 30 mg acitretin/day, respectively, and remained symptom free with reduced dosage for up to 6–12 months. Upon cessation of systemic treatment, relapse occurred after 3 or 6 months, respectively.

Case of erythrokeratoderma variabilis successfully treated with oral Vitamin A. Shizukawa H, Hiragun M, Hiragun T, et al. *J Dermatol* 2015; 42: 1124–5.

A 15-year-old Japanese female with EKVP was treated during childhood with topical vitamin D₃ analog and corticosteroids (unsuccessful), etretinate 0.4–0.6 mg/kg/day (marked improvement but discontinued due to side effects), and ciclosporin 2–3 mg/kg/day (discontinued due to side effects). At age 15, she was treated with oral vitamin A at 10,000 U/day, which was gradually increased by 10,000 U/day every 2 weeks. Improvements were noted at a dose of 30,000 U/day vitamin A, and showed a substantial benefit when the vitamin A dose was increased to 80,000 U/day without any adverse side effects. Halving the vitamin A dose exacerbated the skin lesions again.

Erythrokeratoderma variabilis with adult onset: report of a sporadic case unresponsive to systemic retinoids. Erbagci Z, Tuncel AA, Deniz H. *J Dermatol Treat* 2006; 17: 187–9.

Unusual case with onset of fixed EK at 23 years of age, without known molecular cause. Topical steroids, topical PUVA for 3 months, and keratolytics (10% salicylic acid) did not yield satisfactory results. Subsequent systemic isotretinoin (0.7 mg/kg/day) combined with topical ointments containing 20% urea showed no improvement after 3 months. Acitretin 0.5 mg/kg/day for 5 months was also unsuccessful. Sedating oral H₁-antihistamines were beneficial for relief of pruritus.

Late onset progressive symmetric erythrokeratoderma with pseudoainhum. Asha GS, Lakshmi DV, Shilpa K, et al. *Indian J Dermatol* 2016; 61(4): 448–50.

A 44-year-old male with history of PPK since 19 years of age and fixed EK plaques on the chest and lower abdomen for the past 3 years, which gradually spread to the back and extremities. Development of digital circular constriction bands led to autoamputation of two toes (pseudoainhum). The molecular cause and specific type of PSEK are unknown. Oral treatment with isotretinoin 20 mg/day showed marked improvement of EK on trunk within 6 weeks (unknown if pseudoainhum improved).

Mutations in KDSR cause recessive progressive symmetric erythrokeratoderma. Boyden LM, Vincent NG, Zhou J, et al. *Am J Human Genet* 2017; 100: 978–84.

Two patients with systemic isotretinoin therapy, of whom a 9-year-old child was treated with 1 mg/kg/day for 6 months, showed near complete resolution of skin lesions. The efficacy of retinoic acid derivatives was suggested to result from a retinoic acid-induced increase in sphingosine acetylation and sphingomyelinase upregulation, thus inducing alternate pathways for ceramide synthesis that can compensate in part for the defective ceramide de novo synthesis pathway in this condition.

Biallelic mutations in KDSR disrupt ceramide synthesis and result in a spectrum of keratinization disorders associated with thrombocytopenia. Takeichi T, Torrelo A, Lee JYW, et al. *J Invest Dermatol* 2017; 137: 2344–53.

In two males (15/19 years of age) with *KDSR*-related PSEK and isolated thrombocytopenia, oral acitretin at 0.5 mg/kg/day for several months showed no satisfying effect on skin features. In the younger patient, oral corticosteroids showed no optimal effect on thrombocytopenia. Splenectomy at 11 years of age improved thrombocyte count slightly, although recurrent nose bleeds persist. Another two patients had a more severe phenotype with premature birth and Harlequin ichthyosis presentation, necessitating neonatal intensive care in a humidified incubator. While the platelet count was normal at birth, it dropped drastically within the first weeks of life. One patient was treated with topical emollients, lubricating eye drops, and systemic acitretin, which yielded some reduction in the adherent scale, but he succumbed to pseudomonas septicemia. The other patient was not treated with systemic retinoids and the thickened scales gradually shed over 2 months, transitioning to generalized erythroderma and fine scaling, similar to *ABCA12*-associated Harlequin ichthyosis.

Epidermal growth factor receptor inhibition with erlotinib for palmoplantar keratoderma. Kenner-Bell BM, Paller AS, Lacouture ME. *J Am Acad Dermatol* 2010; 63(2): e58–9.

A 31-year-old female with Olmsted syndrome of unknown molecular cause has since childhood perioral keratoderma, alopecia, and painful, debilitating focal PPK with flexural contractions that render her unable to walk. Pain medications, twice-yearly surgical parings of hyperkeratotic masses on palms and soles, continuous oral retinoids, and keratolytics were not effective. Systemic treatment with the EGFR tyrosine kinase inhibitor *erlotinib* with 100 mg/day initially and 150 mg/day after several months rapidly cleared perioral lesions, improved PPK and range of motion considerably, and allowed walking without much discomfort. Albeit the drastic initial response could not be completely maintained, continuous treatment (over 2 years) in addition to oral retinoids showed no adverse effects.

Use of epidermal growth factor receptor inhibitor erlotinib to treat palmoplantar keratoderma in patients with Olmsted syndrome caused by *TRPV3* mutations. Greco C, Leclerc-Mercier S, Chaumon S, et al. *JAMA Dermatol* 2020; 156(2): 191–5.

Three teenage patients from two families with *TRPV3*-related Olmsted syndrome had massive, focal PPK, intolerable pain with erythromelalgia, severe growth delays, and variable neuropsychiatric symptoms. In one patient pain was resistant to opioids, and he showed temporary improvement of PPK and pain with oral steroids. All three patients were treated with the EGFR inhibitor *erlotinib* hydrochloride, with dosing around 2–2.5 mg/kg/day titrated to treatment effect, plasma levels, and tolerance for up to 12 months. A rapid improvement of pain and keratoderma with almost complete resolution was achieved within the first 3 months. Over time, pain medications could be discontinued, patients were able to wear shoes and walk unassisted, growth and weight parameters improved significantly, and depression, insomnia, and anorexia disappeared. Adverse side effects in all patients were mild acneiform eruptions and moderate diffuse alopecia. Nausea and abdominal pain observed in one patient resolved completely with dose adjustments to blood *erlotinib* concentrations under 500 ng/mL.

Targeted inhibition of the epidermal growth factor receptor and mammalian target of rapamycin signaling pathways in Olmsted syndrome. Zhan A, Duchatelet S, Lakdawala N, et al. *JAMA Dermatology* 2020; 156(2): 196–200.

Report of twins with *TRPV3*-related Olmsted syndrome, who developed after birth EK plaques on the scalp, periorbital and peroral skin, ears, neck, axillae, and genital area, and diffuse alopecia. Severe, painful PPK started around 6 months of age, and impeded normal ambulation. Initial treatment with the oral mTOR inhibitor sirolimus (rapamycin) 0.8 mg/m² twice daily, titrated to a trough concentration of 10–15 ng/mL, showed rapid improvements. After 5 months, erythema had resolved, periorificial hyperkeratotic plaques were substantially reduced, and pain and pruritus scores showed significant improvement. While no adverse effects were noted, PPK continued to progress. Sirolimus was discontinued after 9 months and subsequent treatment with the oral EGFR tyrosine kinase inhibitor *erlotinib* 2 mg/kg/day was started, yielding rapid improvement of PPK and pain scores, which was maintained over the 6-month treatment period. No short-term adverse effects were reported.

Two other male patients with a *TRPV3* missense variant and painful, diffuse PPK without periorificial erythrokeratoderma were initially treated with oral acitretin 10–15 mg daily for >4 years with limited improvement of PPK. Treatment with *erlotinib* 2 mg/kg/day yielded rapid improvement within days, which could be sustained, with almost complete resolution in one of the children.

Third-Line Therapies

• PUVA	E
• H ₁ -antihistamines	E
• mTOR inhibitors	E

Erythrokeratoderma variabilis: successful treatment with retinoid plus psoralen and ultraviolet A therapy. Yüksek J, Sezer E, Köseoglu D, et al. *Jpn Dermatol Assoc J* 2010; 725–7.

A female with EKV was first treated with 10 mg/day acitretin. After 1 week, PUVA therapy was added with 0.5 J/cm² UVA twice weekly, with incremental increases by 0.5 J/cm² UVA up to a cumulative dose of 129 J/cm². A significant improvement of hyperkeratosis and erythema was achieved after 3 months; then PUVA was stopped, and acitretin was continued for up to 9 months. Dry lips were the only side effect observed. Follow-up after discontinued Re-PUVA was not reported.

Case of erythrokeratoderma variabilis successfully treated with narrow band ultraviolet B. Okuda K, Nishida E, Tori K, et al. *J Dermatol* 2020; 47(1): e30–1.

Topical treatment of a 20-year-old female with EKVP due to a pathogenic *GJB3* variant with urea cream and steroid ointment was not effective. NB-UVB therapy with a starting dose of 0.3 J/cm² was increased by 20% each week to a maximum dose of 1.18 J/cm². At the 27th session, the EK plaques had regressed from 72% to 13% of involved surface on the lower extremities. A younger sibling with milder involvement was also treated with NB-UVB and hyperkeratotic lesions gradually resolved.

Erythromelalgia

Cato Mørk, Knut Kvernebo



Erythromelalgia (*erythros* – redness; *melos* – extremity; *algos* – pain) is an uncommon neurovascular disorder characterized by redness, increased skin temperature, and pain that usually occurs in the extremities. Pain is aggravated by warming and relieved by cooling. Symptoms and findings are usually intermittent and often missing during examination. Between attacks acrocyanosis, paresthesia, and Raynaud phenomenon may occur. Severity of symptoms varies from mild discomfort (most common) to disabling pain and gangrene. The diagnosis is often missed in cases with mild symptoms, whereas severe erythromelalgia is a rare condition.

Erythromelalgia can be a primary condition, or secondary to a primary microvascular event, or due to a primary autonomic nervous dysfunction. Regardless of etiology, the final common pathway of the pathogenesis includes maldistribution of skin perfusion with increased deep plexus thermoregulatory perfusion, and a relative lack of papillary nutritive perfusion with a corresponding degree of skin hypoxia.

A minority of erythromelalgia patients have a family history with genetic variants within the *SCN9A* gene encoding for the $Na_v1.7$, a voltage-gated sodium channel located on nerve endings. A gain-of-function mutation in this sodium channel may lead to aberrant sensory neuronal activity and extreme pain, particularly in response to heat. In our patient cohort of 35 patients with primary EM, 14.3% had potentially pathogenetic *SCN9A* variants.

MANAGEMENT STRATEGY

Before starting treatment, the patient's condition should be classified according to whether it is primary or secondary, the etiology

of secondary cases, and its severity. Erythromelalgia may be secondary to underlying diseases, such as myeloproliferative, connective tissue, cardiovascular, infectious, and neurologic diseases, diabetes mellitus, vasculitis, and neoplasia. If present, a primary condition should be optimally treated. There are many reports of remission after treatment of myeloproliferative disorders. Drug-induced erythromelalgia has been reported secondary to substances that may alter vasomotor tone, such as calcium channel blockers, bromocriptine, norepinephrine (noradrenaline), pergolide, ticlopidine, ciclosporin, iodine contrast, and mushroom and mercury poisoning.

All patients benefit from local *skin cooling* (applying cold towels or wet sand, walking on cold floors or even in the snow, air-conditioned rooms, or immersion in cooled water) and from elevation of the affected limb. Aggressive cooling may cause injury and worsen the erythromelalgia. Comfortable shoes to relieve pressure over the soles can help. Aggravating factors such as warmth, exercise, dependency of the extremity, tight shoes and gloves, and alcohol intake should be avoided.

No single medication or other treatment modality has been found to be universally helpful. Spontaneous remissions have occurred without treatment. There is a marked variation in therapeutic responses. Few controlled clinical trials have been published. The main reason may be the low prevalence, the heterogeneity of patients, and the lack of laboratory diagnostic methods.

Analgesics, including opiate analgesics, often have limited effect. Numerous drugs have been used with varying success. A few patients become free of symptoms with *acetylsalicylic acid*. Case reports or series of patients have shown beneficial effect with *vasodilators* (prostaglandin E_1 /prostacyclin or analogs, sodium nitroprusside, naftidrofuryl, calcium channel blockers). Other drugs that may be of benefit are *sodium channel blockers*, *antidepressants*, and *anticonvulsants*.

Numerous treatment alternatives based on case reports have been presented in the literature, such as topical *amitriptyline/ketamine*, *lidocaine*, *capsaicin*, *midodrine*, and *nitroglycerin*. Anecdotally, *ketanserin*, *methysergide*, *pizotifen*, β -blockers, *cycloheptadine* or other *antihistamines*, *carbamazepine*, *clonazepam*, *corticosteroids* or other *immunosuppressants*, *pentoxifylline*, *phenoxybenzamine*, *opiates*, *prazosin*, and *pregabalin* have been presented as effective. *Hyperbaric oxygen* treatment, *spinal cord stimulation*, *thalamic stimulation*, and *epidural blocks* have also been proposed. *Sympathectomy* has been beneficial in some patients and in other patients caused worsening of symptoms. Treatment modalities such as *hypnosis*, *biofeedback*, and learning to avoid triggers can be beneficial for coping with pain. A survey of members of The Erythromelalgia Association (TEA, erythromelalgia.org) shows that more than 50 therapeutic regimens have been tried out. TEA is a non-profit organization that may be helpful in providing information, awareness, and support.

Specific Investigations

- Full blood count with white cell differential count
- Serum chemistry, including blood sugar
- Antinuclear antibody and relevant rheumatologic tests
- Skin biopsy may be considered

Nonspecific capillary proliferation and vasculopathy indicate skin hypoxia in erythromelalgia. Kalgard OM, Clausen OP, Mellbye OJ, et al. Arch Dermatol 2011; 147: 309–14.

Platelet-mediated erythromelalgic, cerebral, ocular and coronary microvascular ischemic and thrombotic manifestations in patients with essential thrombocythemia and polycythemia vera: a distinct aspirin-responsive and Coumadin-resistant arterial thrombophilia. Michiels JJ, Berneman Z, Schroyens W, et al. Platelets 2006; 17: 528–44.

Erythromelalgia – a thrombotic complication in chronic myeloproliferative disorders. Tarach JS, Nowicka-Tarach BM, Matuszek B, et al. Med Sci Monit 2000; 6: 204–8.

Erythromelalgia is seen secondary to platelet aggregation and peripheral microvascular occlusion in myeloproliferative disorders and, untreated, may progress to painful acrocyanosis and even peripheral gangrene. Remission is observed after treatment of the myeloproliferative disorder.

Review of primary and secondary erythromelalgia. Mann N, King T, Murphy R. Clin Exp Dermatol 2019; 44: 477–82.

A brief, excellent overview of the diagnosis and management of primary and secondary forms of erythromelalgia.

First-Line Therapies	
• Treatment of underlying disease	C
• Aspirin	D
• Prostaglandins/prostacyclin or oral analogs	A

Treatment of secondary erythromelalgia addresses treatment of the primary diseases or conditions, and elimination of pharmacologic substances. A beneficial effect on the symptoms of erythromelalgia after successful treatment or elimination of the primary condition indicates a causal relationship.

Aspirin-responsive, migraine-like transient cerebral and ocular ischemic attacks and erythromelalgia in JAK2-positive essential thrombocythemia and polycythemia vera. Michiels JJ, Berneman Z, Gadisseur A, et al. Acta Hematol 2015; 133: 56–63.

Aspirin 250–500 mg daily or less may completely abolish the symptoms in erythromelalgia secondary to myeloproliferative conditions. The response is probably due to the antiplatelet effect. A reduction of platelet numbers by cytostatic treatment may also lead to relief.

The Erythromelalgia Association Survey 2003. www.erythromelalgia.org.

In a survey, 128 respondents had used aspirin (80–250 mg daily): 4 reported complete, 17 moderate, and 22 minimal relief; 78 had no improvement; and 6 reported worsening of their symptoms.

Aspirin is the first-line therapy if without contraindications to its use.

Erythromelalgia – A condition caused by microvascular arteriovenous shunting. Kvernebo K. Vasa 1998; 27: 3–39.

Based on the hypothesis of arteriovenous shunting, prostaglandin E₁ (PGE₁) and prostacyclin were tried as an intravenous infusion to enhance nutritive skin perfusion in severe erythromelalgia. In 9 of 10 patients, PGE₁ given as a continuous infusion for 3 days, starting with 6 ng/kg/min, then 10 ng/kg/min, and finally 12 ng/kg/min, induced remission from 3 months to 2 years. Two children were cured (observation time after treatment >25 years).

Prostacyclin reduces symptoms and sympathetic dysfunction in erythromelalgia in a double-blind randomized pilot

study. Kalgaard OM, Mørk C, Kvernebo K. Acta Derm Venereol 2003; 83: 442–4.

Significant reduction in symptoms and sympathetic dysfunction were demonstrated in eight patients treated with prostacyclin infusion compared with four patients with placebo infusion.

The prostaglandin E1 analog misoprostol reduces symptoms and microvascular arteriovenous shunting in erythromelalgia – a double-blind, crossover, placebo-compared study. Mørk C, Salerud EG, Asker CL, et al. J Invest Dermatol 2004; 122: 587–93.

Oral misoprostol (0.4–0.8 mg/day) reduced symptoms significantly more than placebo. Misoprostol is recommended as a first-line treatment, although many patients do not respond.

Second-Line Therapies	
• Topical: amitriptyline/ketamine, midodrine, capsaicin, lidocaine	C
• Sodium channel blockers (lidocaine, mexiletine, bupivacaine, XEN402)	C, D
• Pregabalin, gabapentin	D
• Antidepressants	D

Topical amitriptyline combined with ketamine for the treatment of erythromelalgia: a retrospective study of 36 patients at Mayo Clinic. Poterucha TJ, Weiss WT, Warndahl RA, et al. J Drugs Dermatol 2013; 12: 308–10.

The authors reported 75% improvement in pain with topical application of a compounded amitriptyline–ketamine formulation. The medication was well tolerated.

Topically applied midodrine, 0.2%, an α 1-agonist, for the treatment of erythromelalgia. Davies MD, Morr CS, Warndahl RA, et al. JAMA Dermatol 2015; 151: 1025–6.

Of 12 patients, 11 improved, with only two of the 12 having adverse reactions (one gastrointestinal discomfort, and the other displaying an increase in blood pressure).

The use of capsaicin cream in a case of erythromelalgia. Muhiddin KA, Gallen IW, Harries S, et al. Postgrad Med J 1994; 70: 841–3.

A 68-year-old woman with erythromelalgia responded to a twice-daily application of capsaicin cream 0.025% within 48 hours.

Lidocaine patch for pain of erythromelalgia: follow-up of 34 patients. Davis MD, Sandroni P. Arch Dermatol 2005; 141: 1320–1.

Anesthetic agents (lidocaine, bupivacaine, mexiletine) that non-selectively partially block the sodium channels may be used topically, intravenously, orally, epidurally, or intrathecally. A 90% reduction in pain was demonstrated with lidocaine IV infusion on a trial basis, but it has a narrow therapeutic window with significant cardiac, cognitive, and motor side effects. A 5% lidocaine patch for 12 hours/day was found helpful as first-line and adjunctive treatment of severely affected patients with erythromelalgia: 16 patients had no improvement, but 18 patients had a 5–90% improvement in pain score.

Treatment of Na_v1.7-mediated pain in inherited erythromelalgia using novel sodium channel blocker. Goldberg YP, Price N, Namdari R, et al. Pain 2012; 153: 80–5.

An exploratory, randomized, double-blind, two-period, crossover pilot study in four *SCN9A* mutation-proven inherited erythromelalgia patients using the orally administered $\text{Na}_v1.7$ antagonist XEN402 demonstrated alleviation of pain.

Pharmacological reversal of a pain phenotype in iPSC-derived sensory neurons and patients with inherited erythromelalgia. Cao L, McDonnell A, Nitzsche A, et al. *Sci Transl Med* 2016; 8: 335–56.

The results for selective sodium channel blockers are promising for patients with variants in the *SCN9A* gene. This is not yet a practical alternative because of limited availability of genetic testing and access to these agents in clinical practice.

Mexiletine as a treatment for primary erythromelalgia: normalization of biophysical properties of mutant L858F $\text{Na}_v1.7$ sodium channels. Gregg R, Cox JJ, Bennett DL, et al. *Br J Pharmacol* 2014; 171: 2255–63.

Mexiletine, an orally available form of lidocaine, has a normalizing effect on the pathologic gating properties of the L858F gain-of-function mutation in $\text{Na}_v1.7$; however, similar to lidocaine, there is variable clinical response

Response of primary erythromelalgia to pregabalin therapy. Kalava K, Roberts C, Adair JD, et al. *J Clin Rheumatol* 2013; 19: 284–5.

Using pregabalin at a dose of 100 mg three times a day, improvement was noted within 6 weeks in a 14-year-old girl.

Pediatric erythromelalgia: a retrospective review of 32 cases evaluated at Mayo Clinic over a 37-year period. Cook-Norris RH, Tollefson MM, Cruz-Inigo AD, et al. *J Am Acad Dermatol* 2012; 66: 416–23.

Earlier treatment with gabapentin (2/6) and antidepressants (4/10) was reported as very or somewhat helpful. Both medications are started at a low dose and titrated to effect.

Treatment of familial erythromelalgia with venlafaxine. Firmin D, Roduedas AM, Greco M, et al. *J Eur Acad Dermatol Venerol* 2007; 21: 836–7.

Venlafaxine helped the mother but not her two sons with erythromelalgia.

Third-Line Therapies

• Sodium nitroprusside	D
• Calcium channel blockers	C
• Magnesium	D

Erythromelalgia – a condition caused by microvascular arteriovenous shunting. Kvernebo K. *Vasa* 1998; 27: 3–39.

Sodium nitroprusside intravenously for 7 days in increasing doses (1, 3, and 5 mcg/kg/min) was successful in two patients with severe acute-onset erythromelalgia. The effect was accompanied by normalization of skin perfusion and transcutaneous oximetry.

Erythromelalgia: new theories and new therapies. Cohen JS. *J Am Acad Dermatol* 2000; 43: 841–7.

Various calcium channel blockers (amlodipine, nifedipine, diltiazem) may be helpful in approximately 25% of patients with erythromelalgia ($n=43$). As they can cause or exacerbate symptoms, they should be used with caution and with the use of short-acting drugs initially.

They are frequently used, but documentation for beneficial effect is sparse (6 of 14 patients). Their mechanism of action may be smooth muscle relaxation and reduced vascular responses elicited by β_2 -adrenoceptors.

High-dose oral magnesium treatment of chronic, intractable erythromelalgia. Cohen JS. *Ann Pharmacother* 2002; 36: 255–60.

Magnesium is a naturally occurring calcium channel blocker. Eight of 13 patients reported improvement, four no response, and one deterioration using magnesium in various doses and forms, starting at 350–400 mg/day and titrated to effect or limited by diarrhea as an adverse effect.

Erythropoietic protoporphyria

Maureen B. Poh-Fitzpatrick



In this metabolic disorder, a genetically determined ferrochelatase enzyme deficiency in bone marrow erythroid cells causes excessive protoporphyrin levels in erythrocytes, plasma, liver, bile, and feces. Protoporphyrin is a photoactive heme synthesis intermediary. In the skin, its exposure to long-wave ultraviolet (UV) or visible-light radiation can elicit oxygen-dependent acute cutaneous phototoxicity. Protoporphyrin undergoes hepatobiliary excretion, facilitating cholelithiasis. Protoporphyrin hepatotoxicity may progress to irreversible liver failure. Hypochromic microcytic anemia, when present, is typically mild and infrequently requires treatment. A rare, phenotypically similar disorder, X-linked dominant protoporphyria (XLP), caused by gain-of-function mutations in the erythroid-specific 5-aminolevulinic acid synthase gene, has a larger ratio of erythrocyte zinc-protoporphyrin to metal-free protoporphyrin than does erythropoietic protoporphyria (EPP). It is generally amenable to the same therapies.

MANAGEMENT STRATEGY

Protoporphyrin photosensitivity typically requires *sun avoidance* (lifestyle changes, protective clothing, physical barriers), which may lead to vitamin D deficiency. *Topical sunscreens* containing *titanium dioxide*, *zinc oxide*, *iron oxide*, or *dihydroxyacetone* block or filter long-wave ultraviolet (UV) and visible-light spectra but offer limited relief. Patients sensitive to light from computer, television, or phone screens or room lighting may benefit from eliminating or filtering offending devices (https://en.wikipedia.org/wiki/Erythropoietic_protoporphyria).

Epidermal melanization and hyperplasia achieved with *ultraviolet B (UVB) phototherapy*, or an *α-melanocyte-stimulating hormone analog (afamelanotide)*, can increase sunlight tolerance. Oral agents believed to photoprotect by quenching excited oxygen species include *β-carotene*, *cysteine*, *vitamin E*, and *vitamin C*. *Antihistamines*

may attenuate phototoxic flaring. Gallstones are managed *surgically*. Exacerbators of protoporphyrin-induced hepatotoxicity (alcohol, cholestatic drugs [including medicinal estrogens], dietary carbohydrate restriction) are best avoided. *Vaccination* against hepatitis A and B is recommended. Deteriorating liver function is only sporadically reversible by *enteric sorbents* (*cholestyramine*, *activated charcoal*) that interrupt enterohepatic porphyrin circulation, *bile acids* (to stimulate biliary protoporphyrin secretion), *blood transfusion or exchange*, *hematin infusion*, *glucose loading* (to retard endogenous porphyrinogenesis), *iron* (to increase protoporphyrin conversion to heme), or various combinations thereof. *Cimetidine* is postulated to inhibit porphyrinogenesis. End-stage liver disease warrants *liver transplantation*, aided by measures to reduce preoperative, intraoperative, and postoperative porphyrin levels (*exchange transfusion*, *hematin infusion*, *plasmapheresis*, *vitamin E*). Operating room lamps should be filtered to exclude wavelengths damaging to porphyrin-photosensitized skin and internal organs. *Hematopoietic cell transplantation* has been curative in highly selected cases and is optimal prevention for protoporphyrin hepatopathy in native or transplanted livers.

Specific Investigations

- Porphyrin analyses in erythrocytes (including metal-free: zinc-protoporphyrin ratio), serum or plasma, urine, feces
- Hematologic profile, iron studies if anemic
- Liver function profile, liver imaging, liver biopsy as clinically indicated
- Mutation analysis (for diagnostic confirmation and family counseling)
- Vitamin D assessment, bone density scan

Liver failure occurs in <5% of all cases. Because urine is typically free of excess porphyrins in uncomplicated protoporphyria, surveillance for coproporphyrinuria may discover patients with asymptomatic hepatic dysfunction.

Erythropoietic protoporphyria. Lecha M, Puy H, Deybach JC. Orphanet J Rare Dis 2009. doi: 10.1186/1750-1172-4-19.

Erythropoietic protoporphyria and X-linked protoporphyria: pathophysiology, genetics, clinical manifestations, and management. Balwani M. Mol Genet Metab 2019. doi: org/10.1016/j.ymgme.2019.01.020 [Epub ahead of print].

Protoporphyria overviews.

First-Line Therapies

• Avoidance of sunlight and harmful radiation from artificial light sources	
• Topical sunscreens, physical barriers or filters	C
• β-carotene	B
• Afamelanotide	A
• Vitamin D and calcium	D

Efficiency of opaque photoprotective agents in the visible light range. Kaye ET, Levin JA, Blank IH, et al. Arch Dermatol 1991; 127: 351–5.

Efficacy and cosmetic quality of sunscreens containing zinc oxide, titanium dioxide, and iron oxide.

Erythropoietic protoporphyria: IV. Protection from sunlight. Fusaro RM, Runge WJ. Br Med J 1970; 1: 730–1.

Seven patients had prolonged sunlight tolerance after applying a 3% dihydroxyacetone and 0.13% lawsone skin cream causing stratum corneum browning.

Beta-carotene therapy for erythropoietic protoporphyria and other photosensitivity diseases. Mathews-Roth MM, Pathak MA, Fitzpatrick TB, et al. Arch Dermatol 1977; 113: 1229–32.

Of 133 patients with EPP, 84% had a threefold increase in sunlight tolerance after ingesting pharmaceutical-grade β -carotene now available without prescription (Lumitene, Tishcon Corp.).

Doses producing serum levels of ≈ 800 mcg/dL (children: 30–120 mg/day, adults: 120–300 mg/day, in 2–3 mealtime doses) should be started 4–6 weeks before seasonal symptoms are anticipated. Efficacy varies and is often nil. Contraindicated in smokers due to increased lung cancer among heavy smokers treated with β -carotene in cancer prevention trials.

Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria. Biolcati G, Marchesini E, Sorge F, et al. Br J Dermatol 2015; 172: 1601–12.

Afamelanotide for erythropoietic protoporphyria. Langendonk JG, Balwani M, Anderson KE, et al. N Engl J Med 2015; 373: 48–59.

Afamelanotide increases skin melanization and may have other beneficial effects. Clinical trials of a subcutaneously implantable form have involved ≈ 300 protoporphyria patients worldwide. Approved for prevention of phototoxicity in adults with EPP by the European Medicines Agency (2014), and by the US Food and Drug Administration (2019).

Osteoporosis in patients with erythropoietic protoporphyria. Biewenga M, Matawlie RHS, Friesema ECF, et al. Br J Dermatol 2017; 177: 1693–8.

Among 44 EPP patients, 50% had low plasma vitamin D and 59% had low bone mineral density. Osteopenia/osteoporosis mitigation by following fracture-prevention measures including vitamin D and calcium supplementation and increased bone-strengthening physical activity is recommended.

Second-Line Therapy

- Phototherapy (narrowband UVB)

D

Narrow-band (TL-01) UVB phototherapy: an effective preventative treatment for the photodermatoses. Collins P, Ferguson J. Br J Dermatol 1995; 132: 956–63.

Six EPP patients had increased sunlight tolerance after serial narrowband UVB treatments.

Third-Line Therapies

• Cysteine	A
• Antihistamines (including cimetidine)	D, (E)
• Vitamin E	D
• Vitamin C	A
• Iron	D
• Cholestyramine, activated charcoal	D
• Blood transfusion or exchange	D
• Hematin infusion	D
• Plasmapheresis	D
• Bile acids	D
• Liver transplantation	B
• Hematopoietic cell transplantation	D

Long-term treatment of erythropoietic protoporphyria with cysteine. Mathews-Roth MM, Rosner B. Photodermatol Photoimmunol Photomed 2002; 18: 307–9.

Forty-seven patients received cysteine 500 mg twice daily in this phase III 3-year trial. Patient history and light exposure diaries were kept; some patients were phototested. Cysteine significantly increased light tolerance subjectively and objectively.

Inhibition of photosensitivity in erythropoietic protoporphyria with terfenadine. Farr PM, Diffey BL, Matthews JNS. Br J Dermatol 1990; 122: 809–15.

Terfenadine 60–120 mg twice daily for 48 days significantly reduced the flare surrounding, but not the erythema within, blue-light phototest sites on seven subjects, compared with pretreatment reactions.

Antihistamines have provided limited relief in clinical practice.

Cimetidine reduces erythrocyte protoporphyrin in erythropoietic protoporphyria. Yamamoto S, Hirano Y, Horie Y. Am J Gastroenterol 1993; 88: 1465–6.

This H_2 receptor antagonist (800 mg four times daily orally) was given to a patient with protoporphyric liver disease. Erythrocyte protoporphyrin fell from 16,000 to 11,000 mcg/dL during treatment. Inhibition of heme synthesis by cimetidine was postulated.

Only three porphyrin measurements were obtained: before and immediately after 2 weeks of cimetidine and 2 weeks after discontinuation.

Novel treatment using cimetidine for erythropoietic protoporphyria in children. Tu JH, Sheu SL, Teng JM. JAMA Dermatol 2016; 152: 1258–61.

Improved photosensitivity, erythrocyte protoporphyrins, and hepatic transaminases reported after cimetidine treatment of three children. Confirmatory studies needed.

A case of erythropoietic protoporphyria with liver cirrhosis suggesting a therapeutic value of supplementation with alpha-tocopherol. Komatsu H, Ishii K, Imamura K, et al. Hepatol Res 2000; 18: 298–309.

A patient with severe protoporphyric hepatopathy received intravenous vitamin E 500 IU/day. Erythrocyte protoporphyrins decreased; liver function improved. Sixteen weeks later, full clinical and biochemical recovery was noted.

Vitamin E has been used sporadically in protoporphyria, usually as adjunctive therapy.

A double-blind, placebo-controlled, crossover trial of oral vitamin C in erythropoietic protoporphyria. Boffa MJ, Ead RD, Reed P, et al. Photodermatol Photoimmunol Photomed 1996; 12: 27–30.

Vitamin C 1 g/day orally for 4 weeks was subjectively assessed by 9 of 12 patients to be associated with less photosensitivity than placebo, but the data did not reach significance.

Antioxidants such as vitamins C and E are postulated to quench porphyrin-generated oxyradicals in vivo.

Iron therapy for hepatic dysfunction in erythropoietic protoporphyria. Gordeuk VR, Brittenham GM, Hawkins CW, et al. Ann Intern Med 1986; 105: 27–31.

Carbonyl iron 400–4000 mg/day orally was given for 15 weeks to a patient with protoporphyria, iron-deficiency anemia, and liver dysfunction. Erythrocyte porphyrins fell, photosensitivity improved, and liver function normalized.

Oral ferrous sulfate 300 mg/day was given when liver function and porphyrin levels worsened again. Liver function again normalized and remained stable for several years.

Symptomatic response of erythropoietic protoporphyria to iron supplementation. Holme SA, Thomas CL, Whatley SD, Bentley AV, Badminton MN. *J Am Acad Dermatol* 2007; 56: 1070–2.

A patient reported greater sunlight tolerance while taking oral ferrous sulfate 200 mg twice daily.

Erythropoietic protoporphyria and iron therapy. McClements BM, Bingham A, Callendar ME, et al. *Br J Dermatol* 1990; 122: 423–4.

Oral ferrous fumarate 580 mg/day was followed by florid photosensitivity in a patient previously tolerant of iron supplements. Abnormal liver enzymes improved and erythrocyte protoporphyrin diminished after iron discontinuation.

In ferrochelatase-deficient protoporphyria patients, ALAS2 expression is enhanced and erythrocytic protoporphyrin concentration correlates with iron availability. Barman-Aksözen J, Minder EI, Schubiger C, et al. *Blood Cells Mol Dis* 2015; 54: 71–7.

It is postulated that iron deficiency may limit protoporphyrin excess in EPP and that iron should be repleted only when symptoms of iron deficiency are incapacitating.

Iron supplementation in EPP/XLP needs more study; some iron-treated protoporphyria patients improved while others worsened; some who improved may have had unrecognized XLP.

X-linked protoporphyria: iron supplementation improves protoporphyrin overload, liver damage and anaemia. Landefeld C, Kentouche K, Gruhn B, et al. *B J Haematol* 2016; 173: 482–4.

Fecal protoporphyrin excretion in erythropoietic protoporphyria: effect of cholestyramine and bile acid feeding. McCullough AJ, Barron D, Mullen KD, et al. *Gastroenterology* 1988; 94: 177–81.

Oral cholestyramine 12 g daily, but not bile acids 300–900 mg, increased fecal protoporphyrin excretion threefold in an EPP patient with hepatic dysfunction. Liver function and photosensitivity improved after 1 year of cholestyramine.

Bile acid ingestion was associated with improved liver function and erythrocyte porphyrin levels in another patient who eventually succumbed to liver failure. Efficacy remains uncertain, but bile acids in conjunction with an enteric sorbent are rational therapy in selected cases.

Liver failure in protoporphyria: long-term treatment with oral charcoal. Gorchein A, Foster GR. *Hepatology* 1999; 29: 995–6.

A patient with deteriorating hepatic function ingesting activated charcoal 10–12.5 g four times daily for 2 years exhibited improved liver function; blood porphyrin and photosensitivity diminished. Other treatments included blood transfusions, vitamin supplements, amiloride, ranitidine, and lactulose, so it is difficult to assess their relative merits.

Liver disease in erythropoietic protoporphyria: insights and implications for management. Anstey AV, Hift RJ. *Gut* 2007; 56: 1009–18.

A detailed review of protoporphyric hepatopathy with recommendations for monitoring and treatment.

Liver transplantation for erythropoietic protoporphyria liver disease. McGuire BM, Bonkovsky HL, Carithers RL, et al. *Liver Transpl* 2005; 11: 1590–6.

Experience with 20 patients receiving liver transplants in the United States from 1999 to 2004 is reviewed, including preoperative use of hematin, with or without plasmapheresis.

Liver transplantation for erythropoietic protoporphyria in Europe. Wahlin S, Stal P, Adam R, et al. *Liver Transpl* 2011; 17: 1021–6.

A European review of 35 liver transplants performed during 1983–2008. Hematopoietic stem cell transplantation was performed in three patients to prevent graft loss due to disease recurrence. Offering curative stem cell transplantation to patients at high risk for liver failure to forestall transplantation is suggested.

Perioperative measures during liver transplantation for erythropoietic protoporphyria. Meerman L, Verwer R, Sloof MJH, et al. *Transplantation* 1994; 57: 155–8.

Protection from phototoxic injury during surgery and endoscopy in erythropoietic protoporphyria. Wahlin S, Srikanthan N, Hamre B, et al. *Liver Transplantation* 2008; 14: 1340–6.

Recommendations for shielding operating room lamps for patients with protoporphyria.

The value of intravenous heme-albumin and plasmapheresis in reducing postoperative complications of orthotopic liver transplantation for erythropoietic protoporphyria. Reichheld JH, Katz E, Banner BF, et al. *Transplantation* 1999; 67: 922–8.

Three months of heme infusions (4 g daily to weekly), high-carbohydrate diet (300 mg/day), intravenous glucose, ursodeoxycholic acid (900 mg/day orally), and cholestyramine (10 g thrice daily orally) initially improved severe liver dysfunction in a patient who then deteriorated and required urgent transplantation. Intensive heme infusions (daily for 18 days), plasmapheresis (exchanges of 1–1.5 × total plasma volume performed 12 times over 19 days), and blood transfusions (14 units packed cells over 19 days) reduced blood porphyrins before successful transplantation was performed in an illumination-filtered environment to exclude 300–480 nm wavelengths.

A barrage of medical therapy is typical in protoporphyric crises, when it is rational to consider any treatments that might reverse deterioration or contribute to successful transplantation.

Treatment of recurrent allograft dysfunction with intravenous hematin after liver transplantation for erythropoietic protoporphyria. Dellon ES, Szczepiorkowski ZM, Dzik WH, et al. *Transplantation* 2002; 73: 911–5.

Hematin given intermittently for 2 years after protoporphyric hepatopathy recurred 700 days posttransplantation aided achievement and maintenance of disease remission in an allograft.

Management of patients with erythropoietic protoporphyria-related progressive liver disease. Ardalan ZS, Chandran S, Vasudevan A, et al. *Liver Transpl* 2019; 25: 1620–33.

An algorithm for monitoring early protoporphyria and managing progressive protoporphyric liver disease, and rationales for treatment decisions and timing in the extremely complex latter situation, including detailed considerations around liver transplantation and/or allogeneic stem cell transplantation, are presented. A review of relevant literature supports recommending treating iron deficiency in all XLP patients but only in severely anemic EPP patients.

Erythropoietic protoporphyria: altered phenotype after bone marrow transplantation for myelogenous leukemia in a patient heteroallelic for ferrochelatase gene

mutations. Poh-Fitzpatrick MB, Wang X, Anderson K, et al. *J Am Acad Dermatol* 2002; 46: 861–6.

A symptomatic woman harboring two ferrochelatase mutations developed leukemia. Bone marrow transplantation from a mildly affected sibling with only one mutation and minimally elevated blood protoporphyrin resulted in marked reduction of the recipient's protoporphyrins and photosensitivity, as well as leukemia remission.

Sequential liver and bone marrow transplantation for treatment of erythropoietic protoporphyria. Rand ER, Bunin ER, Cochran W, et al. *Pediatrics* 2006; 118: e1896–9.

Bone marrow transplanted 6 months after liver transplantation corrected the severe phenotype of a 14-year-old boy and halted further protoporphyrin-induced liver graft damage.

Curative bone marrow transplantation in erythropoietic protoporphyria after reversal of severe cholestasis. Wahlin S, Aschan J, Björnstedt M, et al. *J Hepatol* 2007; 46: 174–9.

Eighty days of medical management normalized liver biochemistry and improved histology in a man who then received a bone marrow transplant. Ten months later, liver and porphyrin tests were normal; no photosensitivity was reported.

Extramammary Paget disease

Caroline R. Morris, Eva A. Hurst



Extramammary Paget disease (EMPD) is a rare malignancy, first described by Crocker in 1889, who reported lesions on the scrotum and penis that were histologically similar to mammary Paget disease. EMPD most commonly occurs on apocrine rich skin of individuals between the ages of 50 and 80 years, with a peak incidence at age 65. It often presents as an erythematous plaque and is commonly misdiagnosed as an inflammatory condition resulting in treatment delays. Controversy exists over the pathogenesis of EMPD, but it is favored to arise as an intraepidermal neoplasm of glandular origin and is considered primary EMPD. More recently, it has been proposed that Toker cells, present in vulvar epidermis, are benign precursors of Paget cells. There may be a small subset called secondary EMPD, which represents intraepithelial spread of malignant adenocarcinoma cells from an underlying malignancy.

MANAGEMENT STRATEGY

Biopsy should be performed immediately upon suspicion of EMPD. Histologically, EMPD is characterized by intraepidermal proliferation of Paget cells (PCs), which have large vesicular nuclei and abundant pale cytoplasm. Extension into adnexal structures is common and may be misinterpreted as dermal invasion. In addition to hematoxylin and eosin, diagnosis is confirmed by utilizing a panel of immunoperoxidase studies including cytokeratin 7, carcinoembryonic antigen (CEA), epithelial membrane antibody, HER-2/neu, and gross cystic disease fluid protein-15. These can be used to differentiate EMPD from pagetoid variants of squamous cell carcinoma in situ and melanoma in situ. The expression of tissue-specific antigens within PCs appears to correlate with that of the underlying malignancy: prostatic antigen, uroplakins, and transcription factor CDX-2 in prostatic, urothelial, and intestinal adenocarcinomas, respectively. However, limitations to the use of tissue-specific markers necessitates careful clinicopathologic correlation.

Patients diagnosed with EMPD must be risk stratified. Ambiguity exists within the literature regarding risk for associated malignancies;

an associated underlying internal cancer has been reported in 7–40% of patients with EMPD. Most reported cases of internal malignancy are in close proximity to the cutaneous EMPD. Therefore, a directed internal malignancy evaluation is appropriate. Dependent on gender, appropriate studies to consider include mammography, Papanicolaou smear, pelvic ultrasonography, cystoscopy, colonoscopy, and computed tomography of the abdomen and pelvis.

The treatment of EMPD has long been *surgical excision* with adjuvant therapies in select cases. *Mohs micrographic surgery* (MMS) has emerged as a promising therapeutic option as it offers complete evaluation of tissue margin, maximal tissue preservation, and the lowest recurrence rates. However, it is limited by ill-defined clinical margins, microscopic extension of tumor cells, multifocal disease, and sometimes lesion size given the outpatient nature of MMS.

Close clinical follow-up of patients with EMPD is recommended due to recurrence risk. Biannual evaluation for at least 3 years, then annually for at least 10 years for non-invasive EMPD, has been suggested. In invasive EMPD or cases associated with a distant, underlying tumor, follow-up should be more frequent with a low threshold to biopsy any suspicious skin lesion. In general, patients with EMPD have a good prognosis with a 5-year overall survival of 75–95%. Dermal invasive EMPD is more frequently associated with regional lymph node metastasis and poor prognosis.

Specific Investigations

- Skin biopsy
- Full-body skin examination and lymph node evaluation
- Age-appropriate cancer screening and directed internal malignancy evaluation
- Sentinel lymph node biopsy in patients with dermal and/or lymphatic extension

Extramammary Paget's disease: a review of the literature – Part I: history, epidemiology, pathogenesis, presentation, histopathology, and diagnostic work-up. Morris C, Hurst E. *Dermatol Surg* 2020; 46: 151–8.

Systematic review of the literature. Patients with EMPD must be risk stratified and evaluated for an underlying internal malignancy. Sentinel lymph node biopsy is recommended in patients with invasive EMPD. The standard of treatment is surgery with new data suggesting that MMS may have superior clinical outcomes with lower recurrence rates.

Extramammary Paget's disease: treatment, prognostic factors and outcome in 76 patients. Hatta N, Yamada M, Hirano T, et al. *Br J Dermatol* 2008; 158: 313–8.

Retrospective review of 76 patients with EMPD. Sixty-six patients underwent curative surgical excision: five developed local recurrence. Surgical margin was not correlated with local recurrence. Thirteen patients developed systemic metastases; 10 died. Nodules in the primary tumor, clinical lymph node swelling, elevated CEA, depth of tumor invasion, and lymph node metastasis were significant prognostic factors. Depth of tumor invasion and CEA level were associated with reduced survival.

First-Line Therapies

• Wide local excision, with or without lymph node dissection	B
• Frozen section–guided wide local excision	B
• Mohs micrographic surgery	B

The role of sentinel lymph node biopsy in the management of invasive EMPD: multi-center, retrospective study of 151 patients. Fujisawa Y, Yoshino K, Kiyohara Y, et al. *J Dermatol Sci* 2015; 79: 38–42.

Retrospective review of 151 patients with invasive EMPD. The rate of lymph node (LN) metastasis was 80% in patients with lymphadenopathy compared to 15% without. Lymphadenopathy was associated with advanced primary tumor (nodule, thicker tumor, deeper invasion, presence of lymphovascular invasion). Survival was not affected by sentinel LN status even when an advanced primary tumor was present. SLNB with subsequent LN dissection may improve survival of patients with early stage lymphatic spread.

Indications for lymph node dissection in the treatment of EMPD. Tsutsumida A, Yamamoto Y, Minakawa H, et al. *Dermatol Surg* 2003; 29: 21–4.

Prospective study of 34 patients with genital or perineal EMPD treated with wide local excision. Patients with clinical or histologic evidence of metastatic disease underwent LN dissection. No patients with in-situ disease or microscopic papillary dermal invasion had LN metastasis and all had 100% 5-year survival. Tumor invasion into reticular dermis correlated with 33% 5-year survival. Tumor invasion into subcutaneous tissue correlated with 100% LN metastasis and 0% 5-year survival.

Possible effectiveness of lymph node dissection in patients with extramammary Paget's disease. Matsushita S, Hatanaka M, Katsue H, et al. *J Dermatol* 2013; 40: 574–5.

Retrospective review of 14 patients with advanced EMPD. Metastatic sentinel node (SN) was confirmed in five patients; one had a metastatic SN on bilateral sides. Their findings suggest that the incidence of distant metastasis is lower in patients with single metastatic SN and recommend LN dissection in patients with a single metastatic SN, thin primary tumor, and slight tumor burden in the metastatic SN.

A proposal for a TNM staging system for EMPD: retrospective analysis of 301 patients with invasive tumors. Ohara K, Fujisawa Y, Yoshino K, et al. *J Dermatol Sci* 2016; 83: 234–9.

Proposed TNM staging system for EMPD based on a retrospective review of 301 Japanese patients with invasive EMPD. Factors associated with survival included tumor thickness, lymphovascular invasion, number of LN metastases, and distant metastases. Patients were classified into five groups, with each showing a distinct survival curve, except stages II and IIIa demonstrated equivalent survival curves. Limitations include the retrospective nature, small number with tumor-related death, and inclusion of only Japanese patients. This classification system should be considered provisional pending further investigation.

Extramammary Paget's disease: a review of the literature – Part II: treatment and prognosis. Morris C, Hurst E. *Dermatol Surg* 2019. Epub.

Systematic review of the literature. Intraoperative pathological examination of frozen sections is often performed to determine margin status; however, this is limited by vertical processing, which limits margin analysis. Standard surgical approach often results in vast tissue loss necessitating extensive reconstruction, which can be associated with significant deformity and morbidity. More recent data suggests that MMS, which provides intraoperative microscopic evaluation of 100% of tissue margin, may have superior clinical outcomes with lower recurrence rates.

Nodal dissection is indicated if clinical or pathologic lymph node metastasis is present, although selective LN dissection is also strongly recommended in the case of invasion into the reticular dermis or subcutaneous tissue even in the absence of clinical or pathologic lymph node metastasis. However, there is no evidence that elective LN dissection, in the absence of palpable nodes, improves survival.

Second-Line Therapies

• Photodynamic therapy (PDT)	B
• Radiation therapy	B
• Topical imiquimod	B
• Systemic chemotherapy	B

Noninvasive extramammary Paget's disease treated with photodynamic therapy: case series from the Roswell Park Cancer Institute. Housel JP, Izikson L, Zeitouni NC. *Dermatol Surg* 2010; 36: 1718–24.

Retrospective case series of eight patients with 24 distinct EMPD lesions treated with photodynamic therapy (PDT). Of those treated with IV porfimer sodium, 78% had a complete response and a disease-free period of 12–96 months. Only 50% (8/16) of lesions treated with topical 5-aminolevulinic acid (ALA) showed complete response and just 38% were disease free at 9–88 months. PDT with IV porfimer sodium or topical ALA may present a useful, surgery-sparing therapeutic option in select patients.

Radiation therapy for extramammary Paget's disease: treatment outcomes and prognostic factors. Hata M, Koike I, Wada H, et al. *Ann Oncol* 2014; 25: 291–7.

Retrospective review of 41 patients with EMPD, including 15 with regional LN metastases, treated with radiation therapy. Total doses of 45–80.2 Gy (median = 60 Gy) were delivered with a median of 33 fractions. The 5-year local progression-free and disease-free rates were 82% and 46%, respectively. Five patients died due to tumor progression. Radiation therapy may be an effective and safe option for inoperable EMPD.

Effects of imiquimod on vulvar Paget's disease: a systematic review of literature. Machida H, Moenini A, Roman LD, et al. *Gynecol Oncol* 2015; 139: 165–71.

A systematic review including 63 cases of untreated or recurrent vulvar EMPD treated with topical imiquimod. The treatment regimens were highly variable, but the most common was topical application 3–4 times per week with a median treatment duration of 4 months. Complete response at 6 months was present in 35 patients. Of the complete responders, three had disease recurrence. Topical imiquimod therapy may be an effective therapeutic option for patients with recurrent or non-operable vulvar Paget disease.

Combination chemotherapy for metastatic EMPD. Oashi K, Tsutsumida A, Namikawa K, et al. *Br J Dermatol* 2014; 170: 1354–7.

Seven patients with metastatic EMPD were treated with combination chemotherapy (FECOM: epirubicin, mitomycin C, vincristine, carboplatin, 5-fluorouracil). Progression-free survival and overall survival (OS) was 6.6 months and 9.4 months, respectively, with a 1-year OS rate of 43%. All patients had at least a partial response or shrinkage in tumor size; none had complete response.

Usefulness of docetaxel as first-line chemotherapy for metastatic EMPD. Yoshino K, Fujisawa Y, Kiyohara Y, et al. *J Dermatol* 2016; 43: 633–7.

Retrospective multicenter analysis that demonstrated successful treatment of 18 metastatic EMPD with docetaxel (average number of treatment cycles = 9.1). Fifty-eight percent experienced partial response (PR), 25% stable disease (SD), and 17% progressive disease (PD) with a 1-year OS rate of 75%.

Docetaxel combined with cisplatin for metastatic EMPD. Cai H, Xu W, Yu B, et al. *Clin Genitourin Cancer* 2018;16: e899–901.

Prospective study of eight patients with metastatic EMPD treated with intermittent combination chemotherapy of docetaxel and cisplatin (average number of cycles = 9.4). In total, 50% experienced PR, 37.5% SD, and 12.5% PD with a 1-year OS rate of 87.5%.

Third-Line Therapies

• Androgen receptor antagonist	E
• Intralesional interferon- α_{2b}	E
• Combination topical imiquimod and PDT	E
• Trastuzumab	E

Androgen-deprivation regimen for multiple bone metastases of EMPD. Yoneyama K, Kamada N, Kinoshita K. *Br J Dermatol* 2005; 153: 853–5.

Case report of EMPD with multiple bone metastases successfully suppressed with bicalutamide (antiandrogen) and leuprorelin (LH-RH agonist). Tumor markers rose at day 70 and other antiandrogen therapies were trialed (flutamide and chlormadinone acetate) as bicalutamide resistance was suspected. The patient died 14 months after initiation of antiandrogen therapy. The authors hypothesize that the rapid development of treatment resistance implicates a mutation or amplification in the androgen receptor gene, which has been demonstrated in prostate cancer.

Intralesional interferon alfa-2b as neoadjuvant treatment for perianal EMPD. Panasiti V, Bottoni U, Devirgilis V, et al. *J Eur Acad Dermatol Venereol* 2008; 22: 522–3.

Case report of a patient with perianal EMPD treated with intralesional IFN- α_{2b} at a dose of 1 million IU three times per week for 3 weeks. Surgical resection was performed at 7 weeks after the tumor had shrunk. Patient had no clinical disease at 108 months follow-up.

EMPD of the scrotum with complete response to imiquimod and photodynamic therapy. Bauman TM, Rosman IS, Sheinbein DM. *BMJ Case Rep* 2018; doi: 10.1136/bcr-2017-221696.

Case report of EMPD treated with imiquimod 5% cream 5 days per week for 1 month and then 3 days per week for 2 months, followed by monthly 5-aminolevulinic acid PDT for 6 months (with continued application of imiquimod 3 days per week), with complete remission in over 5 years of follow-up.

Metastatic EMPD of scrotum responds completely to single agent trastuzumab in a hemodialysis patient: case report, molecular profiling and brief review of the literature. Barth P, Dulaimi Al-Saleem E, et al. *Case Rep Oncol Med* 2015; 895151.

Case report of metastatic EMPD with Her2/neu overexpression treated with trastuzumab as a single agent with complete response. The authors note that Her2/neu overexpression is seen in 30–40% of EMPD cases and this may present a therapeutic option in these cases.

EMPD: what do we know and how do we treat? Adashek J, Leonard A, Nealon S, et al. *Can J Urol* 2019; 26: 10012–21.

A systematic review of EMPD. Recent studies demonstrate expression of HER2 and androgen receptors, which may represent useful targets as future treatment strategies. CEA has shown potential as a possible biomarker for EMPD to aid in detection of metastatic disease and assessment of treatment response. There is growing support for the use of immunotherapy as a therapeutic modality for metastatic EMPD; however, no studies exist to date demonstrating the use of immunotherapy in the treatment of EMPD.

Fabry disease

Jaya Ganesh



Fabry disease (or Anderson–Fabry disease, OMIM 301500) is a progressive, X-linked lysosomal storage disorder caused by the deficiency or absence of the enzyme α -galactosidase A (GLA). This results in the accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids within lysosomes. Systemic manifestations of Fabry disease include renal dysfunction, cardiomyopathy and arrhythmias, cerebrovascular complications, corneal and lenticular opacities, tinnitus and hearing loss, gastrointestinal disturbances, pulmonary disease, osteopenia, and depression. Causes of death include end-stage renal disease (ESRD), cardiac disease, or stroke. Males are more severely affected, but female carriers may exhibit symptoms depending on the pattern of X-chromosome inactivation (lyonization).

There are two major disease phenotypes: type 1 ‘classic’ and type 2 ‘later-onset’ forms. Males with type 1 disease have little or no functional α -Gal A enzymatic activity (<3% of normal mean activity) and develop symptoms in childhood or adolescence. Progressive deposition of Gb3 in the heart leads to arrhythmias, left ventricular hypertrophy, and hypertrophic cardiomyopathy (HCM). In the kidneys the disorder manifests as proteinuria, renal insufficiency, and, ultimately, ESRD, requiring dialysis and renal transplantation. Cerebrovascular disease, including transient ischemic attacks and strokes, may occur. Prior to enzyme replacement therapy (ERT), and without dialysis or renal transplantation, the average age of death of affected males with the type 1 classic phenotype was $\approx$ 40 years.

Type 2 ‘later-onset’ have higher residual α -Gal A activity, and do not show the early manifestations of type 1 males such as acroparesthesias, hypohidrosis, angiokeratomas, or corneal dystrophy. They present with renal and/or cardiac disease much later, typically in the third to seventh decades of life. Cutaneous features of Fabry disease include angiokeratoma, hypohidrosis (53% males

and 28% females), telangiectasia (23% males and 9% females), and lymphedema (16% males and 6% females).

Diffuse angiokeratomas are a characteristic cutaneous manifestation of Fabry disease and should alert the clinician to the possibility of the diagnosis. They typically cluster symmetrically around the umbilicus, hips, back, thighs, buttocks, penis, and scrotum (bathing trunk distribution); increase in number and size over time; and may correlate with the severity of the systemic manifestations of disease. Diffuse angiokeratomas may also be seen in other lysosomal storage diseases including fucosidosis, sialidosis, aspartylglucosaminuria, and β -galactosidase deficiency. Acroparesthesia produces episodic burning, severe pain, and tingling of the palms and soles. Pain crises are thought to result from glycolipid accumulation in the autonomic nervous system and vascular endothelium. A similar mechanism possibly underlies Fabry-associated hypohidrosis.

MANAGEMENT STRATEGY

Comprehensive medical therapy for Fabry disease requires a multidisciplinary approach that includes a combination of *targeted therapy to address the enzyme deficiency* and *medical treatment to address specific organ dysfunction*.

Angiokeratomas due to Fabry disease are typically asymptomatic; when indicated they can be treated with *surgical excision*, *electrocoagulation*, and *cryosurgery*. Various *lasers* have been utilized, including the CO₂, argon, copper vapor, and flashlamp-pumped dye lasers. Copper vapor lasers are superior to argon because of their wavelength specificity for hemoglobin. However, the flashlamp-pumped dye laser may produce less pain and bleeding and pigmentary change.

Neuropathic pain and acroparesthesias may benefit from avoidance of triggers, including physical exertion and temperature changes. *Diphenylhydantoin*, *carbamazepine*, *gabapentin*, *topiramate*, and *tricyclic antidepressants* are used for analgesia. Non-steroidal antiinflammatory drugs are generally ineffective and may worsen the renal disease, and narcotics should be avoided if possible.

Used in conjunction with ERT, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may reduce proteinuria and stabilize glomerular filtration rate (GFR). Peritoneal dialysis, hemodialysis, and renal transplantation are utilized for patients with renal failure. Careful monitoring and prompt intervention for cardiac arrhythmia and HCM are extremely important, and cardiac transplantation may be necessary.

Gastrointestinal complications, including delayed gastric emptying and dyspepsia, have been treated with *metoclopramide*, *pancrelipase*, *loperamide*, and *H₂ blockers*. *Hearing aids* assist in moderate hearing loss, whereas profound deafness requires cochlear implantation. *Aspirin* or *clopidogrel* is recommended for cardiovascular disease prophylaxis.

Two human enzyme products have been utilized in ERT: *agalsidase- β* (Fabrazyme, Sanofi-Genzyme Corporation) and *agalsidase- α* (Replagal, Shire Genetic Therapies). Both were approved by the European Agency for Evaluation of Medical Products in 2001, but only agalsidase- β is approved by the Food and Drug Administration for use in the United States. The enzymes are administered intravenously biweekly at a dose of 0.2 mg/kg for agalsidase- α and 1.0 mg/kg for agalsidase- β . No clear difference in clinical effect between the two preparations was demonstrated in a randomized, controlled, prospective study.

ERT stabilizes or slows progression of renal and cardiac disease, reduces neuropathic pain, stabilizes hearing loss, and improves sweat function and quality of life. Patients treated with ERT have a slowing of progression to ‘major’ clinical events (ESRD, myocardial infarction, stroke, or death). In a recent analysis of 969 male and 442 female patients enrolled in the longitudinal

Fabry Registry, patients with more advanced disease before initiating ERT were at a significantly higher risk of sustaining a severe Fabry-related clinical event compared with those who had milder disease and earlier institution of ERT. ERT has been associated with immunogenicity leading to antibody-mediated infusion reactions that may also reduce its efficacy.

Other therapeutic strategies involve small molecules called *active site-specific chaperones* that are useful with certain types of mutations in the *GLA* gene. In Fabry disease, some missense mutations that cause misfolding of the mutant *GLA* enzyme can result in the retention of the misfolded enzyme in the endoplasmic reticulum. The retained enzyme is then degraded rather than being trafficked to the appropriate location in the cell, i.e., the lysosome. Chaperones are orally active molecules that selectively bind to the misfolded enzyme, promote correct folding, and aid in delivery to lysosomes. Some mutant forms of the enzyme are more amenable to targeting and are responsive to *migalastat* (1-deoxygalactonojirimycin [Galafold, Amicus Therapeutics, NJ, USA]). Migalastat is an orally administered first-in-class molecular chaperone that has been approved for use in patients with amenable mutations in *GLA*. It is administered orally on alternate days. In a cohort of 67 patients, 75% had mutations deemed responsive to migalastat. In that group, improvements included the arrest of decline in GFR, left ventricular mass index, and gastrointestinal symptoms.

New, improved, and more effective treatment approaches are actively being studied. These include trials of gene therapy that are currently in progress.

Information on current clinical trials is posted at www.clinicaltrials.gov.

Fabry disease has now been added to the list of disorders screened for by newborn screening panels in some states in the United States.

Specific Investigations

1 Diagnostic workup

- Obtain family history
- Enzyme analysis (quantitation in plasma and white blood cells [WBCs], cultured cells, blood spot filter paper screening) (most definitive method in males, not reliable for females)
- *GLA* molecular DNA analysis (nearly 100% sensitivity in affected males; most reliable method for females)
- Preimplantation genetic diagnosis or prenatal diagnosis via amniocentesis or chorionic venous sampling (enzymatic and/or molecular assay)

2 Systemic workup (male and female)

- Renal function studies including urinalysis and assessment of 24-hour microalbuminuria and creatinine clearance
- Cardiac evaluation with electrocardiogram, echocardiography, 24-hour Holter monitoring, and cardiac magnetic resonance imaging (MRI) with gadolinium enhancement
- Dermatology evaluation
- Urine GB3, LysoGB3 (Fabry-associated lysosphingolipid) levels in blood
- Audiology
- Fundoscopy and slit-lamp examination
- Neurologic evaluation with surveillance MRI
- Pulmonary function studies
- Gastrointestinal examination with endoscopy as indicated

Angiokeratoma: decision making aid for the diagnosis of Fabry disease. Zampetti A, Orteu CH, Antuzzi D, et al., and the Interdisciplinary Study Group on Fabry Disease. *Br J Dermatol* 2012; 166: 712–20.

This article proposes an algorithm for the diagnosis of Fabry disease and reviews clinical and histologic features of angiokeratomas in detail. The algorithm uses personal and family history, the number and distribution of angiokeratomas, skin biopsy, dermoscopy (to detect more subtle lesions), electron microscopy, and genetic studies as sequential tools in the diagnostic process.

Treatment of Fabry disease: current and emerging strategies. Rozenfeld P, Neumann PM. *Curr Pharm Biotechnol* 2011; 12: 916–22.

This is an excellent overview of therapeutic options, including new treatments such as chaperone therapy.

Fabry disease and the skin: data from FOS, the Fabry Outcome Survey. Orteu CH, Jansen T, Lidove O, et al. *Br J Dermatol* 2007; 157: 331–7.

The Fabry Outcome Survey (FOS), a multicenter European database, was used to capture longitudinal multicenter data on patients with Fabry disease. This paper discusses the dermatologic manifestations present in that cohort.

A case of multiple angiomas without any angiokeratomas in a female heterozygote with Fabry disease. Mirceva V, Hein R, Ring J, et al. *Australas J Dermatol* 2010; 51: 36.

Case report wherein multiple angiomas were the only visible cutaneous manifestation of Fabry disease in an oligosymptomatic female.

Fabry disease. Germain DP. *Orphanet J Rare Dis* 2010; 5: 30.

This is a very comprehensive overview of the clinical characteristics of Fabry disease, current treatment modalities, and therapies on the horizon.

Fabry disease: a review of current management strategies. Mehta A, Beck M, Eyeskens F, et al. *Q J Med* 2010; 103: 641–59.

This review, written by a panel of experts with extensive clinical experience in Fabry disease, summarizes the recent literature and registry data to aid in providing therapy recommendations.

Human Gene Mutation Database: 2008 update. Stenson PD, Mort M, Ball EV, et al. *Genome Med* 2009; 1: 13. <http://www.hgmd.org>. The Institute of Medical Genetics, Cardiff, United Kingdom, 2011.

Over 800 mutations in the *GLA* gene have been identified, including missense and loss of function mutations. Mutation information is used for diagnosis, particularly in female heterozygotes, prenatal testing, and partial correlation with clinical phenotype. Mutation specificity also has major implications for pharmacogenomic management, for example, for the potential use of chaperone therapy in patients with missense mutations that cause protein misfolding.

Fabry disease. Mehta A, Hughes DA. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. *GeneReviews*, Seattle: University of Washington.

This easily accessed, frequently updated database provides a comprehensive review of the clinical, biochemical, and molecular aspects of Fabry disease, with links to information about diagnostic testing and patient resources.

Fabry disease in infancy and early childhood: a systematic literature review. Laney DA, Peck DS, Atherton AM, et al. *Genet Med* 2015; 17: 323–30.

The authors performed a systematic retrospective analysis of 120 peer-reviewed publications and case reports about the pediatric Fabry population. Forty-one individual patients younger than 5 years of age were identified. Acroparesthesia was the most common clinical symptom, reported in nine patients. Other symptoms in very young children included heat sensitivity and gastrointestinal disease, especially recurrent abdominal pain and diarrhea. Importantly, renal damage, including foot process effacement, was noted to occur even before there was clinically evident proteinuria.

First-Line Therapies

• Enzyme replacement therapy	A
• Laser therapy	E
• Intense pulsed light	E
• Surgical excision	E
• Diphenylhydantoin	B
• Cryotherapy	E

Enzyme replacement therapy for Anderson–Fabry disease. El Dib RP, Pastores GM. *Cochrane Database Syst Rev* 2010; 5: CD006663.

This Cochrane review summarizes the available evidence with regard to five randomized-controlled clinical trials (representing 23 publications) involving agalsidase- α and agalsidase- β . The authors concluded that ERT can modify disease course in treated patients with Fabry disease, improving neuropathic pain, cardiac morphology, and renal function. There is also a positive influence on quality of life. Treatment is generally well tolerated, although neutralizing antibodies may affect clinical outcome. Longer-term effects on morbidity and mortality remain to be established.

Response of women with Fabry disease to enzyme-replacement therapy: comparison with men, using data from the FOS – the Fabry Outcome Survey. Hughes DA, Barba Romero MÁ, Hollak CE, et al. *Mol Genet Metab* 2011; 103: 207–14.

Data were obtained from the FOS of 78 affected women and 172 men. Clinical outcomes studied included cardiac structure and function, renal function, quality of life, pain, and a variety of other clinical features and quantifiable measures. Both sexes responded similarly to agalsidase- α . Anhidrosis improved, whereas angiokeratomas did not.

Agalsidase beta treatment is associated with improved quality of life in patients with Fabry disease: findings from the Fabry registry. Watt T, Burlina A, Cazzorla C, et al. *Genet Med* 2010; 12: 703–12.

Seventy-one men and 59 women treated with agalsidase- β had baseline and posttreatment quality of life measurements. Health-related quality of life improved in both sexes, although the effect was more pronounced in men.

Four-year prospective clinical trial of agalsidase alfa in children with Fabry disease. Schiffmann R, Martin RA, Reimschisel T, et al. *J Pediatr* 2010; 156: 832–7.

Of the 24 children who initially completed the 6-month open-label agalsidase- α study, 17 enrolled in this further 3.5-year extension study. Pain severity and Gb3 levels were reduced, and heart rate variability improved. Kidney function and left ventricular mass remained stable.

Risk factors for severe clinical events in male and female patients with Fabry disease treated with agalsidase beta enzyme replacement therapy: data from the Fabry Registry. Hopkin RJ, Cabrera G, Charrow J, et al. *Mol Genet Metab* 2016; 119: 151–9.

This article provides an in-depth review of risk factors for developing severe clinical events in a large cohort of patients treated with ERT, highlighting the need for multidisciplinary care and adjuvant therapies.

Angiokeratomas in Fabry's disease and Fordyce's disease: successful treatment with copper vapor laser. Lapins J, Emtestam L, Marcusson JA. *Acta Derm Venereol* 1993; 73: 133–5.

Angiokeratomas in two treated subjects were undetected at 3-month follow-up; treated skin was smooth, with minimal pigmentary alteration.

Successful treatment of angiokeratoma with potassium titanyl phosphate laser. Gorse SJ, James W, Murison MSC. *Br J Dermatol* 2004; 150: 620–1.

Excellent results using this laser were seen in two subjects with angiokeratomas.

Angiokeratomas of Fabry successfully treated with intense pulsed light. Morais P, Santos AL, Baudrier T, et al. *J Cosmet Laser Ther* 2008; 10: 218–22.

There was almost complete clearance of angiokeratomas in one severely affected subject without recurrence at 12-month follow-up.

Fabry disease: recognition and management of cutaneous manifestations. Möhrenschrager M, Braun-Falco M, Ring J, et al. *Am J Clin Dermatol* 2003; 4: 189–96.

Review article about current laser treatments for the angiokeratomas of Fabry disease, including variable pulse width 532-nm neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, 578-nm copper vapor laser, and flashlamp-pulsed dye laser.

Intravenous infusion of phenytoin relieves neuropathic pain: a randomized, double-blinded, placebo-controlled, crossover study. McClean GJ. *Anesth Analg* 1999; 89: 985–8.

This study evaluated 20 patients with acute flare-ups of neuropathic pain. Phenytoin reduced burning sensation, shooting pain, sensitivity, numbness, and overall pain.

Second-Line Therapies

• Gabapentin	D
• Carbamazepine	D

Use of gabapentin to reduce chronic neuropathic pain in Fabry disease. Ries M, Mengel E, Kutschke G, et al. *J Inher Metab Dis* 2003; 26: 413–4.

Six patients with Fabry disease experienced less pain than at baseline with few side effects after 4 weeks of treatment.

Carbamazepine in Fabry's disease: effective analgesia with dose-dependent exacerbation of autonomic dysfunction. Filling-Katz MR, Merrick HF, Fink JK, et al. *Neurology* 1989; 39: 598–600.

Five of seven patients had moderate to complete relief of pain based upon self-assessment. Complications included exacerbation of preexisting autonomic dysfunction, ileus, urinary retention, and gastrointestinal disturbance.

Third-Line and Future Therapies

• Site-specific molecular chaperone therapy (migalastat)	A
• Substrate reduction therapy (eliglustat tartrate, Genz 112638)	
• Gene replacement therapy	
• Renal transplantation/hemodialysis	C

Co-administration with the pharmacological chaperone AT1001 increases recombinant human α -galactosidase A tissue uptake and improves substrate reduction in Fabry mice. Benjamin ER, Khanna R, Schilling A, et al. *Mol Ther* 2012; 20: 717–26.

This study evaluated the efficacy of combined ERT and chaperone therapy. Coincubation of Fabry fibroblasts with recombinant human α -galactosidase A (rh α -Gal A) and AT1001 (1-deoxygalactonojirimycin, migalastat hydrochloride) resulted in up to fourfold higher levels of cellular α -Gal A and approximately 30% greater Gb3 reduction compared with ERT alone. In rats, AT1001 increased the circulating half-life of rh α -Gal A by >2.5-fold, and in GLA knockout mice resulted in up to fivefold higher α -Gal A levels and fourfold greater GL-3 reduction.

Treatment of Fabry's disease with the pharmacologic chaperone migalastat. Germain DP, Hughes DA, Nicholls K, et al. *New Engl J Med* 2016; 375: 545–55.

Sixty-seven patients with Fabry disease who had never received ERT or had not received ERT within 6 months before enrollment were randomized to 6 months of treatment with migalastat or placebo followed by an open-label migalastat for 6–12 months plus an additional year. All patients were genotyped, and 50 patients had mutant enzyme suitable for targeting by migalastat. Beneficial effects were observed in annualized rates of change in GFRs, reduction in left ventricular mass index (a significant predictor of adverse cardiac events), and improvement in gastrointestinal symptoms that are frequently debilitating. None of the migalastat-treated patients progressed to end-stage kidney disease, had strokes, or had cardiac-related mortality during the study.

Kidney transplant outcomes in patients with Fabry disease. Shah T, Gill J, Malhotra N, et al. *Transplantation* 2009; 87: 280–5.

This study evaluated 197 renal transplant recipients with Fabry disease and ESRD from 1987 to 2007. Rates of graft loss and death were compared with renal transplant recipients with other (non-Fabry) causes of ESRD, as well as a 10:1 matched cohort of transplant recipients with other causes of ESRD. Patients with Fabry disease had a superior graft survival and similar patient survival compared with other (non-Fabry) ESRD patients. However, they had a higher risk of death compared with a matched cohort.

Flushing

Jean S. McGee, Jonathan K. Wilkin



Flushing is defined as visible reddening of the skin over the face, neck, upper portion of the chest, and upper limbs, in association with the sensation of warmth.

MANAGEMENT STRATEGY

The initial step in the management of a patient with a flushing disorder is to make a specific diagnosis. The first algorithmic step is to distinguish between autonomic neurally-mediated flushing, in which eccrine sweating occurs at the time of the flushing ('wet flushing'), and direct vasodilator-mediated flushing, in which there is no accompanying eccrine sweating ('dry flushing'). The dry flushing reactions are further divided into those with prominent dysesthesia and those without.

The most common form of 'wet flushing' is thermoregulatory flushing resulting from exercise and/or exogenous heat. A simple measure such as ice chip therapy, as in holding an ice chip in the mouth, can quickly achieve control. Climacteric flushing in women is associated with inappropriate thermoregulation. Hormone replacement therapy is considered the mainstay of treatment. The second major form of 'wet flushing' is emotional flushing, which can be managed with oral β -blockers, such as nadolol 40 mg every morning or propranolol between 20 mg and 40 mg twice to three times daily.

The 'dry flushing' without dysesthesia is caused by either exogenous or endogenous circulating agents that directly work on the vascular smooth muscle to induce vasodilation. A high-dose nicotinic acid early in the course of therapy for hyperlipidemia can provoke dry flushing. These flushing events can be ameliorated

by simultaneous administration of aspirin. All calcium channel blockers can induce flushing as a side effect. An organic nitrate, such as nitroglycerin, can provoke flushing, followed by tolerance after the first week of therapy. Capsaicin in spicy foods, sodium nitrite in cured meats, and sulfites in salads and wines can provoke dry flushing. Alcohol-induced flushing in Asians can be prophylactically addressed with oral administration of aspirin 0.64 g or a combination of H_1 - and H_2 -antihistamines, 50 mg diphenhydramine and 300 mg cimetidine, respectively.

Endogenous circulating agents from underlying malignancies can induce flushing in association with other prominent features. Itching and urticaria should trigger a laboratory work-up for systemic mastocytosis. Flushing following hypertension, pallor, tachycardia, palpitations, and sweating should prompt an investigation for pheochromocytoma. Flushing with diarrhea should encourage a diagnostic test for carcinoid syndrome. Rare malignancies such as renal cell carcinoma, pancreatic cell carcinoma, and medullary thyroid carcinoma should always be on the differential diagnoses as well.

Specific Investigations

- Serum tryptase
- Urinary catecholamines and metanephrines
- Urinary 5-hydroxyindoleacetic acid and serotonin

First-Line Therapies

• Ice chips	B
• Hormone replacement	A
• Aspirin	A
• Topical brimonidine	A
• Topical oxymetazoline	B

Combined versus sequential hormone replacement therapy: a double-blind, placebo-controlled study on quality of life-related outcome measures. Bech P, Munk-Jensen N, Obel EB, et al. *Psychother Psychosom* 1998; 67: 259–65.

Continuous combined therapy of 2 mg oestradiol (E_2) and 1 mg norethisterone acetate (NETA) daily and sequential therapy of E_2 and NETA were both superior to placebo on the Kupperman scale of sweating, hot flushing, myalgia, and vertigo in 105 normal early postmenopausal women.

Even though hormone replacement therapy is the first-line therapy, contraindications can preclude use of this therapy in many women.

Randomized controlled trial of different aspirin regimens for reduction of niacin-induced flushing. Banka SS, Thachil R, Levine A, et al. *Am J Health Syst Pharm* 2017; 74: 898–903.

Simultaneous administration of aspirin and niacin reduced moderate-to-severe flushing events by a mean of 36.1% in a cohort of healthy adult volunteers.

Aspirin attenuation of alcohol-induced flushing and intoxication in Oriental and Occidental subjects. Truitt EB Jr, Gaynor CR, Mehl DL. *Alcohol Alcohol Suppl* 1987; 1: 595–9.

A group of 11 Oriental and Occidental subjects with histories of alcohol-induced flushing was compared to a similar ethnic group of non-flushing subjects. Prophylactic administration of oral aspirin 0.64 g 1-h prior significantly reduced facial flushing in the flushing group.

Brimonidine gel 0.33% rapidly improves patient-reported outcomes by controlling facial erythema of rosacea: a randomized, double-blind, vehicle-controlled study. Layton AM, Schaller M, Homey B, et al. *J Eur Acad Dermatol Venereol* 2015; 29: 2405–10.

The brimonidine group (once-daily application of brimonidine gel 0.33%) reported significant improvement in patient-reported outcomes on facial redness after 8 days, in comparison to the vehicle group.

Efficacy and safety of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of two randomized, double-blind, and vehicle-controlled pivotal studies. Fowler J Jr, Jackson M, Moore A, et al. *J Drugs Dermatol* 2013; 12: 650–6.

Once-daily brimonidine tartrate application significantly improved severity of erythema based on Clinician's Erythema Assessment and patient's self-assessment, as compared with vehicle application.

Long-term safety and efficacy of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of a 1-year open-label study. Moore A, Kempers S, Murakawa G, et al. *J Drugs Dermatol* 2014; 13: 56–61.

Once-daily brimonidine tartrate gel 0.5% for 1 year, equivalent to 345 subject years of exposure, demonstrated similar safety profile, as compared with vehicle. In addition, the durability of the therapeutic effects was maintained without tachyphylaxis in the brimonidine group.

Efficacy and safety of oxymetazoline cream 1.0% for treatment of persistent facial erythema associated with rosacea: findings from the 52-week open label REVEAL trial. Draeos ZD, Gold MH, Weiss RA, et al. *J Am Acad Dermatol* 2018; 78: 1156–63.

In an open-label study, 440 patients with rosacea applied oxymetazoline 1.0% cream once daily for 52 weeks. At the end of the study, 36.7% and 43.4% of patients achieved a 2-grade or greater composite improvement from baseline in both Clinician Erythema Assessment and Subject Self-Assessment.

Second-Line Therapies

• H ₁ and H ₂ antihistamines	C
• Selective serotonin reuptake inhibitors	A
• Serotonin-norepinephrine reuptake inhibitors	A
• Clonidine	A
• Gabapentin	A

Antihistamine blockade of alcohol-induced flushing in Orientals. Miller NS, Goodwin DW, Jones FC, et al. *J Stud Alcohol* 1988; 49: 16–20.

A combination of 50 mg diphenhydramine (H₁ receptor antagonist) and 300 mg cimetidine (H₂ receptor antagonist) prior to administration of alcohol in Oriental subjects demonstrated a significant reduction in the skin flushing, as compared to placebo.

Scombroid poisoning: prompt resolution of symptoms with cimetidine. Blakesley ML. *Ann Emerg Med* 1983; 12: 104–6.

Four cases of toxic erythema and histamine overload of scombroid poisoning from ingestion of tainted tuna fish promptly resolved with intravenous administration of cimetidine 300 mg.

Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. Stearns V, Slack R, Greep N, et al. *J Clin Oncol* 2005; 23: 6919–30.

In an open-label trial, 151 women were randomly assigned to 4 weeks of paroxetine 10 mg or 20 mg followed by placebo for 4 weeks or placebo for 4 weeks followed by paroxetine 10 mg or 20 mg for 4 weeks. Paroxetine 10 mg was associated with a significant improvement in hot flash frequency with no added benefit of increasing the dose to 20 mg.

Venlafaxine for the control of hot flashes: results of a longitudinal continuation study. Barton D, La Vasseur B, Loprinzi C, et al. *Oncol Nurs Forum* 2002; 29: 33–40.

In 102 postmenopausal women, venlafaxine 37.5–150 mg daily for 8 weeks reduced severity and frequency of hot flashes.

Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. Pandya KJ, Raubertas RF, Flynn PJ, et al. *Ann Intern Med* 2000; 132: 788–93.

In 194 postmenopausal women with breast cancer on adjuvant tamoxifen therapy, oral clonidine 0.1 mg daily was effective against tamoxifen-induced hot flashes.

However, several randomized, double-blind, placebo-controlled clinical trials demonstrate conflicting therapeutic effects of oral clonidine in postmenopausal women with climacteric flushing.

Clonidine and facial flushing in rosacea. Cunliffe WJ, Dodman B, Binner JG. *Br Med J* 1977; 1: 105.

A group of 17 patients with rosacea flushing were given either clonidine 0.05 mg twice daily or matched placebo with crossover after 3 months. Only five patients reported an improvement in the frequency and severity of their facial flushing attacks.

Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. Guttuso T Jr, Kurlan R, McDermott MP, et al. *Obstet Gynecol* 2003; 101: 337–45.

After 12 weeks of treatment, gabapentin 900 mg per day was associated with a 45% reduction in hot flash frequency from baseline, as compared with placebo with a 29% reduction in 59 postmenopausal women with seven or more hot flashes per day.

Third-Line Therapies

• Ibuprofen gel	B
• β-blockers	D
• Pulsed dye laser	D
• Intense pulsed light	D
• Botulinum toxin	A
• Thoracic sympathectomy	B
• Somatostatin analogs	B

Topical ibuprofen inhibits blushing during embarrassment and facial flushing during aerobic exercise in people with a fear of blushing. Drummond PD, Minosora K, Little G, et al. *Eur Neuropsychopharmacol* 2013; 23: 1747–53.

A group of 30 participants topically applied ibuprofen 5% over a 1-cm diameter patch on the cheek. The treatment inhibited prostaglandin-mediated blood flow to the cheek during emotional arousal and aerobic exercise.

Symptomatic treatment of idiopathic and rosacea-associated cutaneous flushing with propranolol. Craige H, Cohen JB. *J Am Acad Dermatol* 2005; 53: 881–4.

Eight of the nine patients with histories of facial erythema or blushing reported fewer flushing episodes and diminished symptoms with propranolol therapy between 20 mg and 40 mg twice daily to three times daily.

Particularly, β -blockers suppressed flushing reactions in patients with associated anxiety.

Carvedilol for the treatment of refractory facial flushing and persistent erythema of rosacea. Hsu CC, Lee JY. *Arch Dermatol* 2011; 147: 1258–60.

In a 48-year-old woman with facial flushing and persistent erythema and edema, carvedilol 6.25 mg one to three times daily maintained therapeutic response for 16 months.

Pulsed dye laser treatment of rosacea improves erythema, symptomatology, and quality of life. Tan SR, Tope WD. *J Am Acad Dermatol* 2004; 51: 592–9.

A group of 16 patients with erythematotelangiectatic rosacea were treated with pulsed dye laser at purpuragenic fluences for a total of two treatments at 8-week intervals. A statistically significant improvement was observed in symptoms, which included flushing, burning, itching, dryness, swelling, and skin sensitivity.

Intense pulsed light for the treatment of rosacea and telangiectasias. Kassir R, Kolluru A, Kassir M. *J Cosmet Laser Ther* 2011; 13: 216–22.

In a prospective study, 102 patients with mild-to-severe rosacea received intense pulsed light treatments at 1–3-week intervals with an average of 7.2 treatments. In this cohort, 78% of patients reported reduced flushing and improved skin texture.

A pilot, double-blind, placebo-controlled study to assess the efficacy and safety of incobotulinumtoxinA injections in the treatment of rosacea. Dayan SH, Ashourian N, Cho K. *J Drugs Dermatol* 2017; 16: 549–54.

Nine subjects with rosacea were randomized into either 20 U of incobotulinumtoxinA injections into both cheeks or equal volumes of saline solution injections. IncobotulinumtoxinA injections demonstrated reduction in rosacea features within 4 weeks and increased patient satisfaction, as compared with saline injections.

Effectiveness and safety of endoscopic thoracic sympathectomy for excessive sweating and facial blushing: a systematic review. Malmivaara A, Kuukasjärvi P, Autti-Ramo I, et al. *Int J Technol Assess Health Care* 2007; 23: 54–62.

A review of 15 prospective studies with a follow-up of shorter than 2 years demonstrated that endoscopic thoracic sympathectomy decreased excessive sweating and facial blushing. However, immediate complications related to the procedure occurred in up to 10% of patients. In addition, compensatory sweating below breast level occurred in up to 90% of the patients.

Treatment of the carcinoid syndrome with the longacting somatostatin analogue lanreotide: a prospective study in 39 patients. Ruzniewski P, Ducreux M, Chayvialle JA, et al. *Gut* 1996; 39: 279–83.

In a prospective multicenter study, 39 patients with carcinoid syndrome received lanreotide 30 mg intramuscularly every 14 days for 6 months. After 1 month of treatment, flushing episodes decreased significantly and completely resolved in 39% of the patients.

Follicular mucinosis

Jing Mia Gao, Malcolm Rustin



Follicular mucinosis is characterized histologically by mucinous degeneration of the follicular outer root sheaths and sebaceous glands with an inflammatory infiltrate composed of lymphocytes, histiocytes, and eosinophils. Clinically it presents as erythematous, scaly, and infiltrated plaques with follicular prominence, acneiform lesions, or focal alopecia (alopecia mucinosa). The disorder may be considered as primary follicular mucinosis, an uncommon, benign, idiopathic form of the disease affecting younger patients with fewer lesions, usually situated on the head and neck. Secondary follicular mucinosis occurs in older patients with more generalized lesions and a chronic course associated with other disorders, particularly cutaneous T-cell lymphoma (15%–30% of cases) and folliculotropic mycosis fungoides. No single clinical or histologic feature predicts a benign course, although an isolated patch in the head and neck region is more likely to be primary follicular mucinosis. Follicular mucinosis associated with hematological malignancies tends (not invariably) to be associated with age over 30 years, a wider distribution of lesions, and systemic features such as night sweats, weight loss, or lymphadenopathy. There are also increasing reports of drug-induced follicular mucinosis.

MANAGEMENT STRATEGY

There is no standard therapy, and because spontaneous resolution occurs in the benign forms, *observation* alone is certainly justified, particularly in the younger patient with limited disease. However, the need for *follow-up and evaluation to exclude lymphoma* must be emphasized. Follicular mucinosis associated with

mycosis fungoides, medications, or other neoplastic or inflammatory disorders is managed by treating the underlying associated condition.

Specific Investigations

- Skin biopsy
- Immunohistochemistry and T-cell gene receptor analysis may be helpful adjuncts
- Consider investigations to rule out lymphoma or other underlying disorders, depending on the presenting clinical features (general examination, plain radiology, and computed tomography scans)

The cutaneous mucinoses. Truhan AP, Roenigk HH. *J Am Acad Dermatol* 1986; 14: 1–18.

Follicular mucinosis: a clinicopathologic, histochemical, immunohistochemical and molecular study comparing the primary benign form and the mycosis fungoides-associated follicular mucinosis. Rongioletti F, De Lucchi D, Meyes D, et al. *J Cutan Pathol* 2010; 37: 15–9.

Two excellent reviews of the follicular mucinosis literature, including histopathology and investigation.

Pediatric follicular mucinosis: presentation, histopathology, molecular genetics, treatment and outcomes over an 11-year period at the Mayo Clinic. Alikhan A, Griffin J, Nguyen N, et al. *Pediatr Dermatol* 2013; 30: 192–8.

A review of the clinical and histopathologic findings as well as the treatment and clinical outcomes in children with follicular mucinosis with and without mycosis fungoides.

Follicular mucinosis in patients with hematologic malignancies other than mycosis fungoides: a clinicopathologic study. Geller S, Gomez CJ, Myskowski PL, et al. *J Am Acad Dermatol* 2019; 80: 1704–11.

A review of the clinicopathological characteristics of follicular mucinosis associated with systemic hematologic malignancies versus those that are cutaneous lymphoma-associated.

First-Line Therapies

• Topical and intralesional corticosteroids	D
• Dapsone	E
• Mepacrine	E
• Tetracycline	E

Follicular mucinosis: a study of 47 patients. Emmerson RW. *Br J Dermatol* 1969; 81: 395–413.

Topical or intralesional corticosteroids improved surface eczematous change in eight of 22 patients with benign disease whose lesions resolved spontaneously, independently of treatment, within 2 years. Six of 10 patients with benign chronic disease of more than 2 years' duration showed slight improvement with topical or intralesional corticosteroids.

Neonatal follicular mucinosis. Dalle S, Marrou K, Balme B, et al. *Br J Dermatol* 2007; 157: 609–10.

A solitary plaque on the scalp of a 21-day-old newborn responded to mild-potency topical corticosteroid with resolution within 2 months.

Urticaria-like follicular mucinosis responding to dapsone. Al Harthi F, Kudwah A, Ajlan A, et al. *Acta Derm Venereol* 2003; 83: 389–90.

Itchy, urticaria-like papules on the face, chest, and back of a 25-year-old man for 2 years responded to dapsone 100 mg daily long term after previously failing to respond to oral prednisolone. Attempts to reduce the dosage resulted in recurrence.

Atypical follicular mucinosis controlled with mepacrine. Sonnex TS, Ryan T, Dawber RPR. *Br J Dermatol* 1981; 105: 83–4.

Facial lesions in a 39-year-old man responded to mepacrine 100 mg twice daily. Lesions redeveloped on cessation of therapy.

A case of follicular mucinosis treated successfully with minocycline. Yotsumoto S, Uchimiya H, Kanzaki T. *Br J Dermatol* 2000; 142: 841–2.

A 36-year-old man with follicular mucinosis failed indomethacin treatment. Minocycline 100 mg daily for 6 weeks induced complete remission.

Follicular mucinosis: clinical, histologic and molecular remission with minocycline. Parker S, Murad M. *J Am Acad Dermatol* 2010; 62: 139–41.

A 28-year-old man with follicular mucinosis and a clonal rearrangement of the T-cell receptor gamma chain gene treated with minocycline 100 mg twice daily for 1 year had clinical, histologic, and molecular remission.

Second-Line Therapies

• Isotretinoin	E
• Psoralen and UVA (PUVA)	E
• UVA1	E
• Indomethacin	E
• Interferon	E
• Systemic corticosteroids	E
• Superficial radiotherapy	D
• Photodynamic therapy	E
• Hydroxychloroquine	D
• Topical tacrolimus	E
• Topical pimecrolimus	E
• Topical bexarotene	E
• Topical imiquimod 5%	E

Follicular mucinosis presenting as an acneiform eruption: report of four cases. Wittenberg GP, Gibson LE, Pittelkow MR, et al. *J Am Acad Dermatol* 1998; 38: 849–51.

Two women under 40 years of age had acneiform facial lesions. One had reduced numbers and size of lesions after tretinoin gel 0.01% daily and oral pentoxifylline 400 mg three times daily, followed 2 years later by isotretinoin 40 mg daily. The second significantly improved after isotretinoin 40 mg daily and intermittent clobetasol cream.

Follicular mucinosis treated with PUVA. Kenicer KJA, Lakshminipathi T. *Br J Dermatol* 1982; 107: 48–9.

A 79-year-old woman with facial, truncal, and limb papules with no evidence of systemic disease failed to respond to topical corticosteroids and localized radiotherapy (100 Gy over 5 days). After 98 sessions of psoralen and ultraviolet A (PUVA) over 5 months (total dose 45.4 J/cm²), she remained disease free.

Treatment of idiopathic mucinosis follicularis with UVA1 cold light phototherapy. Von Kobyletzki G, Kreuter JA, Nordmeier R, et al. *Dermatology* 2000; 201: 76–7.

A 26-year-old Caucasian woman with itchy follicular papules on the trunk for 7 months was diagnosed histologically and started on potent corticosteroids with no success. Ultraviolet A1 (UVA1) cold light source (340–530 nm) was used five times a week for 3 weeks, which induced remission, sustained at 3 months.

Follicular mucinosis: response to indomethacin. Kodama H, Umemura S, Nohara N. *J Dermatol* 1988; 15: 72–5.

Plaques and papules on the face and back of a 48-year-old man with no signs of cutaneous lymphoma were unresponsive to topical corticosteroids, UVA, or dapsone. Topical indomethacin 1% in white petrolatum was applied until the lesions disappeared. Oral indomethacin 75 mg daily reduced untreated lesions but was not tolerated. The patient was lesion free 5 years later.

Successful treatment of recalcitrant primary follicular mucinosis with indomethacin and low-dose intralesional interferon alpha. Kim KR, Lee JY, Kim MK, Yoon TY. *Ann Dermatol* 2009; 21: 285–7.

A 52-year-old woman with plaques on both cheeks failed to respond to minocycline, dapsone, topical steroids, and methotrexate. A remarkable improvement was achieved with indomethacin 25 mg twice daily and intralesional corticosteroid administration after 3 months. Intralesional steroids were discontinued, and half-dose indomethacin maintained remission for a further 4 months until lack of availability led to its discontinuation. A rebound flare was controlled with intralesional interferon- α_{2a} 3×10^6 biweekly for 5 weeks with subsequent increase in the injection interval to four times a week. Complete remission was achieved after 6 months with no recurrence 4 months later.

Acneiform follicular mucinosis. Passaro EMC, Silveira MT, Valente NYS. *Clin Exp Dermatol* 2004; 29: 396–8.

A 36-year-old man presented with a 1-year history of acneiform follicular mucinosis and was commenced on 40 mg prednisolone for 20 days. His symptoms improved quickly, and the prednisolone was weaned off by day 48. He had been clear for 7 months at the time of writing.

Alopecia mucinosa: a follow-up study. Coskey RJ, Mehregan AH. *Arch Dermatol* 1970; 102: 193–4.

Patients with one or two facial lesions were given superficial X-ray therapy in a weekly dose of 7.5 Gy for 4 weeks (three cases) or a combination of X-ray therapy and topical corticosteroid cream (six cases). In all cases lesions resolved.

Primary follicular mucinosis: excellent response to treatment with photodynamic therapy. Fernandez-Guarino M, Harto Castano A, Cariilo R. *J Eur Acad Dermatol Venereol* 2008; 22: 393–404.

A 74-year-old woman with a 4-year history of recalcitrant facial plaques cleared with one session of photodynamic therapy (topical methyl-aminolevulinic acid, red light source, 630 nm, 37 J/cm², 7.5 min). She had previously been recalcitrant to topical corticosteroids, narrowband ultraviolet B (UVB), and sulfone. She remained clinically clear 9 months posttreatment.

Treatment of so-called idiopathic follicular mucinosis with hydroxychloroquine. Schneider SW, Metze D, Bonsmann G. *Br J Dermatol* 2010; 163: 420–3.

Six patients were treated with hydroxychloroquine 200 mg three times daily for 10 days with subsequent adjustment for weight, usually to 200 mg twice daily. All patients demonstrated clinical improvement within 6 weeks and complete remission within 2–5 months with full hair regrowth. Individual patients were observed for 3–23 years, and no relapses were seen.

Follicular mucinosis treated with topical 0.1% tacrolimus ointment. Kluk J, Krassilnik N, McBride S. Clin Exp Dermatol 2014; 39: 227–8.

A 36-year-old man treated with topical 0.1% tacrolimus ointment twice daily for lesions affecting the face and neck. Dramatic improvement was observed at 10 days. Topical 0.1% tacrolimus ointment was then tapered over 4 weeks, and remission has been maintained at 1 year.

A case of follicular mucinosis treated successfully with pimecrolimus. Gorpelioglu C, Sarifakioglu E, Bayrak R. Clin Exp Dermatol 2008; 34: 86–7.

A 24-year-old man applied topical 1% pimecrolimus twice daily to a plaque on his chin after lack of response to local corticosteroids. Complete remission was achieved within 1 month, and treatment was discontinued. He remained clear at 7 months' follow-up.

A case of idiopathic follicular mucinosis treated with bexarotene gel. Heyl J, Mehregan D, Kado J, et al. Int J Dermatol 2014; 53: 838–41.

A 34-year-old man applied topical bexarotene gel twice daily to affected areas on the shins for 6 weeks and then reduced to once daily due to local erythema (known side effect of bexarotene). Complete hair regrowth on shins at 26 weeks.

Treatment of primary follicular mucinosis with imiquimod 5% cream. Alonso de Celada R, Feito Rodriguez F, Noguero Morel L, et al. Pediatr Dermatol 2014; 31: 406–8.

A 10-year-old child who had treatment failure with clobetasol propionate applied topical imiquimod 5% daily for 8 weeks, achieving full resolution. Complete remission persists after 3 years.

Folliculitis

Ellen H. de Moll, Robert G. Phelps



Folliculitis is defined as inflammation of the pilosebaceous unit, which can occur superficially, presenting as tender, red papules and pustules, or within the dermal portion of the follicle manifesting as abscesses and furuncles. The etiology of folliculitis can stem from both infectious and non-infectious causes. Among infectious etiologies, bacteria are common, including Gram-positive *Streptococcus* and *Staphylococcus aureus*, as well as Gram-negative *Pseudomonas* infections. Viral etiologies include herpes and molluscum, and fungi and yeast folliculitis can be caused by dermatophytes and *Pityrosporum*, respectively. Less commonly, parasitic folliculitis may be caused by agents such as *Demodex*, scabies, and larva migrans.

Non-infectious folliculitis can be caused by mechanical factors such as friction, occlusion, and trauma, including epilation and sunshine. Irritant folliculitis is associated with cutting oils and coal tar, while a history of significant sun exposure can trigger actinic folliculitis. Perforating folliculitis is commonly associated with diabetes mellitus and chronic renal failure. Eosinophilic pustular folliculitis can be seen in infants, immunocompromised or HIV patients, or the rarer Ofuji's subtype. Many other inflammatory diseases are associated with sterile folliculitis, including Behçet disease, reactive arthritis, systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, inflammatory bowel disease, lymphoproliferative disease, and pregnancy. There is a growing list of medications that can cause folliculitis including lithium, halogens, corticosteroids (both topically and systemically), androgens, ACTH, isoniazid, phenytoin, and sirolimus. Immune-targeted therapy is a category of medications that cause folliculitis as a side effect, including epidermal growth factor receptor (EGFR) inhibitors, tumor necrosis factor- α (TNF- α) inhibitors, trastuzumab, sorafenib, vemurafenib, and dabrafenib.

A thorough history and physical examination are crucial to highlight the most likely etiology in each case. Prolonged antibiotic use in acne patients, particularly tetracycline use, is associated with the development of Gram-negative folliculitis, caused by *Pseudomonas* and other similar bacteria. Exposure to contaminated pools or Jacuzzis are frequent sources of *Pseudomonas* folliculitis. Pityrosporum folliculitis is seen commonly in young adults as pruritic perifollicular papules on the upper trunk, often in warm climates or seasons.

MANAGEMENT STRATEGY

Once the etiology of the folliculitis is ascertained, infectious folliculitis is best managed with a *pathogen-direct antimicrobial regimen*. Therapeutic options include antiseptics and topical or systemic antibiotics for bacterial folliculitis. Coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) should be considered in high-risk patients, pending culture sensitivities. For viral, fungal, yeast, and parasitic folliculitis, *targeted therapy as appropriate* is suitable. Mechanically induced folliculitis often improves with removal of the precipitant. Eosinophilic folliculitis is responsive to phototherapy, and folliculitis related to underlying inflammatory conditions often improves with treatment of primary disease.

Specific Investigations

- Physical examination and past medical history with particular focus on medication usage, concurrent diseases, sun exposure, and family history
- Bacterial, fungal, or viral culture and polymerase chain reaction (PCR) methods with drug sensitivity testing
- Gram stain, Tzanck smear, potassium hydroxide (KOH) preparation
- Tissue biopsy for histologic examination with microorganism stains
- Complete blood count, workup for immunodeficiencies, blood chemistries, renal function test, HIV status
- Nasal culture in chronic or recurrent bacterial cases

First-Line Therapies

Topical therapy

• Mupirocin, clindamycin, and retapamulin for <i>S. aureus</i>	A
• Mupirocin for decolonization of <i>S. aureus</i> of the nares	A
• Daily chlorhexidine or tea tree oil soap body wash for recurrent <i>Staphylococcus</i> spp.	B
• Selenium sulfide shampoo or propylene glycol for <i>Pityrosporum</i> spp.	C
• Permethrin or metronidazole for <i>Demodex</i> spp.	A
• Topical adapalene as prophylaxis for actinic folliculitis	D
• Corticosteroid or tacrolimus for eosinophilic pustular folliculitis	C, D

Oral therapy

• Dicloxacillin or cephalexin for β -hemolytic streptococci or methicillin-sensitive <i>S. aureus</i> (MSSA)	B
• Trimethoprim/sulfamethoxazole, clindamycin, doxycycline, or linezolid for MRSA	B
• Ciprofloxacin for <i>Pseudomonas</i>	C
• Ampicillin, trimethoprim/sulfamethoxazole, or ciprofloxacin for Gram-negative bacteria	B
• Itraconazole or fluconazole for <i>Pityrosporum</i> spp.	A
• Aciclovir, valaciclovir, or famciclovir for herpes	A
• Ivermectin and metronidazole (combination therapy) for <i>Demodex</i> spp.	A, B
• Ivermectin for <i>Demodex</i> spp.	D
• Indomethacin or ciclosporin for eosinophilic pustular folliculitis	C
• Tetracycline for EGFR inhibitor-induced folliculitis	B

Facial bacterial infections: folliculitis. Laureano AC, Schwartz RA, Cohen PJ. Clin Dermatol 2014; 32: 711–4.

Dicloxacillin (250–500 mg four times per day) or cephalexin (250–500 mg four times per day) for 7–10 days is usually sufficient in eradicating conventional facial folliculitis.

Topical retapamulin ointment, 1%, versus sodium fusidate ointment, 2%, for impetigo: a randomized, observer-blinded, noninferiority study. Oranje AP, Chosidow O, Sacchidanand S, et al. Dermatology 2007; 215: 331–40.

Retapamulin was equally efficacious with sodium fusidate in the topical treatment of superficial skin infections.

Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Stevens DL, Bisno AL, Chambers HF, et al. Clin Infect Dis July 15, 2014; 59: e10–52.

The expert panel's recommendations include a decolonization regimen of 5 days of topical mupirocin and daily chlorhexidine body washes plus daily decontamination of personal items to prevent recurrences.

How resistant is *Staphylococcus aureus* to the topical antibiotic mupirocin? Rakshit, T, Suchitra S. Journal of Global Antimicrobial Resistance 2017; 8: 102–3.

Authors express concern for low- and high-level mupirocin resistance in MRSA but, in a prospective study of 405 cases of MRSA, found no evidence of resistance at a tertiary care hospital in India.

Treatment of MRSA soft tissue infections: an overview. Morgan M. Injury 2011; 42: S11–7.

Suggested antimicrobials for folliculitis include cotrimoxazole, clindamycin, doxycycline, linezolid, rifampicin, and fusidic acid.

Community-acquired methicillin-resistant *Staphylococcus aureus* skin infections: implications for patients and practitioners. Cohen PR. Am J Clin Dermatol 2007; 8: 259–70.

A 10- to 14-day course of oral trimethoprim/sulfamethoxazole (1–2 tablets twice daily), clindamycin (300–450 mg four times per day), or doxycycline (100 mg twice daily) is most useful.

Folliculitis: recognition and management. Luelmo-Aguilar J, Santandreu MS. Am J Clin Dermatol 2004; 5: 301–10.

Pseudomonas folliculitis can resolve within 7–10 days with good skin hygiene and avoidance of contaminated water. Oral ciprofloxacin (250–750 mg twice daily) can be used for severe cases or immunocompromised patients.

Demodex mites: facts and controversies. Elston DM. Clin Dermatol 2010; 28: 502–4.

Topical permethrin 5% cream, oral ivermectin, and oral metronidazole are reasonable treatments.

Recalcitrant papulopustular rosacea in an immunocompetent patient responding to combination therapy with oral ivermectin and topical permethrin. Kallen KJ, Davis CL, Billings SD, et al. Cutis 2007; 80: 149–51.

Resolution of the folliculitis was noted with a treatment combination of 5% permethrin and ivermectin.

First reported case of actinic folliculitis treated successfully with topical retinoid. Rahman S, Powell J, Al-Ismaïl D. Clinical and Experimental Dermatology Jan 2020; E-pub.

Topical adapalene was used as prophylaxis for recurrent actinic folliculitis with success.

Successful treatment of eosinophilic pustular folliculitis with topical tacrolimus 0.1% ointment. Ng SS, Tay YK. Dermatol Online J 2012; 18: 10.

Folliculitis in a patient showed improvement with twice-daily application of 0.1% tacrolimus ointment for 2 weeks. Complete resolution was noted after 1 month.

Short-term treatment of pityrosporum folliculitis: a double blind placebo-controlled study. Parsad D, Saini R, Negi KS. J Eur Acad Dermatol Venereol 1998; 11: 188–90.

A randomized trial showed remarkable response to itraconazole (200 mg/day for 7 days) compared with placebo in 26 patients after 5 weeks.

Evidence-based Danish guidelines for the treatment of *Malassezia*-related skin diseases. Hald M, Arendrup MC, Svejgaard EL, et al. Acta Derm Venereol 2015; 95: 12–9.

Despite the greater evidence for efficacy of itraconazole, oral fluconazole is still used more due to its more favorable side-effect profile and lower risk for drug interactions.

Evaluation of the efficacy of oral ivermectin in comparison with ivermectin-metronidazole combined therapy in the treatment of ocular and skin lesions of *Demodex folliculorum*. Salem DA, El-Shazly A, Nabih N, et al. Int J Infect Dis 2013; 17: e343.

In this trial of 120 patients with skin lesions and blepharitis, combination therapy with oral ivermectin and oral metronidazole was more effective for reducing mite counts than oral ivermectin monotherapy.

Therapeutic effectiveness of various treatments for eosinophilic pustular folliculitis. Fukamachi S, Kabashima K, Sugita K, et al. Acta Derm Venereol 2009; 89: 155–9.

Oral ciclosporin was highly effective, as was indomethacin, in alleviating the folliculitis of 11 patients.

Doxycycline for prevention of erlotinib-induced rash in patients with non-small-cell lung cancer (NSCLC) after failure of first-line chemotherapy: a randomized, open-label trial. Deplanque G, Gervais R, Alain Vergnenegre A, et al. JAAD 2016; 74(6): 1077–85.

An open-label, randomized, prospective phase II trial of 147 patients demonstrated that doxycycline reduced the severity, but not the incidence, of EGFR-inhibitor-associated folliculitis.

Second-Line Therapies

Antimicrobial therapies

- Topical fusidic acid for *S. aureus* **A**
- Topical benzoyl peroxide washes and bleach baths for recurrent *Staphylococcus* **B**
- Oral tigecycline and vancomycin for MRSA **A**
- Benzoyl benzoate 10% or crotamiton 10% for *Demodex* spp. **B**

Other treatment modalities

- Intramuscular immunoglobulin **B**
- Photodynamic therapy **D**

High usage of topical fusidic acid and rapid clonal expansion of fusidic acid-resistant *Staphylococcus aureus*: a cautionary tale. Williamson DA, Monecke S, Heffernan H, et al. Clin Infect Dis 2014; 59: 1451.

Topical fusidic acid was once a first-line treatment option but increasing resistance of *S. aureus* to fusidic acid has been observed, and the drug is not as readily available in the United States.

***Demodex folliculorum* and topical treatment: acaricidal action evaluated by standardized skin surface biopsy.** Forton F, Seys B, Marchal JL, et al. Br J Dermatol 1978; 138: 461–6.

Benzyl benzoate 10% and crotamiton 10% as well as 6.4% sublimed sulfur led to a substantial decrease in *Demodex* mites, in an open-label study of randomized patients.

Efficacy and safety of tigecycline compared with vancomycin or linezolid for treatment of serious infections with methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococci*: a Phase 3, multicenter, double-blind,

randomized study. Florescu I, Beuran M, Dimov R, et al. J Antimicrob Chemother 2008; 62(Suppl 1): i17–28.

Tigecycline and vancomycin showed similar clinical cure rates in patients with skin and skin structure infections caused by MRSA.

Intramuscular immunoglobulin for recalcitrant suppurative diseases of the skin: a retrospective review of 63 cases. Goo B, Chung HJ, Chung WG, et al. Br J Dermatol 2007; 157: 563–8.

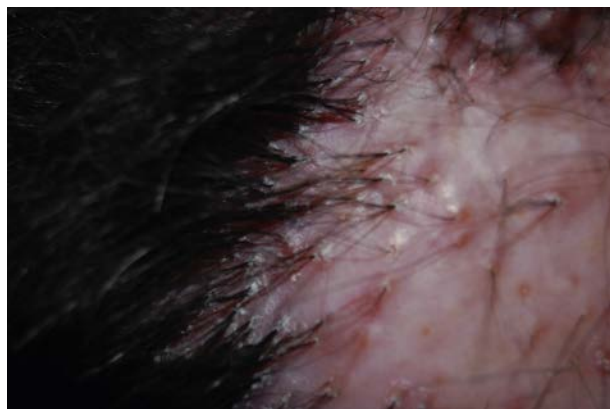
Intramuscular human immunoglobulin injections reduced the severity and the appearance of new lesions in patients with intractable suppurative skin diseases, including folliculitis.

Topical methyl aminolevulinate photodynamic therapy for the treatment of folliculitis. Horn M, Wolf P. Photodermatol Photoimmunol Photomed 2007; 23: 145–7.

Six of seven patients with recalcitrant folliculitis had significant reduction in inflammation with one session of methyl aminolevulinate photodynamic therapy.

Folliculitis decalvans

Nekma Meah, Matthew Harries



Folliculitis decalvans (FD) is a rare, neutrophilic, inflammatory scalp condition presenting as single or multiple areas of alopecia, characterized by pustule formation, erythema, and increased scale with 'tufted' hair follicles evident at the edge of the scarring hair loss patch. FD can involve any areas of the scalp, although the vertex and occiput are most affected; non-scalp involvement is uncommon. FD tends to run a chronic, progressive course. Multivariate analysis from one large retrospective case series suggests that onset at <25 years of age and presence of pustules are independently associated with severe disease.

The condition can occur in either sex but has a predilection for adult men. Frequent isolation of *Staphylococcus aureus* from lesional skin and observed improvement with antistaphylococcal therapy has implicated this bacterium in disease development. An abnormal host response in genetically susceptible individuals may also be contributory. However, recent identification of a persistent, abnormal subepidermal microbiota and non-staphylococcal bacterial biofilms deeper in lesional hair follicles may suggest alternative microbial factors contributing to disease activity.

MANAGEMENT STRATEGY

The goal of therapy in FD is to arrest the inflammatory process and prevent extension of irreversible alopecia. Initial investigations should exclude other conditions known to mimic FD (e.g., tinea capitis) and the rare complication of squamous cell carcinoma. A confirmatory scalp biopsy is often performed, and a bacteriology swab should be taken from lesional skin to determine culture and sensitivity (as bacterial resistance is common). Nasal staphylococcal eradication should also be considered in confirmed carriers.

To date, there are no reported randomized controlled trials for treatment in FD. Efficacy data are available from case reports, case series, and small studies only. *Systemic antibiotics* (tetracyclines, flucloxacillin, macrolides, and third generation cephalosporins) remain the mainstay of initial therapy, although relapses are common on stopping treatment. The combination of oral rifampicin and clindamycin administered as a 10-week course has been shown to reduce activity and induce sustained remission, and thus is considered the most effective treatment for FD. Occasionally, repeat

courses may be required. Rifampicin monotherapy is not advised due to the risk of developing drug resistance.

Second-line treatment options include isotretinoin, corticosteroids, dapsone, and oral zinc sulfate. Isotretinoin is reported to have lower relapse rates than antibiotics with treatment cessation, while corticosteroids (topical, intralesional, and oral) are recognized adjunctive therapies. Dapsone (75–100 mg) may also produce a satisfactory outcome but often requires low-dose maintenance therapy to sustain remission. Oral zinc sulfate, as monotherapy or combined with fusidic acid, may also be efficacious.

Third-line treatment options include a range of topical, physical, biological, and cellular therapy. Topical tacrolimus ointment, medical (manuka) honey, photodynamic therapy, and human immunoglobulin therapy may be effective. More recently, biological therapy (adalimumab/biosimilar, infliximab, and secukinumab) have been successful in treating severe recalcitrant disease.

In those unresponsive to medical therapy surgical interventions, such as scalp excision, laser epilation or superficial radiotherapy may be considered to permanently epilate the scalp, thereby removing the inflammatory focus of the condition.

Specific Investigations

- Scalp skin swab for bacteriology
- Nasal swab for bacteriology
- Scrapings and plucked hairs for mycology
- Scalp biopsy
- Consider immunodeficiency screen

How not to get scar(r)ed: a guide to diagnosis in primary cicatricial alopecias. Harries MJ, Trueb R, Messenger A, et al. Br J Dermatol 2009; 160: 482–501.

A systematic approach is presented to accurately diagnose scarring alopecias, including FD.

Tinea capitis mimicking folliculitis decalvans. Tangjaturonruamee C, Piraccini BM, Vincenzi C, et al. Mycoses 2011; 54: 87–98.

A case of tinea capitis caused by *Microsporum canis* mimicking FD.

Folliculitis decalvans and cellular immunity – 2 brothers with oral candidiasis. Shitara A, Igareshi R, Morohashi M. Jpn J Dermatol 1974; 28: 133.

Severe FD in two siblings who also had chronic oral candidiasis; defective cell-mediated immunity was demonstrated.

Updates in therapeutics for folliculitis decalvans: a systematic review with evidence-based analysis. Rambhia PH, Conic RR, Murad A, et al. J Am Acad Dermatol 2019; 80: 794–801.

A systematic review of current treatments for FD and treatment outcomes.

First-Line Therapies

Topical antibiotics

- Fusidic acid, clindamycin, erythromycin, mupirocin **E**

Systemic antibiotics

- Rifampicin and clindamycin **C**
- Tetracycline antibiotics, flucloxacillin, fluoroquinolones, and third generation cephalosporins **C**
- Azithromycin **D**

Folliculitis decalvans: a multicenter review of 82 patients. Vañó-Galván S, Molina-Ruiz AM, Fernández-Crehuet P, et al. *J Eur Acad Dermatol Venereol* 2015; 29: 1750–7.

A retrospective review of 82 patients with FD. Between 90% and 100% of patients on either oral doxycycline 100 mg daily, azithromycin 500 mg three times a week, or combination of clindamycin and rifampicin demonstrated improvement.

Effective treatment of folliculitis decalvans using selected antimicrobial agents. Sillani C, Bin Z, Ying Z, et al. *Int J Trichology* 2010; 2: 20–3.

Thirteen patients with mild-to-moderate FD. Minocycline 100 mg twice daily as monotherapy was effective in six patients, with a further three patients responding to minocycline and rifampicin in combination.

Folliculitis decalvans including tufted folliculitis: clinical, histological and therapeutic findings. Powell JJ, Dawber RPR, Gatter K. *Br J Dermatol* 1999; 140: 328–33.

Eighteen patients with folliculitis decalvans were treated with oral rifampicin 300 mg twice daily and oral clindamycin 300 mg twice daily combination for 10 weeks. All patients reported improvement during treatment, with 10 patients achieving a lasting remission.

Second-Line Therapies

• Isotretinoin	C
• Systemic/intralesional corticosteroids	D
• Fusidic acid and oral zinc sulfate	E
• Dapsone	E

Oral isotretinoin as the most effective treatment in folliculitis decalvans: a retrospective comparison of different treatment regimens in 28 patients. Tietze JK, Heppt MV, von Preußen A, et al. *J Eur Acad Dermatol Venereol* 2015; 29: 1816–21.

Nine of 10 patients receiving oral isotretinoin (0.2–0.5 mg/kg daily for 5–7 months followed by 10 mg daily two to three times a week) achieved complete remission. Three patients required low-dose isotretinoin long term.

Isotretinoin treatment for folliculitis decalvans: a retrospective case-series study. Aksoy B, Hapa A, Mutlu E. *Int J Dermatol* 2018; 57: 250–3.

Thirty-nine male patients with FD treated with isotretinoin monotherapy 0.1–1.02 mg/kg/day (median duration of therapy of 2.5 months): 82% (32) achieved complete response, 84.6% (22) had hair regrowth, and 44% (16) achieved durable remission. Of note, 66% of patients on higher dose of treatment and longer duration of therapy (≥ 0.4 mg/kg for ≥ 3 months) did not experience disease relapse.

Retrospective review of folliculitis decalvans in 23 patients with course and treatment analysis of long-standing cases. Bunagan MJ, Banka N, Shapiro J. *J Cutan Med Surg* 2015; 19: 45–9.

The combination of oral tetracycline, intralesional triamcinolone every 4–6 weeks, and clobetasol lotion resulted in remission in seven out of 10 patients on this regimen.

Folliculitis decalvans. Long-lasting response to combined therapy with fusidic acid and zinc. Abeck D, Korting HC, Braun-Falco O. *Acta Derm Venereol* 1992; 72: 143–5.

Three patients responded to oral fusidic acid (500 mg three times a day) and topical fusidic acid cream for 3 weeks combined with oral zinc sulfate 200 mg twice a day for 6 months and once a day thereafter. Disease relapse coincided with stopping zinc sulfate.

Dapsone treatment of folliculitis decalvans. Paquet P, Pierard GE. *Ann Dermatol Venereol* 2004; 131: 195–7.

Two patients treated with dapsone 75–100 mg daily showed clinical response 1–2 months into treatment. A maintenance dose of 25 mg daily resulted in sustained remission.

Third-Line Therapies

• Topical photodynamic therapy	C
• Systemic photodynamic therapy	E
• Tacrolimus 0.1% ointment	E
• Keratolytics and tar shampoo	E
• Medical honey	E
• Oral L-tyrosine	E
• Surgical excision	E
• Shaving of scalp	E
• Laser epilation	E
• Superficial radiotherapy	E
• Anti-TNF therapy	E
• Secukinumab	E
• Immunoglobulin therapy	E
• Autologous fat transplantation	E

Treatment of folliculitis decalvans with photodynamic therapy: results in 10 patients. Miguel-Gomez L, Vañó-Galván S, Perez-Garcia B, et al. *J Am Acad Dermatol* 2015; 72: 1085–7.

A prospective study of topical photodynamic therapy delivered every 4 weeks. Nine patients (90%) achieved clinical improvement at 16 weeks.

Systemic photodynamic therapy in folliculitis decalvans. Collier NJ, Allan D, Diaz Pesantes F, et al. *Clin Exp Dermatol* 2018; 43: 46–9.

A case of recalcitrant FD demonstrating clinical and histological response to systemic photodynamic therapy (PDT) (ultraviolet light (100–140 J/cm²) with the photosensitizer porfimer sodium (1 mg/kg)). Four treatments were administered over several months. Adverse effects were mild photosensitivity.

Treatment of folliculitis decalvans with tacrolimus ointment. Bastida J, Valeron-Almazan P, Santana-Molina N, et al. *Int J Dermatol* 2012; 51: 216–20.

Tacrolimus 0.1% ointment applied twice daily in four patients with recalcitrant disease. A favorable outcome was achieved in all four cases.

Resolution of folliculitis decalvans with medical honey. Yeh J, Hartman R, Xu J. *Dermatol Online J* 2019; 25: 14.

Nightly applications of manuka honey combined with oral cephalixin in one patient resulted in resolution of pustules allowing the antibiotic to be discontinued.

Tufted hair folliculitis. Tong AK, Baden HP. *J Am Acad Dermatol* 1989; 21: 1096–9.

Tufted folliculitis successfully treated by surgical excision.

Nd:YAG laser treatment of recalcitrant folliculitis decalvans. Parlette EC, Kroeger N, Ross EV. *Dermatol Surg* 2004; 30: 1152–4.

Remission achieved with laser epilation in a patient with Fitzpatrick skin type VI.

Treatment of folliculitis decalvans using intensity-modulated radiation via tomotherapy. Elsayad K, Kriz J, Haverkamp U, et al. *Strahlenther Onkol* 2015; 191: 883–8.

A case of recalcitrant FD responding to 11 Gy delivered in two radiation series.

Therapy-resistant folliculitis decalvans and lichen planopilaris successfully treated with adalimumab. Kreutzer K, Effendy I. *J Dtsch Dermatol Ges* 2014; 12: 74–6.

Two patients with FD responded well to adalimumab 40 mg administered fortnightly. Marked improvement was noted after 8–12 weeks.

A case of isotretinoin therapy-refractory folliculitis decalvans treated successfully with biosimilar adalimumab (Exemptia). Shireen F, Sudhakar A. *Int J Trichology* 2018; 10: 240–1.

A 23-year-old male with refractory FD is effectively treated with biosimilar adalimumab (Exemptia). The treatment regimen included 80 mg subcutaneously (SC) weekly for 2 weeks; 40 mg SC weekly in weeks 3, 4, 6, 8, 10, 12, 14, and 16; and then

monthly thereafter. The patient remained in remission on maintenance therapy.

Successful treatment of refractory folliculitis decalvans with secukinumab. Ismail FF, Sinclair R. *Aus J Dermatol* 2020; 61(2): 165–166.

A 30-year-old female with recalcitrant FD was treated with secukinumab (300 mg SC in weeks 0, 1, 2, 3 and 4, followed by 300 mg SC every 4 weeks thereafter). Significant improvement was reported 4 months after initiation of therapy.

Intramuscular immunoglobulin for recalcitrant suppurative diseases of the skin: a retrospective review of 63 cases. Goo B, Chung HJ, Chung WG, et al. *Br J Dermatol* 2007; 157: 563–8.

Three patients with FD were rated to have a 'good response' after intramuscular human immunoglobulin administered once a month.

Adipose tissue transplant in recurrent folliculitis decalvans. Tedesco M. *Int J Immunopathol Pharmacol* 2018; 32: 2058738418814688.

Two sessions of autologous fat transplantation were successful in controlling active FD in a 41-year-old female. Twenty milliliters of fat were aspirated from the median knee and administered into the inflamed scalp per session. Presumably the adipose tissue is functioning as a source of stem cells.

Fox–Fordyce disease

Ian H. Coulson



Obliteration of the follicular infundibulum with keratin in the apocrine gland-bearing skin is the cause of this rare, paroxysmally intensely itchy condition. Apocrine sweat retention and rupture of the gland duct under periods of apocrine sudomotor stimulation, particularly emotional stress, result in the development of an itchy, spongiotic intraepidermal vesicle. It mainly affects women between the ages of 13 and 35 years but has rarely been reported before puberty, after menopause, and in men. Itchy, dome-shaped, flesh-colored or keratotic papules that develop peripubertally in the apocrine areas of the axillae, pubic, periumbilical, and periareolar skin characterize this condition. Sparsity of axillary hair and hypohidrosis are usual, although rarely the disease can be exacerbated by hyperhidrosis. Improvement observed in pregnancy and during the administration of oral contraceptives has led to speculation regarding an endocrine etiology, although this has been unsubstantiated by blood sex hormone investigations. Very few reports in twins and within families suggest a possible genetic component. Fox–Fordyce disease (FFD) can occur after laser hair removal and has been reported in Turner syndrome.

MANAGEMENT STRATEGY

There are no controlled trials of any agents in FFD.

Topical and intralesional corticosteroids are frequently tried and may be of limited benefit, but atrophy in the axillary area will limit their potency and duration of use. Topical *tretinoin* and *adapalene* have been reported to reduce itch, but alternation with a mild corticosteroid may be needed to reduce retinoid irritancy.

Clindamycin lotion may be of help. The oral contraceptive pill (OCP) may bring relief to some women. Oral *isotretinoin* may give temporary relief. *Electrocautery* and *excision* of the periareolar skin may offer permanent solutions. A recent report advocates an ingenious method of removal of the apocrine glands using a micro-liposuction cannula. There is a single report of axillary disease responding to intralesional botulinum toxin injection. Physical modalities such as *microwave devices* and CO₂ and erbium glass lasers have their advocates.

Specific Investigation

- Biopsy

Fox–Fordyce disease: diagnosis by transverse histologic sections. Stashower ME, Krivda SJ, Turiansky GW. *J Am Acad Dermatol* 2000; 42: 89–91.

Transverse sectioning demonstrates the follicular plugging and infundibular spongiosis more readily than conventional sections.

Dilation of apocrine glands. A forgotten but helpful histopathological clue to the diagnosis of axillary Fox–Fordyce disease. Macarenco RS, Garces S JC. *Am J Dermatopathol* 2009; 31: 393–7.

Apocrine gland dilation may be used as a low-power magnification clue, which should be followed by a search for further histologic changes to confirm or rule out the diagnosis.

Clinicopathological study of Fox–Fordyce disease. Kao PH, Hsu CK, Lee JY. *J Dermatol* 2009; 36: 485–90.

Focal spongiosis in the upper infundibulum with perifollicular fibrosis and lymphohistiocytic infiltrate were consistent features in their case series.

Fox–Fordyce-like disease following laser hair removal appearing on all treated areas. Helou J, Maatouk I, Moutran R, et al. *Lasers Med Sci* 2013; 28: 1205–7.

The most recent of reports highlighting that laser epilation in several anatomic sites may induce FFD.

Perifollicular xanthomatosis as a key histologic finding in Fox–Fordyce disease. Mataix J, Silvestre JE, Niveiro M, et al. *Actas Dermosifiliogr* 2008; 99: 145–8.

There are occasional conditions to consider in the differential diagnosis! There is even controversy as to whether perifollicular xanthomatosis is part of the spectrum of this disorder.

First-Line Therapies

• Topical and intralesional corticosteroids	D
• Topical clindamycin	E
• Oral contraceptive pill	D
• Topical retinoids	D
• Ultraviolet B (UVB)	D
• Topical pimecrolimus and tacrolimus	D
• Topical calcipotriol betamethasone	E

A new treatment of Fox–Fordyce disease. Helfman RJ. *South Med J* 1962; 55: 681–4.

A single report of successful symptom relief of axillary lesions with 10 mg/mL triamcinolone diluted with an equal volume of 1% lidocaine to four sites on nine occasions over 3 months.

Fox-Fordyce disease: a report of 2 cases responding to topical clindamycin. George A, Bhatia A, Thomas E. *Int J Dermatol* 2013; 52: 1571–2.

Some authors speculate that the keratolytic effect of propylene glycol may have been responsible for the therapeutic effect.

Fox-Fordyce disease. Treatment with an oral contraceptive. Kronthal HI, Pomeranz JR, Sitomer G. *Arch Dermatol* 1965; 91: 243–5.

Two female patients responded to a high-estrogen dose combined OCP (norethynodrel and mestranol).

Fox-Fordyce disease: response to adapalene 0.1%. Kassuga LE, Medrado MM, Chevrant NS, et al. *An Bras Dermatol* 2012; 87: 329–31.

The authors report that 0.1% adapalene cream produced satisfactory improvement of the signs and symptoms of a single patient with FFD. In acne, this product is less irritating than tretinoin, so it may be a more tolerable topical retinoid option.

Topical tretinoin use is reported but likely to be more irritant.

Treatment of Fox-Fordyce disease. Pinkus H. *JAMA* 1973; 223: 924.

Erythemogenic doses of UVB (once weekly for 4–6 weeks) produced long-lasting relief to several patients.

Pimecrolimus is effective in Fox-Fordyce disease. Pock L, Svrcková M, Machácková R. *Int J Dermatol* 2006; 45: 1134–5.

A series of three patients who benefited from topical pimecrolimus.

Clinical effects of topical tacrolimus on Fox-Fordyce disease. Kaya Erdoğan H, Bulur I, Kaya Z. *Case Rep Dermatol Med* 2015: 205418.

Two case reports, one with a successful response in terms of itch, from twice-daily 0.1% tacrolimus ointment applied for 3 months.

Rapid remission with calcipotriol betamethasone in refractory Fox-Fordyce disease. Yang L, Zhang S, Wang T, et al. *Dermatol Ther* 2020; 33: e13223. doi: 10.1111/dth.13223.

A case report of a 26-year-old woman with recalcitrant FFD who responded to calcipotriol betamethasone within 2 weeks, with no recurrence at 3 months.

Second-Line Therapies

• Oral isotretinoin	E
• Electrocautery	D
• Excision	D
• Apocrine gland removal using microliposuction	E
• Botulinum toxin	E
• Microwave and lasers	E

Fox-Fordyce disease in a male patient – response to oral retinoid treatment. Effendy I, Ossowski B, Happle R. *Clin Exp Dermatol* 1994; 19: 67–9.

Oral treatment with isotretinoin (30 mg daily for 8 weeks and then 15 mg daily for 2 months) resulted in temporary relief. Relapse occurred 3 months after discontinuation.

Fox-Fordyce disease in the postmenopausal period treated successfully with electrocoagulation. Pasricha JS, Nayyar KC. *Dermatologica* 1973; 147: 271–3.

Electrocoagulation to a level of 3–4 mm under local anesthetic produced a permanent resolution of symptoms in the axillae of two patients.

Surgical treatment of areolar hidradenitis suppurativa and Fox-Fordyce disease. Chavoin J-P, Charasson T, Barnard J-D. *Ann Chir Plast Esthet* 1994; 39: 233–8.

A simple technique involving dermal detachment of the areola, excision of the underlying apocrine glands, and reattachment of the areola with good cosmetic results.

This treatment has not proved beneficial long term.

Axillary Fox-Fordyce disease treated with liposuction-assisted curettage. Chae KM, Marshall MA, Marshall SE. *Arch Dermatol* 2002; 138: 452–4.

A novel technique of curettage removal of the apocrine glands using a small liposuction cannula with symptom relief, great cosmesis, and a follow-up at publication of 8 months. A liposuction cannula was introduced through a stab incision in the axilla and, with the aperture of the cannula turned up toward the underside of the dermis, the deeper dermis was curetted to create inflammation and subsequent fibrosis. The same technique can be used to treat axillary hyperhidrosis.

Successful treatment of refractory pruritic Fox-Fordyce disease with botulinum toxin type A. González-Ramos J, Alonso-Pacheco ML, Goiburú-Chenú B, et al. *Br J Dermatol* 2016; 174: 458–9.

A single case report of a woman receiving 100 U of Botox to each axilla; itching completely abated and papules partially regressed, and the response was sustained over 8 months of follow-up after a single treatment.

Successful treatment of areolar Fox-Fordyce disease with surgical excision and 1550-nm fractionated erbium glass laser. Han HH, Lee JY, Rhie JW. *Int Wound J* 2016; 13: 1016–9.

Fox-Fordyce disease treatment with fractional CO₂ laser. Ahmed Al-Qarqaz F, Al-Shannag R. *Int J Dermatol* 2013; 52: 1571–2. Single reports regarding different laser modalities.

A novel modality using microwave technology for the treatment of Fox-Fordyce disease. Taylor D, Au J, Boen M, et al. *JAAD Case Rep* 2015; 2(1): 1–3.

A single report of utilizing the MiraDry microwave system for axillary disease. Two treatments were required.

Furunculosis

Charles A. Gropper, Karthik Krishnamurthy



Furunculosis, commonly referred to as *boils*, is a deep infection of the pilosebaceous unit. Lesions may occur on any hair-bearing surface, including the nares. Coalescing multiple lesions (carbuncles) are usually very tender and may have multiple draining sites.

MANAGEMENT STRATEGY

The infectious agent most commonly implicated is *Staphylococcus aureus*; methicillin-resistant strains of *S. aureus* (MRSA) are now recognized as the dominant isolate overall. In recent years, the designations of community-acquired MRSA (CA-MRSA) versus hospital-acquired MRSA (HA-MRSA) have become blurred due to a convergence in both antibiotic susceptibility profiles and risk of sequelae. There are rare reports of dissemination causing epidural abscess, bacterial endocarditis, and pulmonary infection.

Group A beta-hemolytic *Streptococcus*, Gram-negative bacteria, and yeast-forms should remain in the differential diagnosis. In addition, *Mycobacterium* spp., especially *M. fortuitum*, have been implicated in furunculosis in patients using footbaths in beauty salons.

Nasal, pharyngeal, axillary, perineal, and rectal pathogen carriage is implicated in recurrent disease. In rare cases, patients with impaired neutrophil function and immunodeficiency syndromes, such as common variable immunodeficiency and hyper-IgE syndrome, also present with recurrent 'cold abscess' furunculosis.

Isolated lesions should be *incised and drained*. Multiple, mostly observational, studies indicate high postsurgical cure rates (85%–90%) whether or not an active antibiotic is used. Therefore, according to the Centers for Disease Control (2006) and Infectious Diseases Society of America (2011), empiric antibiotics should be reserved for those with:

- Severe or extensive disease (e.g., involving multiple sites of infection)

- Rapid progression in presence of associated cellulitis
- Signs and symptoms of systemic illness
- Associated comorbidities/immunosuppression (diabetes mellitus, human immunodeficiency virus, neoplasm)
- Extremes of age
- Abscess in area difficult to drain completely (e.g., face, hand, and genitalia)
- Associated septic phlebitis
- Lack of response to incision and drainage alone

Swabs of any purulent discharge should be collected for bacterial culture; antibiotic therapy may be redirected based on sensitivities and clinical scenario. Acid-fast staining and culture may be warranted if a temporal relationship to a pedicure is noted. Currently, antibiotics carrying a Food and Drug Administration (FDA) indication for use against MRSA include *linezolid*, *ceftaroline* ('advanced'-generation cephalosporin), *telavancin* (similar to vancomycin), *tigecycline* (derivative of minocycline), and *teicoplanin*. Other antibiotics with anti-MRSA activity include *trimethoprim-sulfamethoxazole* (TMP-SMX), *daptomycin*, *vancomycin*, *doxycycline*, *minocycline*, *clindamycin*, *rifampin*, and *quinupristin-dalfopristin*. Evidence of nasal carriage of staphylococci should be sought in those with recurrent disease and eradicated with either *oral rifampicin* (not as monotherapy) or *nasal mupirocin* or *fusidic acid*.

Specific Investigations

- Culture and sensitivity of purulent drainage
- Acid-fast stain and culture (if indicated)
- Moistened nasal swab for culture (if recurrent)
- Neutrophil count and immunoglobulin levels (if relevant and/or recurrent)

First-Line Therapy

- Surgery: incision and drainage

A

Randomized, double-blind, placebo-controlled trial of cephalexin for treatment of uncomplicated skin abscesses in a population at risk for community-acquired methicillin-resistant *Staphylococcus aureus* infection. Rajendran PM, Young D, Maurer T, et al. Antimicrob Agents Chemother 2007; 51: 4044–8.

Randomized, double-blind trial of 166 outpatient subjects comparing placebo to cephalexin at 500 mg orally four times daily for 7 days after incision and drainage of skin and soft tissue abscesses. The primary outcome was clinical cure or failure 7 days after incision and drainage. Of the isolates tested 87.8% were MRSA. Clinical cure rates (90.5% in the 84 placebo recipients and 84.1% in the 82 cephalexin recipients) provides strong evidence that antibiotics may be unnecessary after surgical drainage of uncomplicated skin and soft tissue abscesses caused by community strains of MRSA.

Second-Line Therapies

- Doxycycline or minocycline
- Trimethoprim/sulfamethoxazole
- Clindamycin
- Linezolid

B
B
B
B

Adjunctive for patients meeting criteria are listed in Management Strategy earlier.

Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. Liu C, Bayer A, Cosgrove SE, et al. Clin Infect Dis 2011; 52: 285–92.

Oral antibiotics that may be used as empiric therapy for CA-MRSA include TMP-SMX, doxycycline (or minocycline), clindamycin, and linezolid. Several observational studies and one small, randomized trial suggest that TMP-SMX, doxycycline, and minocycline are effective for such infections. Clindamycin is effective in children with CA-MRSA skin and soft tissue infection (SSTI). Linezolid is FDA-approved for SSTI but is not superior to less expensive alternatives.

Tetracyclines as an oral treatment option for patients with community onset skin and soft tissue infections caused by methicillin-resistant *Staphylococcus aureus*. Ruhe JJ, Menon A. Antimicrob Agents Chemother 2007; 51: 3298–303.

Retrospective study of 276 outpatients. The median percentage of patients infected with MRSA strains that were susceptible to tetracycline was 95%. A total of 225 patients (80%) underwent incision and drainage. Doxycycline or minocycline was administered in 90 episodes (32%); the other 192 SSTIs were treated with β -lactams. Receipt of β -lactam antibiotics was associated with treatment failure.

Prevalence, severity, and treatment of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) skin and soft tissue infections in 10 medical clinics in Texas: a South Texas Ambulatory Research Network (STARNet) study. Forcade NA, Parchman ML, Jorgensen JH, et al. J Am Board Fam Med 2011; 24: 543–50.

A community-based study. Overall, 73 of 119 (61%) patients presenting with SSTIs meeting eligibility requirements had CA-MRSA. Most received incision and drainage plus an antibiotic (64%). Antibiotic monotherapy was frequently prescribed: TMP-SMX (78%), clindamycin (4%), doxycycline (2%), and mupirocin (2%). The rest received TMP-SMX in combination with other antibiotics. Isolates were 93% susceptible to clindamycin and 100% susceptible to TMP-SMX, doxycycline, vancomycin, and linezolid.

Trimethoprim-sulfamethoxazole or clindamycin for treatment of community-acquired methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections. Hyun DY, Mason EO, Forbes A, et al. Pediatr Infect Dis J 2009; 28: 57–9.

A retrospective study of 508 patients who had MRSA isolated either from surgically obtained drainage or from spontaneous drainage of the infection site; 215 patients were prescribed oral TMP-SMX therapy, and 200 were prescribed oral clindamycin. No significant differences were observed in the percentage who returned because of worsening or incomplete resolution. Most of the patients had incision and drainage (94% of TMP-SMX patients, 86% of clindamycin patients), so results may reflect improvement from incision and drainage than antibiotic choice.

Third-Line Therapies/Prevention

• Topical nadifloxacin	B
• Nasal mupirocin	B
• Bleach bath	E
• Colonization with less pathogenic staphylococci	E
• Retapamulin	E
• Fusidic acid	B

Efficacy and safety of nadifloxacin for bacterial skin infections: results from clinical and postmarketing studies. Narayanan V, Motlekar S, Kadhe G, et al. Dermatol Ther 2014; 4: 233–48.

A total of 272 subjects were enrolled in the study, and subjects were randomly assigned to one of the three treatment groups: 92 in the nadifloxacin group, 90 in the mupirocin group, and 90 in the framycetin group. A significant reduction in the mean scores for bacterial infection symptoms in the nadifloxacin groups was observed compared with the mupirocin, framycetin, and fusidic acid groups. No adverse events (AEs) were reported in the clinical studies.

Randomized controlled trial of chlorhexidine gluconate for washing, intranasal mupirocin, and rifampin and doxycycline versus no treatment for the eradication of methicillin-resistant *Staphylococcus aureus* colonization. Simor AE, Phillips E, McGeer A, et al. Clin Infect Dis 2007; 44: 178–85.

Treatment with this regimen for 7 days was safe and effective in eradicating MRSA colonization in hospitalized patients for at least 3 months.

Hypochlorite killing of community-associated methicillin-resistant *Staphylococcus aureus*. Fisher RG, Chain RL, Hair PS. Pediatr Infect Dis J 2008; 27: 934–5.

In vitro study of hypochlorite (bleach) against CA-MRSA. Maximal killing was found after 5 minutes in 2.5 μ L/mL bleach. A 2.5- μ L/mL bleach solution is approximately equivalent to one-half cup of bleach in one-quarter tub of water. In vivo studies will be required to show clinical effectiveness.

Recurrent staphylococcal infection in families. Steele R. Arch Dermatol 1980; 116: 189–90.

Fifteen of 17 families inoculated with less pathogenic strains of *S. aureus* remained disease free at 6 months, whereas only four of the 15 control families had no recurrences.

In vitro activity of retapamulin against *Staphylococcus aureus* isolates resistant to fusidic acid and mupirocin. Woodford N, Afzal-Shah M, Warner M, et al. J Antimicrob Chemother 2008; 766–8.

Retapamulin inhibited 99.9% of all *S. aureus* isolates. Further in vivo studies are indicated to assess efficacy in the treatment of furunculosis.

Treatment and prevention of recurrent staphylococcal furunculosis: clinical and bacteriologic follow-up. Hedström SA. Scand J Infect Dis 1985; 17: 55–8.

Sodium fusidate ointment was used twice daily for a month as prophylaxis for nasal furunculosis with cessation of furuncles in 10 of 20 cases. Controls took antibiotics systemically, and three of 20 had no furuncles. After a year, those who used topical therapy had fewer recurrent lesions.

Geographic tongue

Jessica Shiu, Jennifer K. Chen, Janellen Smith



Geographic tongue is a reactive mucosal inflammatory condition characterized by arcuate or annular alternating hypertrophic or atrophic filiform papillae producing a geographic pattern. Synonyms include *benign migratory glossitis* and *glossitis areata migrans*. Geographic tongue may be an asymptomatic incidental finding. Similar changes may occur in oral sites other than the tongue (geographic stomatitis or benign migratory stomatitis).

MANAGEMENT STRATEGY

Geographic tongue is a common glossitis that affects 2% of the population. If asymptomatic, no treatment is necessary other than reassurance that the condition is benign and usually not a sign of systemic illness. Geographic tongue will remit spontaneously but may persist for years. Occasionally, patients may complain of a burning discomfort, particularly in atrophic areas. Effective therapy can be challenging.

Geographic tongue has been associated with psoriasis (especially pustular psoriasis); the two diseases share a strong association with human leukocyte antigen (HLA)-Cw6. It has also been associated with reactive arthritis; pityriasis rubra pilaris; atopic diathesis; Down syndrome; nutritional deficiency; diabetes; hormonal changes; and medications including lithium, oral contraceptives, and vascular endothelial growth factor or multikinase inhibitors such as bevacizumab, sunitinib, and sorafenib. The clinician should also consider acute or chronic atrophic candidiasis as a differential diagnosis.

For symptomatic patients, measures that may be considered include the avoidance of hot, spicy, or acidic foods;

gentle brushing of the tongue; avoidance of harsh antibacterial mouthwashes, chewing gum, and breath mints; and soothing rinses with saline solutions. Occasionally, the topical application of *fluorinated corticosteroids* or *diphenhydramine elixir* after meals and at bedtime may be recommended. *Topical anesthetic rinses or gels* provide temporary relief. *Antiyeast treatments* may be palliative.

Specific Investigations

- Culture for candidiasis
- If symptomatic, consider complete blood cell count, iron panel, vitamin B₆, vitamin B₁₂, vitamin D, folate, and zinc levels; glucose; and hemoglobin A_{1c}
- No investigation necessary in asymptomatic patients

Geographic tongue. Shareef S, Etefagh L. [Updated 2020 Feb 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2020 Jan. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK554466/>.

The topic and the differential diagnosis are reviewed. Patients without symptoms do not require additional studies.

Geographic tongue and psoriasis: clinical, histopathological, immunohistochemical and genetic correlation – a literature review. Picciani BL, Domingos TA, Teixeira-Souza T, et al. *An Bras Dermatol* 2016; 91: 410–21.

Review and discussion on how geographic tongue and psoriasis share clinical, histological, and genetic features.

First-Line Therapies

• Avoidance of spicy food, mouthwashes, chewing gum, and breath mints	D
• Topical corticosteroids (e.g., fluocinonide 0.05% gel, dexamethasone elixir, triamcinolone 0.1% in oral base)	C
• Topical antihistamines (e.g., diphenhydramine elixir 12.5 mg/5 mL diluted 1:4 with water)	C
• Antiyeast therapy	E
• Swish-and-spit tacrolimus regimen twice daily (e.g., dissolve 1-mg tacrolimus capsule dissolved in 500 mL of water, swish for 2 minutes and spit)	C

Symptomatic benign migratory glossitis: report of two cases and literature review. Sigal MJ, Mock D. *Pediatr Dent* 1992; 14: 392–6.

Management with topical corticosteroids and topical antihistamines is discussed.

Effectiveness of the tacrolimus swish-and-spit treatment regimen in patients with geographic tongue. Aung-Din D, Heath M, Wechter T, et al. *JAMA Dermatol* 2018; 154: 1481–2.

Retrospective medical record review of 20 patients with geographic tongue receiving twice daily tacrolimus spit-and-swallow regimen. Patients were instructed to dissolve 1-mg tacrolimus capsule dissolved in 500 mL of water, then swish for 2 minutes, and then spit out the solution. The risk of systemic effects is minimal because inadvertent consumption of a single dose is approximately 0.01 mg of tacrolimus. Most patients were also on topical steroids, clotrimazole trenches, or gabapentin (100–200 mg daily).

Glossitis and other tongue disorders. Byrd JA, Bruce AJ, Rogers RS III. *Dermatol Clin* 2003; 21: 123–34.

A review of geographic and other tongue disorders.

Painful geographic tongue (benign migratory glossitis) in a child. Menni S, Boccardi D, Crosti C. *J Eur Acad Dermatol Venerol* 2004; 18: 737–8.

Prevalence of fungi in cases of geographic tongue and fissured tongue. Dudko A, Kurnatowska AJ, Kurnatowski P. *Ann Parasitol* 2013; 59: 113–7.

In this case series, fungal cultures most commonly grew *Candida* species, which were more sensitive to nystatin than miconazole. The prevalence of fungi was highest in those who do not brush the tongue.

Treatment of symptomatic geographic tongue with triamcinolone acetonide alone and in combination with retinoic acid: a randomized clinical trial. Najafi S, Gholizadeh N, Akhavan Rezayat E, et al. *J Dent* 2016; 13: 23–8.

Randomized, controlled trial comparing 28 patients, demonstrating that the combination of triamcinolone and retinoic acid was not more effective than triamcinolone alone. However, it lacks a placebo group and includes a small number of patients.

Treatment of symptomatic benign migratory glossitis: a systematic review. De Campos WG, Esteves CV, Fernandes LG, et al. *Clin Oral Investig* 2018; 22: 2487–93.

Eleven studies were included, which consisted of 150 patients. Of all treatments for geographic tongue, only 8 of 150 cases had reported improvement with substantial heterogeneity in treatments tried. Most common treatments included topical steroids, topical tacrolimus, and topical diphenhydramine.

Second-Line Therapies

• Topical anesthetics	C
• Topical tretinoin	E
• Discontinue dentifrices and other oral flavoring agents	D
• Topical tacrolimus	E
• Pregabalin	E

The treatment of geographic tongue with topical Retin-A solution. Helfman RJ. *Cutis* 1979; 24: 179–80.

The use of topical Retin-A solution is described in three cases.

Anecdotally, we have found that tretinoin gel is longer acting and better tolerated by patients.

Geographic tongue treated with topical tacrolimus. Ishibashi M, Tojo G, Watanabe M, et al. *J Dermatol Case Rep* 2010; 4: 57–9.

Topical tacrolimus 0.1% ointment twice daily for 2 weeks cleared symptoms in two cases.

Geographic tongue that responds to the treatment of pregabalin: can it be a new treatment choice? Kurtipek GS, Sari N, Akyurek FT. *Dermatol Ther* 2019; 32: e12776.

Case report of using pregabalin oral therapy (25mg twice daily for the first month, then 25mg daily).

Third-Line Therapy

• Cyclosporin	E

Successful treatment with cyclosporine administration for persistent benign migratory glossitis. Abe M, Sogabe Y, Syuto T, et al. *J Dermatol* 2007; 34: 340–3.

Unusually symptomatic geographic tongue treated with 3 mg/kg/day, tapering to 1.5 mg/kg/day.

Gianotti–Crosti syndrome

Vijay Zawar, Antonio A.T. Chuh



MANAGEMENT STRATEGY

In its classical clinical presentation, Gianotti–Crosti syndrome (GCS) is not difficult to diagnose with a presentation of a young child with symmetrical, erythematous, monomorphic papules, or vesicles, on the distal extensor extremities, and sometimes on the face and gluteal areas. Itching is usually slight to moderate. Subsidence within 2–6 weeks is the rule. Recurrences are exceptional. Regional lymphadenopathy is not uncommon. Non-icteric hepatitis may be associated in hepatitis B virus (HBV)-related GCS.

Atopic children are more predisposed to acquiring GCS. A prodrome involving the respiratory tract or gastrointestinal tract may be present.

HBV was associated with the earliest reported cases of GCS, especially in Italy and other European countries. However, Epstein–Barr virus (EBV) is now the predominant association worldwide. Many other viruses have also been implicated, including hepatitis A virus (HAV), hepatitis C virus, cytomegalovirus (CMV), Coxsackievirus, adenovirus, enterovirus, human herpesvirus-6B (HHV-6B), herpes simplex viruses, reovirus, varicella, roseola, rotavirus, respiratory syncytial virus, mumps, measles, parainfluenza, molluscum contagiosum, and human immunodeficiency virus (HIV). Non-viral microbial agents have also been implicated including *Borrelia burgdorferi*, *Mycoplasma pneumoniae*, *Mycobacterium avium intracellulare*, beta-hemolytic streptococci, meningococci, and *Bartonella henselae*. GCS has also been recognized following vaccinations, including oral poliomyelitis vaccine, and vaccines against diphtheria, pertussis, measles, HBV, and H1N1 influenza.

Abnormal liver enzymes and viral parameters may be present during active systemic infection involving the liver. However, chronic hepatitis is extremely rare.

GCS is typically a self-limiting disorder. Treatment is meant for symptomatic patients, consisting of oral antihistamines and topical soothing lotions like calamine. Emollients help children with an atopic background. Topical corticosteroids may be utilized for faster resolution of persistent inflammatory lesions in highly symptomatic patients. Systemic antibiotics may be required should pruritic lesions become secondarily infected.

Antiviral treatment has no role in managing GCS, as it does not resolve the dermatitis associated with proven active systemic viral disease.

Recurrences are exceptional. The long-term prognosis is good, with the possible exception of GCS patients associated with chronic active hepatitis due to HBV. Such patients should be assessed by expert hepatologists.

Diagnostic Criteria

A set of clinical diagnostic criteria has been validated in two independent studies, including positive and negative clinical features. Patients should exhibit all positive clinical features on at least one occasion or clinical encounter, and must not exhibit any negative clinical feature on any occasion or clinical encounter related to the rash. Additionally, no differential diagnosis should be considered more likely than GCS based on clinical judgment. If a lesional biopsy is performed, findings should be consistent with GCS.

Positive clinical features include:

- Symmetrical rash
- Monomorphic, flat-topped, pink-brown papules or papulovesicles, 1–10 mm in diameter
- At least three of the following four sites involved: (i) cheeks; (ii) buttocks; (iii) extensor surfaces of forearms; and (iv) extensor surfaces of legs
- Lasting for at least 10 days

Negative clinical features include:

- Extensive truncal lesions
- Scaly lesions

Box 91.1 Common Differential Diagnoses of Gianotti–Crosti syndrome

1. Atopic dermatitis
2. Papular urticaria
3. Scabies
4. Insect bite reaction
5. Lichenoid eruptions
6. Erythema multiforme
7. Drug rash
8. Henoch–Schönlein purpura
9. Acrodermatitis enteropathica

Specific Investigations

The diagnosis of GCS is usually based on clinical criteria alone. Laboratory investigations are characteristically not required unless the patient's clinical features suggest other possibilities as noted in the differential diagnosis of GCS.

- Liver enzymes
- Viral serologies: Epstein–Barr virus, hepatitis B, hepatitis A, hepatitis C, cytomegalovirus

Gianotti–Crosti syndrome. Brandt O, Abeck D, Gianotti R, et al. *J Am Acad Dermatol* 2006; 54: 136–45.

EBV is now the most common cause of GCS. Other viruses have been associated with GCS, including HAV; CMV; HHV-6B; Coxsackie A16, B4, and B5; rotavirus; parvovirus B19, respiratory syncytial virus, mumps virus, and parainfluenza virus types 1 and 2. HIV also appears to be capable of triggering GCS. The associations between various immunizations and GCS have long been known. Despite the proven connection between HBV and GCS, immunization against HBV only rarely causes GCS.

Gianotti–Crosti syndrome in a child following hepatitis B virus vaccination. Karakas M, Durdu M, Tuncer I, et al. *J Dermatol* 2007; 34: 117–20.

A five-year-old boy presented with 1-month history of GCS. The lesions had appeared 3 weeks after a first dose of HBV recombinant vaccine.

Gianotti–Crosti syndrome in India is not associated with hepatitis B infection. Zawar V, Chuh A. *Dermatology* 2004; 208: 87.

Of 89 children clinically diagnosed as GCS, only one patient was HBsAg positive. The authors indicated that GCS was not significantly associated with HBV, at least in the Asian children.

A case-control study on the association of pulse oral polio-myelitis vaccination and Gianotti–Crosti syndrome. Zawar V, Chuh A. *Int J Dermatol* 2017; 56(1): 75–9.

The Indian government launched intensified immunization against polio in 1995 by administering oral polio vaccine on specified days annually to cover children under the age of five.

In this study, 116 cases of GCS were found to be associated with the pulse polio immunization program.

Gianotti–Crosti syndrome associated with cytomegalovirus antigenemia after bone marrow transplantation. Haki M, Tsuchida M, Kotsuji M, et al. *Bone Marrow Transplant* 1997; 20(8): 691–3. doi: 10.1038/sj.bmt.1700945.

In this case of a 3-year-old girl, GCS was related to CMV primary infection and was considered to be the presenting sign of the infection.

Atypical Gianotti–Crosti syndrome in two HIV and hepatitis B co-infected adults. Cocciolone R, Morey A, Panasiuk P. *Australas J Dermatol* 2011; 52: 32–56.

Atypical GCS in two unrelated adult male patients with coexistent hepatitis B and HIV infection are described. Immunoperoxidase studies suggested the presence of HBsAg within acute disseminated erythematous papulovesicular skin lesions.

First-Line Therapies

Topical

- Emollients E
- Antipruritic (calamine lotion) E

Systemic

- Antihistamines E

Second-Line Therapies

Topical

- Corticosteroids (low potency; e.g., hydrocortisone cream) E
- Antibiotics (if secondarily infected) E

Systemic

- Antihistamines (chlorpheniramine maleate, hydroxyzine, cetirizine) E
- Antibiotics (if secondarily infected; e.g., ampicillin, amoxicillin, erythromycin, cephalexin) E

Recurrent Gianotti–Crosti syndrome. Metelitsa AI, Fiorillo L. *J Am Acad Dermatol* 2011; 65: 876–7.

A two-year-old boy presented with GCS. Two weeks after onset of the eruption, he was immunized with influenza vaccination and new lesions appeared at the immunization site. Investigations revealed a positive urine culture for CMV and positive IgM against EBV. He was treated with hydrocortisone cream, and the eruption resolved. Twelve months later, he presented with a similar eruption at the site of influenza vaccination. Because GCS is a mild and self-limiting disease, further vaccinations are not contraindicated.

Third-Line Therapies

Topical

- Corticosteroids (mid- to high potency; e.g., mometasone, betamethasone propionate) E
- Antibiotics E

Systemic

- Corticosteroids (short course; prednisone, prednisolone) E

Antiviral agents

- Interferons (only if related to HBV infection) E
- Lamivudine (only if related to HBV infection) E
- Ribavirin E
- Aciclovir (only if related to susceptible viruses) E

Gianotti–Crosti syndrome in two adult patients. Ting PT, Barankin B, Dytoc MT. *J Cutan Med Surg* 2008; 12(3): 121–5.

This was a report of two otherwise healthy adults presenting with GCS. The authors used a potent topical steroid in one case and an additional short course of oral prednisone in another.

Efficacy of ribavirin in a case of long lasting and disabling Gianotti–Crosti syndrome. Zawar V, Chuh A. *J Dermatol Case Rep* 2008; 2: 63–6.

A six-year-old girl presented with a history of a pruritic rash consistent with GCS after a febrile illness with common cold symptoms. Remission was not achieved despite several medications: topical emollients, topical and systemic corticosteroids, topical and systemic antibiotics, and oral histamines. A course of oral ribavirin at a dose of 300 mg daily for 5 days led to dramatic remission 5 days later.

Successful treatment of hepatitis B-associated leukocytoclastic vasculitis with lamivudine treatment in a child patient. Surmeli Onay O, Baskin E, Ozçay F, et al. *Rheumatol Int* 2007; 27: 869–72.

A child diagnosed clinically as GCS was investigated and led to a final diagnosis of leukocytoclastic vasculitis, which successfully resolved with lamivudine treatment.

Gonorrhea

Ted Rosen, Avi Bitterman



Gonorrhea is a common and potentially severe sexually transmitted disease caused by the Gram-negative aerobic diplococcus *Neisseria gonorrhoeae*. This organism primarily infects the mucous membranes of the urethra, endocervix, rectum, and pharynx. The disease can also become disseminated, causing petechial or acral pustular skin lesions, tenosynovitis, arthralgia, true septic arthritis, perihepatitis, and, less commonly, endocarditis or meningitis.

MANAGEMENT STRATEGY

Individuals with gonorrhea should be treated as promptly as possible (1) to prevent regional infection such as epididymitis or pelvic inflammatory disease leading to infertility or ectopic pregnancy; (2) to prevent disseminated gonococcal infection, which occurs in about 1%–3% of cases; and (3) to stop transmission to sexual partners. Prompt management has become especially important due to a resurgence in incidence of gonococcal disease in the United States and increasing multidrug antimicrobial resistance worldwide.

Gonococcal urethritis is typically characterized by mucopurulent to frankly purulent discharge along with a burning sensation during urination. Dysuria may be the only symptom.

Gonococcal cervicitis is characterized by a mucopurulent or purulent endocervical exudate. However, a cervical discharge is not specific for a gonococcal infection, and gonococcal infection of the cervix is often asymptomatic.

Pharyngeal infection is asymptomatic in more than 90% of cases, but when symptomatic it presents as a pharyngitis of variable severity.

Rectal infection is prevalent in homosexual men, causing anal discharge and pain. In women, rectal infection results from spread through vaginal secretions and does not necessarily imply anal intercourse.

Patients infected with *N. gonorrhoeae* are often coinfecting with *Chlamydia trachomatis* and should be treated with *azithromycin* to cover this organism, with or without diagnostic evidence of chlamydial disease. Patients with gonorrhea have engaged in unprotected intercourse and, therefore, always should be tested for both syphilis and HIV.

Patients should be instructed to return for evaluation if symptoms persist or recur after therapy and to abstain from sexual intercourse until they and their sexual partners are cured. Because reinfection is so common, the Centers for Disease Control (CDC) recommends that all patients with known gonorrhea return for retesting 3 months posttreatment. A test of cure 3–4 weeks post-treatment is no longer recommended.

Antimicrobial resistance is a real and increasing threat, and treatment options for gonococcal disease are increasingly limited. To abate further spread of resistant strains of *N. gonorrhoeae*, physicians should strongly encourage patient referral of any sexual partner within the preceding 60 days for evaluation and treatment and obtain culture(s) to evaluate individual antimicrobial susceptibility in any patient whose symptoms do not resolve with initial treatment.

Specific Investigations

Men

- Microscopic examination of Gram-stained urethral secretions
- Culture on Thayer–Martin medium
- Non-culture test based upon immunodiagnosics, as available

Women

- Culture on Thayer–Martin medium
- Non-culture test based upon immunodiagnosics, as available

Diagnosis and treatment of urethritis in men. Brill JR. Am Fam Physician 2010; 1; 81: 873–8.

In the context of male urethritis without discharge, recommended tests include urinalysis with microscopy in conjunction with venereal disease research laboratory or rapid plasma regain test, in addition to HIV and hepatitis B testing. If urine test results are negative, treatment should be deferred unless the patient is at high risk of sexually transmitted infections and is unlikely to return for treatment. Gonorrhea is uncommon in patients without discharge.

Sexually transmitted diseases treatment guidelines, 2015. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. MMWR Recomm Rep 2015; 64: 1–137.

Because of its high specificity (>99%) and sensitivity (>95%), a Gram stain of a male urethral specimen that demonstrates polymorphonuclear leukocytes with intracellular Gram-negative diplococci can be considered diagnostic for infection with *N. gonorrhoeae* in symptomatic men. Culture is the most widely available option for diagnosis in asymptomatic men, in women, and in non-genital sites (rectum and pharynx). Non-culture tests cannot provide antimicrobial susceptibility results, but can rapidly and accurately confirm a clinical diagnosis.

Screening tests to detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections – 2002. Johnson RE, Newhall WJ, Papp JR, et al. MMWR Recomm Rep 2002; 51: 1–38.

Non-culture tests called nucleic acid hybridization tests and nucleic acid amplification tests (NAATs) have been developed. Commercial NAATs differ in their amplification methods and their target nucleic acid sequences. The majority of commercial NAATs have been cleared by the Food and Drug Administration to detect *C. trachomatis* and *N. gonorrhoeae* in endocervical swabs and urethral swabs from men. The sensitivity of NAATs might be less when

using urine than when using an endocervical swab. Testing of rectal and oropharyngeal specimens with NAATs is not recommended.

First-Line Therapies for Uncomplicated Gonorrhea of the Cervix, Urethra, Rectum, Pharynx, and Conjunctiva

- Ceftriaxone 250 mg intramuscularly (IM) in a single dose + azithromycin 1 g orally **B**
- Only if ceftriaxone is NOT immediately available: cefixime 400 mg orally in a single dose + azithromycin 1 g orally **B**

Sexually transmitted diseases treatment guidelines, 2015. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. MMWR Recomm Rep 2015; 64: 1–137.

The minimum concentrations of cefixime needed to inhibit in vitro growth of the *N. gonorrhoeae* strains circulating in the United States and many other countries have progressively increased since 2006. This suggests that the effectiveness of cefixime might be waning. In addition, treatment failures with cefixime (or other similar oral cephalosporins) have been reported in Asia, Europe, South Africa, and Canada. As a result, the CDC no longer recommends the routine use of cefixime as a first-line regimen for treatment of gonorrhea at any anatomic site in the United States. Ceftriaxone in a single injection of 250 mg is a safe, effective dose for uncomplicated gonococcal infection at all anatomic sites. However, ceftriaxone failures have also been rarely reported. Consequently, only one regimen, dual treatment with ceftriaxone and azithromycin, is currently recommended for gonorrhea treatment at all anatomic sites in adults. All patients with gonorrhea should also be treated with azithromycin to (1) treat possible coinfection with *Chlamydia trachomatis*; and (2) gain additive microcidal effects for *N. gonorrhoeae*.

First *Neisseria gonorrhoeae* strain with resistance to cefixime causing gonorrhoea treatment failure in Austria, 2011. Unemo M, Golparian D, Sary A, et al. Euro Surveill 2011; 16: 1–3.

Globally the susceptibility of *N. gonorrhoeae* to antimicrobial therapy, including first-line treatment options ceftriaxone and cefixime, is decreasing.

Epidemiological trends of antibiotic resistant gonorrhoea in the United Kingdom. Whittles LK, White PJ, Paul J, et al. Antibiotics (Basel) 2018; 7(3): 60.

In the UK, gonococcal resistance to tetracycline, ciprofloxacin, and penicillin is high, with resistance levels in 2016 at 41%, 34%, and 14%, respectively. Resistance to cefixime peaked at 6% in 2010 but has fallen to 2% since cefixime was removed from the recommended first-line treatments.

Second-Line Therapies (No Advantage over First-Line Therapies)

- Ceftriaxone 500 mg IM as a single dose + azithromycin 1 g orally **B**
- Cefixime 2 g IM with probenecid 1 g orally + azithromycin 1 g orally **B**
- Cefotaxime 500 mg IM as a single dose + azithromycin 1 g orally **B**

***Neisseria gonorrhoeae* with high-level resistance to azithromycin: case report of the first isolate identified in the United States.** Katz AR, Komeya AY, Soge OO, et al. CID 2012; 54: 841–3.

Eight isolates with reduced susceptibility to azithromycin were identified in Hawaii followed by laboratory documentation of the first isolate with high-level azithromycin resistance in California. Previously, strains with high-level resistance had been documented in Argentina, Scotland, England, Wales, and Ireland.

Update to CDC's sexually transmitted diseases treatment guidelines 2006: fluoroquinolones no longer recommended for treatment of gonococcal infections. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 2007; 56: 332–6.

Due to the increasing resistance, the CDC no longer recommends the use of fluoroquinolones for patients who acquired their infection in the United States, Asia, or the Pacific Islands. Recent data suggest that resistant strains comprise about 13% of all American-acquired isolates. Fluoroquinolones remain off the recommended treatment list for gonorrhea 10 years later.

Surveillance of antibiotic resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific and South East Asian Regions, 2009. WHO Western Pacific and South East Asian Gonococcal Antimicrobial Surveillance Programmes. Commun Dis Intell 2011; 35: 2–7.

Recent data from China, Hong Kong, Japan, and elsewhere in Asia also demonstrate a very high rate of fluoroquinolone resistance. Australia and New Zealand are experiencing 35%–45% of isolates being quinolone resistant.

Annual report of the Australian Gonococcal Surveillance Programme, 2010. Australian Gonococcal Surveillance Programme. Commun Dis Intell 2011; 35: 229–36.

Penicillin has been removed from the standard treatment regimen in Australia because of nationwide isolate resistance (up to 44% in some regions). However, in remote areas of Australia with extremely high disease rates, treatment with penicillin often remains effective. The same is also true in other industrialized countries.

Gentamicin compared with ceftriaxone for the treatment of gonorrhoea (G-ToG): a randomised non-inferiority trial. Ross JDC, Brittain C, Cole M, et al. Lancet 2019; 393: 2511–20.

A randomized controlled trial ($n=328$) failed to find non-inferiority of a single dose of gentamycin 240 mg IM compared with a single dose of ceftriaxone 500 mg IM in adults with uncomplicated genital, pharyngeal, or rectal gonorrhea. When comparing ceftriaxone with gentamycin, clearance rates for genital, pharyngeal, and rectal infections were 98% vs. 94%, 96% vs. 80%, and 98% vs. 90%, respectively. In the context of cephalosporin-resistant gonococcal infection or in patients allergic to cephalosporins, gentamycin may be a useful alternative. However, gentamycin is not appropriate as a first-line treatment for gonorrhea.

***Neisseria gonorrhoeae* antimicrobial susceptibility surveillance — The Gonococcal Isolate Surveillance Project, 27 sites, United States, 2014.** Kirkcaldy RD, Harvey A, Papp JR, et al. MMWR Surveill Summ 2016; 65: 1–19.

This is the first report to present comprehensive surveillance data from the US Gonococcal Isolate Surveillance Project and summarize gonococcal susceptibility over time, as well as underscore the public health implications of emerging cephalosporin

resistance. Antimicrobial susceptibility patterns vary by geographic region within the United States and by sex of sexual partner. For example, the percentage of isolates resistant to tetracycline, ciprofloxacin, penicillin, or all three antimicrobials was greater in isolates from men who have sex with men than from men who exclusively have sex with women. Because dual therapy with ceftriaxone plus azithromycin is the only recommended gonorrhea treatment, increases in azithromycin and cephalosporin minimal inhibitory concentrations are cause for concern that resistance to these antimicrobial agents might be emerging. Reduced azithromycin susceptibility (defined as minimum inhibitory concentration ≥ 2.0 mcg/mL) increased from 0.6% in 2013 to 2.5% in 2014. It is unclear whether increases in the percentage of isolates with reduced susceptibility to azithromycin mark the beginning of an adverse trend.

SPECIAL CONSIDERATIONS

Pharyngeal Infection

Sexually transmitted diseases treatment guidelines, 2015. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. MMWR Recomm Rep 2015; 64: 1–137.

Few antimicrobial regimens, including those involving oral cephalosporins, can reliably cure >90% of gonococcal pharyngeal infections. The recommended treatment for uncomplicated gonococcal infections of the pharynx is ceftriaxone 250 mg IM in a single dose and azithromycin 1 g orally in a single dose.

Disseminated Gonococcal Infection

Hospitalization is recommended for initial therapy. The experts recommend ceftriaxone 1 g intramuscularly or intravenously every 24 hours as the initial regimen, plus azithromycin 1 g orally as a single dose. The provider can switch to an oral agent guided by antimicrobial susceptibility testing 24–48 hours after substantial clinical improvement, for a total treatment course of at least 7 days. Acceptable alternative therapies include cefotaxime or ceftizoxime, with both drugs given in a dosage of 1 g intravenously every 8 hours, along with a single dose of azithromycin (1 g).

Antibiotics for treating gonorrhoea in pregnancy. Comuñán-Carrasco G, Peña-Martí GE, Martí-Carvajal AJ. Cochrane Database Syst Rev 2018; CD011167.

A Cochrane review found two randomized controlled trials regarding the treatment of gonorrhea in pregnancy. One trial compared ceftriaxone 125 mg IM with cefixime 400 mg oral, and the other trial assessed a higher dose of ceftriaxone 250 mg IM versus either one dose of amoxicillin 3 g oral plus probenecid 1 g oral, or spectinomycin 2 g IM. Spectinomycin data was not included as it is no longer available in the USA. Cure rates were as follows: ceftriaxone 125 mg IM (95.2%), cefixime 400 mg

(96.2%), amoxicillin 3 g plus oral probenecid 1 g (89.3%), ceftriaxone 250 mg IM (95.5%). There was not enough evidence to support one particular regimen over another.

The CDC currently recommends dual therapy of ceftriaxone 250 mg IM in a single dose and azithromycin 1 g orally in a single dose as first-line treatment for pregnant women infected with N. gonorrhea.

Ophthalmia Neonatorum

To prevent gonococcal ophthalmia neonatorum, a prophylactic agent should be instilled into both eyes of all newborn infants; this procedure is, in fact, required by law in most states. Prophylaxis consists of erythromycin (0.5%) ophthalmic ointment in each eye in a single application at birth. Ocular prophylaxis is warranted because it can prevent sight-threatening gonococcal ophthalmia, has an excellent safety record, is easy to administer, and is inexpensive. Gonococcal ophthalmia is strongly suggested when typical Gram-negative diplococci are identified in conjunctival exudate, justifying presumptive treatment after appropriate cultures have been obtained. The recommended regimen is ceftriaxone 25–50 mg/kg IV or IM in a single dose, not to exceed 125 mg. Local treatment, with or without systemic antibiotics, is inappropriate.

Men Who Have Sex with Men

Gonorrhea screening among men who have sex with men: value of multiple anatomic site testing, San Diego, California, 1997–2003. Gunn RA, O'Brien CJ, Lee MA, et al. Sex Transm Dis 2008; 35: 845–8.

This population should be screened annually for gonorrhea infection at the urethral, pharyngeal, and rectal sites.

The CDC also now recommends annual screening for N. gonorrhoeae infection for all sexually active women aged <25 years and for older women at increased risk for infection (e.g., those who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has a sexually transmitted infection [STI]). Additional risk factors for gonorrhea include inconsistent condom use among persons who are not in mutually monogamous relationships, previous or coexisting sexually transmitted infections, and exchanging sex for money or drugs. Individuals who fall into those categories should also be screened annually.

Treatment Failure

Patients with suspected treatment failure or persons infected with a strain found to demonstrate in vitro resistance should consult an infectious disease specialist, where the use of gentamicin or gemifloxacin may be entertained. Patients should be retreated with at least 250 mg of ceftriaxone IM or IV and ensure partner treatment. The situation should be promptly reported to public health agencies.

Graft-versus-host disease

Melissa Hoffman, Robert G. Micheletti



Graft-versus-host disease (GVHD) is the most significant source of morbidity and mortality among survivors of allogeneic hematopoietic stem cell transplantation, occurring in 30%–70% of transplant recipients. Affecting the skin, liver, gastrointestinal tract, and other organs, it occurs when donor immune cells (the graft) recognize the transplant recipient (host) as foreign, resulting in inflammation and end organ damage. Of the organs involved, the skin is the most common and often the most severely affected.

MANAGEMENT STRATEGY

The risk, timing, presentation, and treatment of GVHD depend on many factors, including the type of transplant, the degree of human leukocyte antigen (HLA) mismatch, donor and recipient sex, the intensity of pretransplant conditioning, and the GVHD prophylactic regimen used. Evolution of transplant strategies, such as reduced-intensity conditioning, increasing age of some transplant recipients, novel prophylaxis and treatment regimens, and donor lymphocyte infusion, together with improved recognition of overlap phenomena and late-onset acute GVHD, have blurred the classic understanding of a temporally defined disease. Acute and chronic GVHD are best differentiated on the basis of clinical manifestations because features of either may occur at any time posttransplant. Atypical manifestations, particularly of chronic GVHD, can mimic other dermatologic diseases and present a diagnostic dilemma; input of a dermatologist and skin biopsy, when appropriate, can help shape diagnosis and management.

Initial management of GVHD includes adjustment of GVHD prophylaxis. Optimization of organ-specific supportive care and *topical therapies* may be sufficient for mild cutaneous GVHD, whereas in more severe disease, maximizing topical care can minimize the need for systemic immunosuppression and related side effects. For moderate or severe GVHD, *systemic corticosteroids* are first-line therapy, but in many cases GVHD becomes steroid

refractory or dependent. Evidence for second- and third-line therapies is derived from small trials or series and is frequently contradictory. The optimal approach in patients with steroid-refractory acute or chronic GVHD is therefore not known. Commonly used agents with reported activity and adequate safety profiles include *calcineurin inhibitors*, *extracorporeal photopheresis*, *mycophenolate mofetil*, *mTOR inhibitors*, *ruxolitinib*, and several others. Additional skin-directed therapies such as *narrowband ultraviolet B (NB-UVB)* and *psoralen and ultraviolet A (PUVA)* phototherapy can benefit some patients.

Future work to identify effective therapies, using standardized criteria, is needed. In addition to aiding diagnosis and optimizing skin-directed therapies, dermatologists can play an important role in assessment of response, severity scoring, and research.

ACUTE GVHD

Specific Investigations

- Skin biopsy
- Medication history
- Liver function tests
- Complete blood count
- Serum chemistry
- Biomarker panel (investigational)
- Consider viral testing (e.g., cytomegalovirus)
- Consider colonoscopy/endoscopy

Clinical differentiation of acute cutaneous graft-versus-host disease from drug hypersensitivity reactions. Byun HJ, Yang JJ, Kim BK, et al. *J Am Acad Dermatol* 2011; 65: 726–32.

Cutaneous manifestations of acute GVHD are generally non-specific. However, a morbilliform eruption involving the face (including pinnae), palms, and soles is suggestive of acute GVHD (aGVHD), as is the presence of diarrhea or hyperbilirubinemia, typically developing within 2–3 days of rash onset. Absence of these findings favors a diagnosis of drug hypersensitivity reaction but does not rule out GVHD.

Quantitative analysis of eosinophils in acute graft-versus-host disease compared with drug hypersensitivity reactions. Weaver J, Bergfeld WF. *Am J Dermatopathol* 2010; 32: 31–4.

Interface dermatitis with basilar vacuolization and dyskeratotic keratinocytes with satellite cell necrosis are characteristic but non-specific histologic findings of GVHD. Only significant tissue eosinophilia (≥ 16 eosinophils per 10 high-powered fields) safely excludes aGVHD in favor of drug hypersensitivity reaction. Therefore, the decision to diagnose and treat aGVHD should not depend on skin biopsy findings.

An early-biomarker algorithm predicts lethal graft-versus-host disease and survival. Hartwell M, Ozbek U, Holler E, et al. *JCI Insights* 2017; 2: e89798.

Serum biomarkers to help diagnose and predict the severity and outcome of GVHD are under investigation but are not yet available for clinical use. A biomarker algorithm based on blood samples taken 7 days after hematopoietic stem cell transplantation identifies patients at high risk for lethal GVHD and non-relapse mortality. The algorithm uses ST2 and REG3 α concentrations to identify a high-risk group with 28% non-relapse mortality, compared with a low-risk group with non-relapse mortality of 7% ($p < 0.001$).

First-Line Therapies

- Topical corticosteroids **D**
- Systemic corticosteroids (methylprednisolone 1–2 mg/kg/day) **B**

Topical corticosteroids, along with sensitive skin care measures and optimization of prophylactic medications (e.g., ciclosporin, tacrolimus, methotrexate), may be sufficient therapy for mild cutaneous grade I aGVHD (defined as cutaneous GVHD involving ≤50% body surface area [BSA] without liver or gastrointestinal [GI] involvement).

Effectiveness and safety of lower dose prednisone for initial treatment of acute graft-versus-host disease: a randomized controlled trial. Mielcarek M, Furlong T, Storer BE, et al. Haematologica 2015; 10: 842–8.

For patients with grade II or higher aGVHD (skin involvement >50% BSA or with any liver or GI involvement), systemic corticosteroids are the mainstay of initial therapy, typically 2 mg/kg/day prednisone equivalent in divided doses, followed by gradual taper. A randomized controlled trial comparing standard vs. lower dose (0.5–1 mg/kg/day) glucocorticoids showed that initial treatment of aGVHD with lower-dose prednisone may be sufficient.

Second-Line Therapies

- Ruxolitinib **B**
- Mycophenolate mofetil **C**
- Extracorporeal photopheresis **C**
- Etanercept **C**
- Calcineurin inhibitors (tacrolimus, ciclosporin) **C**
- α1-antitrypsin **C**

For patients with glucocorticoid-resistant acute GVHD, ruxolitinib is now the favored second-line agent on the basis of superior efficacy data and side-effect profile.

Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. Zeiser R, von Bubnoff N, Butler J, et al.; REACH2 Trial Group. N Engl J Med 2020; 382: 1800–10.

In this randomized, multicenter, phase 3 trial of 309 patients with glucocorticoid-refractory aGVHD, those assigned to receive ruxolitinib 10 mg twice daily had response rates superior to those receiving alternative therapies, such as mycophenolate mofetil, sirolimus, etc. (62% versus 39%, respectively; OR 2.64, 95% CI 1.65–4.22). Ruxolitinib is now approved by the US Food and Drug Administration (FDA) for treatment of steroid-refractory acute GVHD.

Etanercept, mycophenolate, denileukin, or pentostatin plus corticosteroids for acute graft-versus-host disease: a randomized phase 2 trial from the Blood and Marrow Transplant Clinical Trials Network. Alousi AM, Weisdorf DJ, Logan BR, et al. Blood 2009; 114: 511–7.

In this randomized, phase II trial, the addition of mycophenolate to systemic corticosteroids resulted in higher complete response and overall survival rates and fewer infectious complications than did prednisone combined with etanercept, pentostatin, or denileukin diftitox.

Phase 3 clinical trial of steroids/mycophenolate mofetil vs steroids/placebo as therapy for acute GVHD: BMT CTN 0802. Bolaños-Meade J, Logan BR, et al. Blood 2014; 124: 3221–7.

Although mycophenolate mofetil appears to be more effective than other second-line agents for aGVHD (except ruxolitinib) and is commonly used for this purpose, its actual efficacy appears to be limited. This phase III randomized, double-blind trial was ended early for futility after showing no benefit to therapy with glucocorticoids plus mycophenolate versus glucocorticoids alone.

Etanercept plus methylprednisolone as initial therapy for acute graft-versus-host disease. Levine JE, Paczesny S, Mineishi S, et al. Blood 2008; 111: 2470–5.

A regimen of etanercept plus corticosteroids was more likely to achieve complete response (69% vs. 33%) and 100-day survival (82% vs. 66%) than were steroids alone.

α1-Antitrypsin infusion for treatment of steroid-resistant acute graft-versus-host disease. Magenau J, Goldstein S, Peltier D, et al. Blood 2018; 131: 1372–9.

A total of 40 patients were treated with α1-antitrypsin for up to 4 weeks at a dose of 60 mg/kg every 4 days in this prospective, multicenter phase II trial. The overall response rate was 65% (26/40 patients). Of these patients, 14 had a complete response, and 12 had a partial response. At 30 days posttreatment cessation, a sustained response was observed in 73% (19 of 26) of the responders.

Extracorporeal photopheresis versus anticytokine therapy as a second-line treatment for steroid-refractory acute GVHD: a multicenter comparative analysis. Jagasia M, Greinix H, Robin M, et al. Biol Blood Marrow Transplant 2013; 19: 1129–33.

A retrospective analysis of 98 patients with steroid-refractory aGVHD receiving photopheresis revealed superior complete response rates (54% vs. 20%) and survival compared with those receiving anticytokine therapy (etanercept or inolimomab). The safety profile of extracorporeal photopheresis was excellent.

Third-Line Therapies

- Pentostatin **C**
- Anti-CD52 antibody (alemtuzumab) **C**
- mTOR inhibitors (sirolimus) **C**
- Infliximab **C**
- Interleukin-2 receptor antibodies (basiliximab) **C**
- Mesenchymal stem cells **B**
- Methotrexate **C**
- Tocilizumab **C**
- Antithymocyte globulin **C**
- Denileukin diftitox **C**
- PUVA **C**
- Narrowband UVB **C**

Diagnosis and management of acute graft-versus-host disease. Dignan FL, Clark A, Amrolia P, et al. Br J Haematol 2012; 158: 30–45.

Evidence-based guidelines for aGVHD are reviewed. Pentostatin, alemtuzumab, mesenchymal stem cells, and methotrexate are among third-line therapies used after second-line agents have failed or in the context of clinical trials. Most such drugs have limited or negative/conflicting data.

Other agents with a possible therapeutic role in steroid-refractory aGVHD include infliximab, anti-IL-2 receptor antibodies, tocilizumab, antithymocyte globulin, and others.

Basiliximab for the treatment of steroid-refractory acute graft-versus-host disease after unmanipulated HLA-mismatched/haploidentical hematopoietic stem cell transplantation. Wang JZ, Liu KY, Xu LP, et al. *Transplant Proc* 2011; 43: 1928–33.

The chimeric IL-2 receptor antagonist basiliximab yielded a therapeutic response in 46/53 patients with steroid-refractory aGVHD.

Effective treatment of steroid and therapy-refractory acute graft-versus-host disease with a novel mesenchymal stromal cell product (MSC-FFM). Bader P, Kuçi Z, Bakhtiar S, et al. *Bone Marrow Transplant* 2018; 53: 852–62.

This study included 69 patients with treatment-refractory acute GVHD treated with mesenchymal stromal cells (MSC-FFM). On day 28, the overall response was 83%, 22 (32%) with a complete response and 35 (51%) with a partial response.

Sirolimus for treatment of steroid-refractory acute graft-versus-host disease. Hoda D, Pidala J, Salgado-Vila N, et al. *Bone Marrow Transplant* 2010; 45: 1347–51.

Sirolimus was initiated in 34 patients with steroid-refractory aGVHD. The overall response rate was 76%, with 44% achieving complete response. Complications included myelosuppression and hemolytic uremic syndrome.

Narrowband ultraviolet B phototherapy for treatment of steroid-refractory and steroid-dependent acute graft-versus-host disease. Feldstein JV, Bolaños-Meade J, Anders VL, et al. *J Am Acad Dermatol* 2011; 65: 733–8.

Of 14 patients with skin-predominant, steroid-refractory or dependent aGVHD, 11 had a complete or partial response, suggesting NB-UVB phototherapy is a potentially effective and low-risk skin-directed therapy for selected patients with aGVHD.

CHRONIC GVHD

Specific Investigations

- Skin biopsy
- Liver function tests
- Complete blood count
- Quality-of-life assessment
- Range of motion/physical therapy evaluation
- Pulmonary function tests
- Schirmer test
- Evaluation of other organs (ocular, oral, genital, gastrointestinal, musculoskeletal)

National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Filipovich AH, Weisdorf D, Pavletic S, et al. *Biol Blood Marrow Transplant* 2005; 11: 945–56.

Cutaneous signs that are considered diagnostic of chronic GVHD (cGVHD) include poikiloderma; lichen planus-like lesions; and lichen sclerosis-like, morphea-like, and sclerotic features. Standardization of response criteria, staging, and grading are detailed.

Atypical manifestations of graft-versus-host disease. Cornejo CM, Kim EJ, Rosenbach M, et al. *J Am Acad Dermatol* 2015; 72: 690–5.

Numerous common and atypical manifestations of GVHD may be seen. Biopsy or additional investigations may help confirm a diagnosis of cGVHD in patients without diagnostic features.

First-Line Therapies

• Systemic corticosteroids	B
• Systemic corticosteroid and calcineurin inhibitor	C

Organ-specific management and supportive care in chronic graft-versus-host disease. Dignan FL, Scarisbrick JJ, Cornish J, et al. *Br J Haematol* 2012; 158: 62–78.

The choice of initial therapy depends on disease severity, organ involvement, and other factors. Organ-specific supportive care (e.g., emollients, sun protection), topical corticosteroids, and topical calcineurin inhibitors (tacrolimus and pimecrolimus) are skin-directed therapies that can help minimize the need for toxic systemic agents. There are no randomized controlled trials of these therapies for cGVHD, but they are used widely and considered best practice.

Diagnosis and management of chronic graft-versus-host disease. Dignan FL, Amrolia P, Clark A, et al. *Br J Haematol* 2012; 158: 46–61.

For those with moderate or severe cGVHD, corticosteroids are first-line systemic therapy, usually beginning at a daily dose of 1 mg/kg prednisone tapered slowly based on clinical response. There are no randomized studies comparing standard to higher or lower steroid doses. Optimization of skin-directed therapies may enable dose reduction in those with skin-limited cGVHD.

Therapy for chronic graft-versus-host disease: a randomized trial comparing cyclosporine plus prednisone versus prednisone alone. Koc S, Leisenring W, Flowers ME, et al. *Blood* 2002; 100: 48–51.

Initial treatment with prednisone plus ciclosporin may reduce some steroid-related toxicities compared with treatment with prednisone alone, but there is no difference in mortality or time at which therapy can be discontinued. Randomized trials of other agents for the initial treatment of cGVHD have failed to show benefit compared with prednisone alone.

Second-Line Therapies

• Calcineurin inhibitors (tacrolimus, ciclosporin)	C
• Extracorporeal photopheresis	C
• Mycophenolate mofetil	C
• Ruxolitinib	C
• Rituximab	B
• mTOR inhibitors (sirolimus, everolimus)	C
• Ibrutinib	C
• UVB, NB-UVB	C
• PUVA, UVA1	C

Consensus conference on clinical practice in chronic GVHD: second-line treatment of chronic graft-versus-host disease. Wolff D, Schleuning M, von Harsdorf S, et al. *Biol Blood Marrow Transplant* 2011; 17: 1–17.

Additional therapy is warranted for those with cGVHD that progresses despite 1 mg/kg/day prednisone for 2 weeks, fails to respond after 4–6 weeks of therapy, or flares with attempts to taper below 0.5 mg/kg/day. Initial second-line therapy should include agents with documented activity and adequate safety

profiles, such as calcineurin inhibitors, extracorporeal photopheresis, mycophenolate mofetil, mTOR inhibitors, imatinib, or rituximab. Unfortunately, without available predictors of response, 'trial and error' is the only way to determine efficacy of a particular agent or combination regimen for a given patient.

Extracorporeal photopheresis for the treatment of acute and chronic graft-versus-host disease in adults and children: best practice recommendations from an Italian Society of Hemapheresis and Cell Manipulation (SIdEM) and Italian Group for Bone Marrow Transplantation (GITMO) consensus process. Pierelli L, Perseghin P, Marchetti M, et al. *Transfusion* 2013; 53: 2340–52.

Among 735 patients with steroid-resistant or dependent cGVHD included for review, photopheresis resulted in a response rate of 50%–65% (complete response 30%–35%). Approximately 25%–35% of patients were able to taper steroid use significantly.

Efficacy of mycophenolate mofetil in the treatment of chronic graft-versus-host disease. Lopez F, Parker P, Nademane A, et al. *Biol Blood Marrow Transplant* 2005; 11: 307–13.

Eighteen of 24 (75%) patients receiving mycophenolate mofetil as second-line therapy responded to treatment, and 14 of 22 (64%) patients on prednisone were able to taper the dose of steroids. Complications included gastrointestinal side effects, hematologic toxicities, and infectious episodes.

Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. Zeiser R, Burchert A, Lengerke C, et al. *Leukemia* 2015; 29: 2062–8.

In a multicenter retrospective study, 35 of 41 (85%) patients with steroid-refractory cGVHD responded to the JAK1/2 inhibitor ruxolitinib. Relapse rate was low at 6% (2/35). Complications included cytopenias and cytomegalovirus reactivation.

Rituximab-based first-line treatment of cGVHD after allogeneic SCT: results of a phase 2 study. Malard F, Labopin M, Yakoub-Agha I, et al. *Blood* 2017; 130: 2186–95.

This prospective, multicenter, phase II study included 24 patients with a new diagnosis of cGVHD. Rituximab was added to the first-line treatment of corticosteroids and ciclosporin. At 1 year, the overall response rate was 83%, including seven patients with a complete response and 13 with a partial response. Fourteen patients were able to taper off corticosteroids, and four reduced the dose by $\geq 30\%$.

Therapy of sclerodermatous chronic graft-versus-host disease with mammalian target of rapamycin inhibitors. Jedlickova Z, Burlakova I, Bug G, et al. *Biol Blood Marrow Transplant* 2011; 17: 657–63.

Thirty-four patients with severe scleroderma-like cGVHD had an overall response rate of 76% to sirolimus or everolimus. Hyperlipidemia, poor wound healing, cytopenias, infections, and thrombotic microangiopathy were seen in a minority.

Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. Miklos D, Cutler CS, Arora M, et al. *Blood* 2017; 130: 2243–50.

This phase 1b/2 study evaluated the safety and efficacy of ibrutinib in 42 patients with cGVHD who had failed treatment with systemic corticosteroids. The overall response rate was 67%, with 21% of patients having a complete response and 45% having a partial response. Of the 28 patients with a response, 20 (71%) had a sustained response for 20 or more

weeks. Responders were able to lower corticosteroid doses successfully. Based on these results, the FDA approved ibrutinib for the treatment of adults with cGVHD who have failed one or more systemic therapy.

Graft-versus-host disease: Part II. Management of cutaneous graft-versus-host disease. Hymes SR, Alousi AM, Cowen EW. *J Am Acad Dermatol* 2012; 66: 535.

PUVA, PUVA bath, UVB, NB-UVB, and UVA1 have all shown efficacy for cGVHD in small series. UVB and NB-UVB may work best for lichen planus–like manifestations, whereas PUVA and UVA1 penetrate more deeply and are better suited for scleroderma-like disease.

Third-Line Therapies

1 Systemic

• Pulse corticosteroids	C
• Interleukin-2	B
• Imatinib	B
• Pentostatin	B
• Thalidomide	C
• Low-dose methotrexate	C
• Hydroxychloroquine	C
• Infliximab	C
• Etanercept	C
• Alefacept	C
• Alemtuzumab	C
• Cyclophosphamide	C
• Etreinate/isotretinoin/acitretin	C
• Clofazimine	C
• Thoracoabdominal irradiation	C
• Mesenchymal stromal cell therapy	C

2 Oral GVHD

• Topical corticosteroids	C
• Topical calcineurin inhibitors	C
• Intraoral PUVA	C
• Oral UVB	C

Efficacy, durability, and response predictors of low-dose interleukin-2 therapy for chronic graft-versus-host disease. Koreth J, Kim HT, Jones KT, et al. *Blood* 2016; 128: 130–7.

Low-dose IL-2 stimulates T-regulatory cell expansion. Of 33 evaluable patients with steroid-refractory cGVHD in this phase 2 trial, 20 (61%) had clinical response by week 12, and 10 (30%) had stable disease.

Long-term outcome and prospective validation of NIH response criteria in 39 patients receiving imatinib for steroid-refractory chronic GVHD. Olivieri A, Cimminiello M, Corradini P, et al. *Blood*. 2013; 122: 4111–8.

In a prospective trial of imatinib for steroid-refractory cGVHD, 20 of 39 (51.3%) patients responded per NIH criteria.

Phase II study of pentostatin in patients with corticosteroid-refractory chronic graft-versus-host disease. Jacobsohn DA, Chen AR, Zahurak MJ, et al. *J Clin Oncol* 2007; 25: 4255–61.

Fifty-eight heavily pretreated patients (median four prior regimens) with cGVHD were given pentostatin 4 mg/m² every 2 weeks for 12 doses. The overall response rate was 32 of 58 (55%), with major improvements seen in 31 patients. Survival was 70% at 2 years, with infectious complications predominant.

Granuloma annulare

Bridget E. Shields, Misha Rosenbach



Granuloma annulare (GA) is an inflammatory cutaneous disease thought to be driven by immune mechanisms. Previous studies have suggested that some variants of GA represent delayed-type (type IV) hypersensitivity reactions to an unknown variety of antigenic triggers. GA may occur as an isolated, idiopathic entity but has also been described in association with multiple systemic processes. Diabetes, dyslipidemia, and thyroid disease are the most commonly reported associated conditions (though contrary studies exist as well); however, GA has also been reported in association with infections and, rarely, some malignancies. This relationship may be coincidental rather than correlative. GA-associated infections include human immunodeficiency virus (HIV), infectious hepatitis, and *Borrelia burgdorferi* most commonly; however, conflicting evidence surrounding the strength of these associations exists. GA developing in the setting of hepatitis C infection, and improving with interferon- α therapy, has been reported and screening for hepatitis C is recommended. GA has developed after bacillus Calmette-Guérin, hepatitis B, tetanus and diphtheria toxoid, and anti-tetanus vaccination. The health benefits of vaccinations greatly outweigh the exceedingly rare and potential risks of GA development in all cases. GA has developed as an isotopic response at prior sites of herpes zoster infection. While a temporal relationship between GA and malignancy has occasionally been reported, recent studies suggested there is no consistent causative link. Expert consensus remains that age appropriate screening is indicated, but extended malignancy screening should be considered in older patients with extensive GA, or those with widespread, atypical (such as palmar plaques), or recalcitrant disease.

GA encompasses a spectrum of disease and may be localized GA (LGA) or generalized GA (GGA). Children may present with subcutaneous GA, which often self-resolves in adolescence. LGA is the most common variant and is characterized by pink to red, arciform and annular, non-scaly papules and plaques on the extremities. Other variants include perforating, patch, and palmoplantar forms of GA. Histology shows palisading (about one-third of cases) or interstitial (about two-thirds of cases) granulomatous inflammation with a central core of necrobiotic collagen surrounded by a lymphohistiocytic infiltrate, typically with mucin.

MANAGEMENT STRATEGY

LGA is often diagnosed clinically, but a skin biopsy may be required to exclude other entities or confirm the diagnosis of less common variants. Patients with GA may benefit from screening for diabetes, hyperlipidemia, thyroid disease, and hepatitis C.

Approximately half of LGA cases are self-limiting within 2 years. As most patients are asymptomatic, reassurance that the disease is benign and may resolve spontaneously is sufficient. For patients with symptomatic or cosmetically sensitive lesions, treatment may be desired. There have been numerous reported treatment options for GA; unfortunately, a review of GA publications shows the median number of patients per study was one over a 25-year period.

LGA may be treated with topical or intralesional steroids. Super-potent topical steroids under occlusion with a hydrocolloid dressing, changed weekly, can be used for up to 6 weeks. Alternatively, intralesional triamcinolone injections may be used at intervals of 6–8 weeks. Liquid nitrogen cryotherapy can be repeated every 3–4 weeks as required. Treatment of refractory lesions includes photodynamic therapy, ultraviolet A1 (UVA1) phototherapy, intralesional interferon, and laser therapy; large, tumid lesions may rarely require excision. Recalcitrant lesions can also be treated with some of the treatments described below for generalized disease.

Generalized GA may be persistent, and its unsightly appearance causes patients to seek active treatment. *Antimalarial therapy* is often effective in GGA; initial reports were with *chloroquine*, though *hydroxychloroquine* is also effective and confers a more favorable side-effect profile. *Phototherapy* can be an effective treatment. While both *psoralen and ultraviolet A (PUVA)* and *UVA1 phototherapy* have been reported, *narrowband phototherapy* is also effective and may be used, but relapses can occur. Intertriginous, patch-type GA may be particularly responsive to phototherapy. *Isotretinoin* and *dapsone* have been associated with improvement or clearance of generalized GA. Topical tacrolimus and pimecrolimus have been used, with some reports describing greater success in generalized disease than in the localized variety. Other reported treatments for this condition include *laser*, *fumaric acid esters*, *methotrexate*, *chlorambucil*, *ciclosporin*, *hydroxyurea*, *doxycycline*, *pulsed triple-antibiotic therapy*, *systemic corticosteroids*, *adalimumab*, *infliximab*, *anthralin*, *vitamin E*, *allopurinol*, *nicotinamide*, *pentoxifylline*, *apremilast*, and *defibrotide*. Biopsy alone has reportedly improved patch GA and GGA. New, emerging reports describe response to *oral and topical tofacitinib*, with JAK-inhibitors showing promise for multiple granulomatous diseases.

Specific Investigations

- Check glycated hemoglobin (HbA1c)
- Thyroid stimulating hormone
- Fasting lipid panel
- Consider hepatitis C screening for at risk patients

The relationship between GA and diabetes remains unclear; however, screening HbA1c in patients with risk factors or symptoms of glucose intolerance should be considered. Hyperlipidemia and thyroid disease are both seen at increased rates in patients with granulomatous diseases, including GA, and are easy to screen for with low risk, cost effective tests.

Generalized granuloma annulare: clinical and laboratory findings in 100 patients. Dabski K, Winkelmann RK. J Am Acad Dermatol 1989; 20: 39–47.

Retrospective review identifying GGA in 20% of 100 biopsy-proven cases of GA at a tertiary referral institution.

Localized granuloma annulare is associated with insulin-dependent diabetes mellitus. Muhlemann MF, Williams DR. Br J Dermatol 1984; 111: 325–9.

Retrospective study of 557 insulin-dependent diabetics. Sixteen patients had GA, significantly more than the 0.9 cases that might have been expected.

Laboratory abnormalities in granuloma annulare: a case-control study. Veraldi S, Bencini PL, Drudi E, et al. Br J Dermatol 1997; 136: 652–3.

Retrospective case-control study of 61 patients showing significantly increased risk of insulin-dependent diabetes in patients with GA. Higher prevalence of diabetes mellitus (DM) identified in patients with LGA versus GGA.

Lack of an association between granuloma annulare and type 2 diabetes mellitus. Nebesio CL, Lewis C, Chuang TY. Br J Dermatol 2002; 146: 122–4.

Study of 126 patients with GA in which no association was found between GA and DM in comparison to controls with psoriasis. Notably, potential associations between DM and psoriasis have recently been identified.

LOCALIZED GRANULOMA ANNULARE

First-Line Therapies

- Intralesional corticosteroids **B**
- Cryotherapy **B**
- Topical corticosteroids **E**

Granuloma annulare and necrobiosis lipoidica treated by jet injector. Sparrow G, Abell E. Br J Dermatol 1975; 93: 85–9.

Comparison of 45 patients with LGA treated with intralesional injection of triamcinolone 5 mg/mL or sterile saline over 6- and 8-week intervals. Of those treated with steroid injection, 68% experienced complete clearance versus 44% in the sterile saline group. Partial clearance was higher in the saline group (33%) versus in the steroid group (24%), and less than 50% of patients in both groups had recurrence of GA.

Successful outcome of cryosurgery in patients with granuloma annulare. Blume-Peytavi U, Zouboulis CH, Jacobi H, et al. Br J Dermatol 1994; 130: 494–7.

In a study of 31 patients with GA, 22 patients were treated with liquid nitrogen and nine with nitrous oxide. After a single freeze-thaw cycle, 81% of GA lesions treated with liquid nitrogen cleared. Four cases had persistent atrophic scars at sites of treatment.

Granuloma annulare of childhood successfully treated with potent topical corticosteroids previously unresponsive to tacrolimus ointment 0.1%: report of three cases. Rallis E, Stavropoulou E, Korfitis C. Clin Exp Dermatol 2009; 34: e475–6.

Twice-daily application of clobetasol propionate 0.05% or mometasone furoate 0.1% without occlusion for 2–3 weeks led to complete remission of LGA in three children.

Successful treatment of chronic skin diseases with clobetasol propionate and a hydrocolloid occlusive dressing. Volden G. Acta Derm Venereol 1992; 72: 69–71.

One in three cases of GA showed a complete response after 4 weeks of treatment with clobetasol propionate under occlusion.

Second-Line Therapies

- Pulsed dye laser **C**
- 308-nm excimer laser **E**
- Topical photodynamic therapy **D**
- Topical imiquimod **E**
- Topical dapsone **E**
- Topical tacrolimus **E**
- Topical pimecrolimus **E**
- Scarification **E**
- Surgery **E**
- UVA1 **E**
- Intralesional interferon **E**
- Pulsed monthly rifampicin, ofloxacin, and minocycline **D**
- Topical tofacitinib **E**

Treatment of granuloma annulare with the 595 nm pulsed dye laser (PDL), a multicenter retrospective study with long-term follow-up. Passeron T, Fusade T, Vabres P, et al. J Eur Acad Dermatol Venereol 2013; 27: 785–8.

Five patients with LGA and eight patients with GGA were treated with three sessions of PDL. A significant response was seen only in the localized forms while GGA showed weak improvement, with a high recurrence rate.

Granuloma annulare treated with excimer laser. Bronfenbrenner R, Ragi J, Milgraum S. J Clin Aesthet Dermatol 2012; 5: 43–5.

A 73-year-old woman with an over 40-year history of GGA underwent treatment with excimer laser on the dorsal hands. The regimen comprised fluence of 300 mJ/cm² with five doses per treatment session. After 15 treatments there was complete resolution with no recurrence at treated sites at 6-month follow-up.

Photodynamic therapy for granuloma annulare: more than a shot in the dark. Weisenseel P, Kuznetsov AV, Molin S, et al. Dermatology 2008; 217: 329–32.

Seven patients with GA were treated with three sessions of photodynamic therapy with topical aminolevulinic acid (ALA-PDT) and an interval of 2–4 weeks between each session. In two patients, GA cleared completely; in two patients, the skin lesions improved markedly; and in three patients, no response was observed.

A retrospective analysis of real-life practice of off-label photodynamic therapy using methyl aminolevulinate (MAL-PDT) in 20 Italian dermatology departments. Part 1: inflammatory and esthetic indications. Calzavara-Pinton PG, Rossi MT, Aronson E, et al. J Photochem Photobiol Sci 2013; 12: 148–57.

Retrospective observational study of patients treated with MAL-PDT in Italian hospital centers. Nine out of 13 patients with GA showed improvement.

Successful treatment of granuloma annulare with imiquimod cream 5%: a report of four cases. Badavanis G, Monastirli A, Pasmatzis E, et al. Acta Derm Venereol 2005; 85: 547–8.

Four patients with multiple lesions of LGA treated with imiquimod 5% cream once daily. The majority of lesions cleared within 12 weeks of treatment with no recurrence observed at 18 months follow-up. *There is also a report of GA worsening after treatment of adjacent warts with imiquimod.*

Management of periocular granuloma annulare using topical dapsone. Kassardjian M, Patel M, Shitabata P, et al. J Clin Aesthet Dermatol 2015; 8: 48–51.

A 41-year-old male with arciform LGA of the right upper eyelid and lateral canthus was treated with dapsone 5% gel applied twice daily, with significant improvement at 3 weeks.

Periorbital granuloma annulare successfully treated with tacrolimus 0.1% ointment. Gomez-Moyano E, Vera-Casaño A, Martinez S, et al. *Int J Dermatol* 2014; 53: e156–7.

A 6-year-old child with LGA of the upper eyelid was successfully treated with topical tacrolimus 0.1% ointment twice daily. Significant improvement was noticed at 6 weeks with sustained response.

Multiple localized granuloma annulare: ultraviolet A1 phototherapy. Frigerio E, Franchi C, Garutti C, et al. *Clin Exp Dermatol* 2007; 32: 762–4.

Four patients responded to high-dose UVA1, starting with 60 J/cm² on day 1, followed by fixed daily doses of 100 J/cm² five times weekly for 3 weeks.

Treatment of granuloma annulare by local injections with low dose recombinant human interferon gamma. Weiss JM, Muchenberger S, Schöpf E, et al. *J Am Acad Dermatol* 1998; 39: 117–9.

Three patients achieved clearance of LGA with intralesional rHu-interferon- γ 2.5 $\times$ 10⁵ IU/lesion on 7 consecutive days continued three times weekly for 2 weeks. Two similar GA lesions were treated as controls with 0.9% normal saline or via corticosteroid under occlusion without improvement. No flu-like symptoms or blood chemistry changes were noted.

Triple antibiotic combination therapy may improve but not resolve granuloma annulare. Simpson B, Foster S, Ku JH, et al. *Dermatol Ther* 2014; 27(6): 343–7.

Open-label prospective study of 21 patients with at least five lesions of LGA who received once-monthly rifampin (400mg), ofloxacin (400mg), and minocycline (100mg) for 6 months with improvement measured on the Granuloma Annulare Severity Index (GASI) scoring system. Fifteen patients completed the study and 10 subjects achieved at least 50% reduction in GASI. Six subjects had no change or worsening of their GA. Mean GASI scores decreased significantly by 15 points ($p < 0.01$) although number and LGA subtypes were not detailed. Clinical significance remains unknown.

Treatment of granuloma annulare with tofacitinib 2% ointment. Damsky W, King BA. *JAAD Case Rep* 2020; 6(1): 69–71.

A 69-year-old man with a 1-year history of LGA was treated with tofacitinib 2% ointment twice daily. After 15 weeks there was marked improvement and near resolution in all treated lesions. One lesion was not treated and did not improve. No adverse effects were noted.

GENERALIZED (DISSEMINATED) GRANULOMA ANNULARE

First-Line Therapies

• UVA1	B
• PUVA	C
• Narrowband ultraviolet B (NB-UVB)	D
• Isotretinoin	C
• Oral dapsone	C
• Hydroxychloroquine	C
• Chloroquine	C
• Topical photodynamic therapy	E

UVA1 phototherapy for disseminated granuloma annulare. Schnopp C, Tzaneva S, Mempel M, et al. *Photodermatol Photoimmunol Photomed* 2005; 21: 68–71.

Twenty patients with disseminated GA underwent phototherapy with UVA1 (340–400nm), which provided good to excellent results in half of patients and satisfactory responses in the majority of patients. Discontinuation of treatment was followed by early recurrence.

Psoralen and ultraviolet A in the treatment of granuloma annulare. Browne F, Turner D, Goulden V. *Photodermatol Photoimmunol Photomed* 2011; 27: 81–4.

A retrospective study of 33 patients treated with twice-weekly PUVA resulted in clearance in 50% of patients and good improvement in 16%, 25% with moderate benefit, and 9% with no improvement. Seventy-nine percent remained in remission at 6 months but only 32% remained in remission at 12 months.

The efficacy of PUVA and narrowband UVB phototherapy in the management of generalized granuloma annulare. Cunningham L, Kirby B, Lally A. *J Dermatolog Treat* 2016; 27(2): 136–9.

Retrospective review of 20 female patients with GGA treated with PUVA and NB-UVB. Twelve patients underwent 15 courses of PUVA (oral or bath) and 10 patients were treated with NB-UVB for 12 treatments (2 patients had both). Minimal residual disease or clearance was noted for 8 of 12 patients after PUVA resulting in a 6-month (7 patients) to 1-year (2 patients) remission. Minimal residual disease or clearance was reported for 7 patients treated with NB-UVB and remission was for 6 months (3 patients) to greater than 1 year (2 patients).

Generalized granuloma annulare in a patient with type 2 diabetes mellitus: successful treatment with isotretinoin. Sahin M, Türel-Ermertcan A, Öztürkcan S, et al. *J Eur Acad Dermatol Venereol* 2006; 20: 111–4.

A 49-year-old man with type 2 DM and GGA was treated with isotretinoin at 5 mg daily, leading to complete resolution without relapse beyond 3-month follow-up.

The response of generalized granuloma annulare to dapsone. Czarnecki DB, Gin D. *Acta Derm Venereol* 1986; 66: 82–4.

Six patients (11–76 years old) with GGA were treated with dapsone 100 mg daily resulting in complete clinical response. Five cleared within 8 weeks and four remained clear for 20 months after stopping treatment.

Efficacy of dapsone on disseminated granuloma annulare: a case report and review of the literature. Martín-Sáez E, Fernández-Guarino M, Carrillo-Gijón R, et al. *Actas Dermosifilogr* 2008; 99: 64–8.

A patient with GGA showed clinical improvement taking dapsone 100 mg daily for 2 months with clearance at 15 months without recurrence several months after treatment discontinuation.

Treatment of generalized granuloma annulare with hydroxychloroquine. Cannistraci C, Lesnoni La Parola I, Falchi M, et al. *Dermatology* 2005; 211: 167–8.

Four of nine patients achieved complete remission when treated with hydroxychloroquine for 4 months with the following regimen: 9 mg/kg/day for 2 months, 6 mg/kg/day for month 3, and 2 mg/kg/day for month 4. One child was treated with 50% of the dose delineated.

Long lasting interstitial generalized granuloma annulare on sun-exposed areas. Andreu-Barasoain M, Gomez de la Fuente E, Pinedo F, et al. Photodermatol Photoimmunol Photomed 2012; 28: 216–8.

Case report of photodistributed GGA that responded to chloroquine with multiple recurrences when off the medication.

Antimalarials for control of disseminated granuloma annulare in children. Simon M, Van Den Driesch P. J Am Acad Dermatol 1994; 31: 1064–5.

Six children achieved complete clearance of their GGA within 6 weeks of treatment with 3–6 mg/kg/day hydroxychloroquine and remained clear for 2.5 years of follow-up.

Generalized granuloma annulare treated with methylaminolevulinate photodynamic therapy. Piaserico S, Zattra E, Linder D, et al. Dermatology 2009; 218: 282–4.

Three patients with persistent generalized GA responded to MAL-PDT.

Second-Line Therapies

• Topical corticosteroids	E
• Systemic corticosteroids	E
• Topical pimecrolimus	E
• Tofacitinib	E
• Topical tacrolimus	E
• Fumaric acid esters	C
• Chlorambucil	D
• Doxycycline	E
• Allopurinol	E
• Nicotinamide	E
• Pentoxifylline	E
• Apremilast	E
• Oral calcitriol	E
• Monthly rifampicin, ofloxacin, and minocycline	D
• Ciclosporin	E
• Methotrexate	E
• Hydroxyurea	E
• Defibrotide	E
• Anthralin	E
• Adalimumab	D
• Infliximab	E
• Etanercept	E
• Laser (neodymium-doped yttrium aluminum garnet [Nd:YAG])	E
• Oral vitamin E and leukotriene inhibitor	E
• Topical vitamin E	E

A contact dermatitis reaction to clobetasol propionate cream associated with resolution of recalcitrant, generalized granuloma annulare. Agarwal S, Berth-Jones J. J Dermatol Treat 2000; 11: 279–82.

A 22-year-old woman with GGA developed contact sensitization to clobetasol propionate cream during treatment of her GA, raising the possibility that this reaction may have played a therapeutic role.

Generalized granuloma annulare presenting as arcuate dermal erythema. Miličić V, Ravić-Nikolić A, Jovović-Dagović B, et al. Acta Dermatovenereol Alp Pannonica Adriat 2010; 19: 25–7.

A case report describing treatment of GGA with a 7-day course of intramuscular methylprednisolone (40 mg daily dose) and

low-dose oral prednisone (20 mg daily, then 10 mg daily over 2 months).

Systemic corticosteroids may exacerbate preexisting diabetes.

Pimecrolimus 1% cream in the treatment of disseminated granuloma annulare. Rigopoulos D, Prantsidis A, Christofidou E, et al. Br J Dermatol 2005; 152: 1364–5.

An adult improved with twice-daily treatment for 3 months.

Successful treatment of disseminated granuloma annulare with topical tacrolimus. Jain S, Stephens CJM. Br J Dermatol 2004; 150: 1042–3.

Four patients were treated with twice-daily application of tacrolimus 0.1% ointment. At 6 weeks, two patients showed clearance and the remaining two patients showed significant improvement. There was no evidence of recurrence 6 weeks after treatment discontinuation.

Janus kinase inhibition induces disease remission in cutaneous sarcoidosis and granuloma annulare. Damsky W, Thakral D, McGeary MK, et al. J Am Acad Dermatol 2020; 82(3): 612–21.

A 66-year-old woman with refractory GGA was treated with tofacitinib 5 mg twice daily, resulting in complete or near-complete clinical remission within 6–10 months and histologic resolution of granulomatous inflammation. Molecular analysis showed normalization of the IFN- γ gene expression signatures in previously affected skin.

Therapy of noninfectious granulomatous skin diseases with fumaric acid esters. Breuer K, Gutzmer R, Völker B, et al. Br J Dermatol 2005; 152: 1290–5.

Thirteen patients with generalized GA were treated with Fumaderm, 1 tablet daily for 1 week, increased to 3–6 tablets per day. Eight patients experienced improvement of disease. Treatment courses were between 3 months and greater than 14 months.

Fumaric acid esters in combination with oral PUVA may result in further improvement.

Generalized granuloma annulare: response to doxycycline. Duarte AF, Mota A, Pereira MA, et al. J Eur Acad Dermatol Venereol 2009; 23: 84–5.

A woman with GA achieved almost complete resolution after treatment with doxycycline 100 mg/day for 10 weeks.

Treatment of disseminated granuloma annulare with allopurinol: case report. Mazzatenta C, Ghilardi A, Grazzini M. Dermatol Ther 2010; 23(Suppl 1): S24–7.

Allopurinol 300 mg twice daily is an alternative treatment for GGA in therapy-resistant patients.

Response of generalized granuloma annulare to high dose niacinamide. Ma A, Medenica M. Arch Dermatol 1983; 119: 836–9.

A patient with GGA experienced resolution of her lesions after 6 months of treatment with niacinamide 1500 mg daily.

Successful treatment of generalized granuloma annulare with pentoxifylline. Nambiar KG, Jagadeesan S, Balasubramanian P, et al. Indian Dermatol Online J 2017; 8: 218–20.

A 60-year-old woman with GGA was treated with pentoxifylline at 400 mg three times daily with response within 1 month, dramatic improvement at 3 months, and no recurrence at 6 months.

Given the favorable safety profile of pentoxifylline, it should be considered as an adjunct treatment.

Granuloma annulare responsive to oral calcitriol. Boyd AS. *Int J Dermatol* 2012; 51: 120–2.

One patient described improvement in pruritus at 1 month, and improvement in appearance was noted at 3 months with 0.25 mcg oral calcitriol daily.

Refractory generalized granuloma annulare treated with oral apremilast. Bishnoi A, Raj D, Vinay K, et al. *JAMA Dermatol* 2019; 155(11): 1318–20.

Four patients with treatment-refractory GGA underwent therapy with oral apremilast at 30 mg twice daily. All patients exhibited a positive response after 6 to 8 weeks. All patients continued a maintenance dose of 30 mg once daily with sustained remission.

Disseminated granuloma annulare: efficacy of cyclosporine therapy. Spadino S, Altomare A, Cainelli C, et al. *Int J Immunopathol Pharmacol* 2006; 19: 433–8.

Four patients with GGA were treated with cyclosporin 4 mg/kg/day and achieved complete clearance within 3 weeks with no relapses in the 12 months following treatment.

Successful treatment of disseminated granuloma annulare with methotrexate. Plotner AN, Mutasim DF. *Br J Dermatol* 2010; 163: 1123–4.

A patient with GGA experienced resolution of the majority of lesions with methotrexate 15 mg weekly and daily folic acid supplementation for 6 weeks. Discontinuation of methotrexate upon two occasions for surgical procedures resulted in a recurrence of disease within 1 month.

Treatment of recalcitrant granuloma annulare (GA) with adalimumab: a single-center, observational study. Min MS, Lebwohl M. *J Am Acad Dermatol* 2016; 74: 127–33.

Seven patients with generalized GA were administered adalimumab 80 mg subcutaneously, followed by 40 mg every other week, 1 week after initiation. Patients were asked to return in 1 and 3 months. Adalimumab was either discontinued with disease clearance or patient wish or escalated to weekly injections if minimal improvement was noted after 3 months. In cases in which lesions recurred after discontinuing adalimumab, patients were permitted to restart therapy. All seven patients experienced clearance, with two requiring weekly injections. Three patients maintained remission at 40 months after discontinuation of treatment.

Antitumor necrosis factor- α treatment with infliximab for disseminated granuloma annulare. Murdaca G, Colombo BM, Barabino G, et al. *Am J Clin Dermatol* 2010; 11: 437–9.

A 62-year-old woman was administered infliximab intravenously at a dosage of 5 mg/kg at weeks 0, 2, and 6 and thereafter at monthly intervals for 10 additional months. The majority of her GGA lesions improved within 8 weeks and resolved within 10 months of treatment.

Rapid improvement of recalcitrant disseminated granuloma annulare upon treatment with the tumor necrosis factor- α inhibitor, infliximab. Hertl MS, Haendle I, Schuler G, et al. *Br J Dermatol* 2005; 152: 552–5.

A 59-year-old woman with type 1 diabetes and a 4-year history of recalcitrant generalized GA was administered infliximab at 5 mg/kg/day at weeks 0, 2, and 6 and thereafter at a monthly interval for an additional 4 months. The majority of disease cleared within 4 to 6 weeks. New lesions were not seen in follow-up to 16 months.

Resolving granuloma annulare with etanercept. Shupack J, Siu K. *Arch Dermatol* 2006; 142: 394–5.

A case report of improvement in GGA after 12 weeks of treatment with etanercept at 50 mg biweekly.

Conflicting evidence exists regarding the treatment of GGA with etanercept.

Fractional photothermolysis for the treatment of granuloma annulare: a case report. Karsai S, Hammes S, Rütten A, et al. *Lasers Surg Med* 2008; 40: 319–22.

Remission of four lesions (in a patient with GGA) after two to three treatment sessions with a 1440-nm Nd:YAG laser.

Granuloma annulare successfully treated using fractional photothermolysis with a 1,550-nm erbium-doped yttrium aluminum garnet fractionated laser. Liu A, Hessel CL, Moy RL, et al. *Lasers Surg Med* 2008; 40(5): 319–22.

A 60-year-old with GGA underwent treatment with fractional photothermolysis using a 1550-nm Er:YAG fractionated laser. Eleven treatments were performed at 1-month intervals with 80%–90% improvement. A total energy of 5.8–6.8 kJ was used at a setting of 70 J/cm², with 8–14 passes over each lesion.

Treatment of disseminated granuloma annulare with a 5-lipoxygenase inhibitor and vitamin E. Smith KJ, Norwood C, Skelton H. *Br J Dermatol* 2002; 146: 667–70.

Three patients were treated with vitamin E 400 IU daily and zileuton 2400 mg daily. All responded within 3 months with complete clinical clearing.

Disseminated granuloma annulare as a presentation of acquired immunodeficiency syndrome (AIDS). McGregor JM, McGibbon DH. *Clin Exp Dermatol* 1992; 17: 60–2.

Patient undergoing treatment of AIDS with zidovudine with the associated resolution of cutaneous lesions.

Generalized granuloma annulare associated with chronic hepatitis B virus infection. Ma H, Zhu W, Yue X. *J Eur Acad Dermatol Venereol* 2006; 20: 186–9.

Generalized GA resolved after 3 months of treatment with interferon- α for hepatitis B.

Granuloma faciale

Nevianna Bordet



Granuloma faciale is a rare, benign, chronic inflammatory dermatosis caused by a localized form of cutaneous vasculitis. It presents primarily in middle-aged Caucasian males, usually as an asymptomatic single lesion on the face. Extensive involvement of the nose can mimic rhinophyma. Multiple lesions occur in up to one-third of patients. Extrafacial granuloma faciale is rare and usually found in association with facial lesions. The etiology of granuloma faciale is unclear.

Lesions are red-brown, violaceous, or flesh-colored plaques or nodules with accentuation of follicular openings giving a 'peau d'orange' appearance. Clinical diagnosis is difficult. Differential diagnosis includes sarcoid, lupus, lymphocytoma cutis, persistent insect bite reactions, leishmaniasis, and lymphoma. The histologic differential diagnosis includes erythema elevatum diutinum and angiolymphoid hyperplasia with eosinophilia.

MANAGEMENT STRATEGY

Granuloma faciale is notoriously resistant to treatment and spontaneous remission is unusual. Because it is rare, there are no formal trials of therapy. Treatment modalities can be divided into destructive techniques (*cryotherapy*, *laser*, *surgical excision*) and antiinflammatory approaches. The optimal treatment depends on the size and extent of lesions.

Granuloma faciale treatment: a systematic review. Lindhaus C, Elsner P. *Acta Derm Venereol* 2018; 98: 14–8.

In the last few years, there have been increasing numbers of case reports of successful treatment with topical calcineurin

inhibitors for isolated or multiple lesions, and a recent systematic review of 94 patients recommended this as first-line treatment and pulsed-dye laser for drug-resistant lesions.

Specific Investigations

- Skin biopsy
- Hematology (full blood count)
- Dermoscopy

Histologic findings include a dense eosinophilic and neutrophilic infiltrate, often perivascular, affecting the upper and sometimes deep dermis. The epidermis is spared, and there is a grenz zone. Telangiectasia is common. Vasculitis with leukocytoclasia is reported. Dermal fibrosis is often seen.

Granuloma faciale: a clinicopathologic study of 66 patients. Ortonne N, Wechsler J, Bagot M, et al. *J Am Acad Dermatol* 2005; 53: 1002–9.

Peripheral blood eosinophilia is sometimes found.

Dermoscopic patterns of common facial inflammatory skin disease. Lallas A, Argenziano G, Apalla Z, et al. *J Eur Acad Dermatol Venereol* 2014; 28: 609–14.

Dermoscopy is increasingly used to aid diagnosis in granuloma faciale. Follicle abnormalities such as dilated follicular openings, perifollicular whitish halo, follicular keratotic plugs, and linear slightly arborizing vessels in a parallel arrangement are the most commonly described dermoscopic criteria.

First-Line Therapies

• Corticosteroids	D
• Calcineurin inhibitors	D
• Cryotherapy	D
• Laser therapy	D

Granuloma faciale treated with intradermal dexamethasone. Arundell FD, Burdick KH. *Arch Dermatol* 1960; 82: 437–8.

This paper reports response to dexamethasone, but triamcinolone acetonide and triamcinolone hexacetonide have also been used. Patients should be warned of the risk of skin atrophy and pigment change.

Granuloma faciale: is it a new indication for pimecrolimus? A case report. Eetam I, Ertekin B, Unal I, et al. *J Dermatol Treat* 2006; 17: 238–40.

A case report of a lesion showing 'dramatic recovery' after pimecrolimus cream 1% twice daily for 2 months.

Granuloma faciale: treatment with topical tacrolimus. Marcial J, Moreno A, Bordas X, et al. *J Am Acad Dermatol* 2006; 55: S110–1.

This and other papers describe response to topical tacrolimus, typically within a few months. In some patients, lesions had previously failed to respond to other therapies. Remission for up to 2 years is described.

Assessment of the efficacy of cryosurgery in the treatment of granuloma faciale. Panagiotopoulos A, Anyfantakis V, Rallis E, et al. *Br J Dermatol* 2006; 154: 357–60.

Nine patients were treated with either the open-spray technique given as one or two freeze–thaw cycles of 20–30 seconds, or the cryoprobe given as one to three freeze–thaw cycles of 15–20 seconds, with retreatment at 1 and 3 months, resulted in clearance at 6 months. Two patients experienced hypopigmentation that resolved in 4 months. There was no recurrence within 2–4 years' follow-up.

Granuloma faciale: successful treatment of nine cases with a combination of cryotherapy and intralesional corticosteroid injection. Dowlati B, Firooz A, Dowlati Y. *Int J Dermatol* 1997; 36: 548–51.

Cryotherapy for 20–30 seconds was followed by triamcinolone acetonide 5 mg/mL intralesionally. Lesions cleared completely in all nine cases.

Granuloma faciale treated with pulsed-dye laser: a case series. Cheung S-T, Lanigan SW. *Clin Exp Dermatol* 2005; 30: 373–5.

Four patients who had all failed with cryotherapy were treated with pulsed-dye laser at 595 nm. In two patients the lesions resolved. Nasal lesions, especially flatter ones, seem to respond better to treatment.

Reports of granuloma faciale responding to argon laser and KTP laser are described in the literature, but the pulsed-dye laser is the type most frequently reported as achieving improvement.

Rhinophyma-like granuloma faciale successfully treated with carbon dioxide laser. Bakkour W, Madan V. *Br J Dermatol* 2014; 170: 474–5.

A patient who failed to respond to topical and intralesional steroids as well as 150 mg dapsone showed an excellent response with no recurrence at 18 months.

A handful of other case reports show benefit with carbon dioxide laser.

Second-Line Therapies

• Dapsone	D
• 5-Fluorouracil	E
• Surgery	E

On the efficacy of dapsone in granuloma faciale. Van de Kerkhof PCM. *Acta Derm Venereol* 1994; 74: 61–2.

A 4-cm plaque showed 'impressive improvement' with dapsone 200 mg daily. Dapsone needs careful monitoring, and many patients would not tolerate 200 mg daily.

Many authors mention dapsone as a treatment that has been tried but failed.

Granuloma faciale treated with topical dapsone: a case report. Babalola O, Zhang J, Kristjansson A, et al. *Dermatol Online J* 2014; 20: 25148282.

In a single patient, twice-daily topical dapsone 5% gel resulted in near-complete resolution at 9 months with no recurrence at 18 months.

Treatment of laser resistant granuloma faciale with intralesional triamcinolone acetonide and 5-fluorouracil

combination therapy. Norris DL, Apikian M, Goodman GJ. *J Cutan Aesthet Surg* 2015; 8: 111–3.

Case report of one patient who failed to respond to topical tacrolimus and pulsed-dye laser achieving 'an excellent response' with intralesional 0.8 mL 5-fluorouracil 50 mg/mL combined with 0.2 mL triamcinolone acetonide 10 mg/mL. No more than 2 mL per treatment should be used according to the authors.

Recurrent facial plaques following full-thickness grafting. Phillips DK, Hymes SR. *Arch Dermatol* 1994; 130: 1436–7.

Although surgery is mentioned in many papers, recurrence can occur even after full-thickness excision and grafting.

Third-Line Therapies

• Colchicine	E
• Ingenol mebutate	E
• Rituximab	E
• Topical PUVA	E

Granuloma faciale treated successfully with colchicine. Ohata C, Nakama T. *Acta Derm Venereol* 2019; 99: 833–4.

Failure to colchicine has been reported several times but this case reports that colchicine 0.5 mg/day for 1 week caused partial clearance and 1 mg/day for 2 weeks cleared granuloma faciale fully, with no recurrence at 16 months.

Granuloma faciale successfully treated with ingenol mebutate. Bobyr I, Campanati A, Consales V, et al. *Dermatol Ther* 2016; 29(5): 325–9.

Ingenol mebutate 0.015% gel, used to treat concomitant actinic keratosis, successfully cleared two adjacent small granuloma faciale (GF) plaques. Follow-up for 8 months showed no recurrence. In January 2020, following final results from a 3-year safety study indicating a higher occurrence of skin cancer, the European Medicines Agency suspended the marketing authorization (licence) for ingenol mebutate gel as a precaution while the evidence is reviewed.

Assessment of treatment of refractory granuloma faciale with intralesional rituximab. Morgado-Carrasco D, Giavedoni P, Mascaró JM, et al. *JAMA Dermatol* 2018; 154(11): 1312–5.

Three cases treated with 0.5–1 mL/cm² of intralesional rituximab (10 mg/mL) once monthly for at least 6 months resulted in complete clearance in two patients and partial response in the third. Treatment was well tolerated and the authors state that it was not costly due to the low doses of rituximab used.

Granuloma faciale: treatment with topical psoralen and UVA. Hudson LD. *J Am Acad Dermatol* 1983; 8: 559.

A 62-year-old man with a 1-month history of biopsy-proven granuloma faciale affecting the nasal alae responded to 24 J UVA given over 10 weeks, showing a very marked improvement with no evidence of residual lesion at 6 months.

There are old reports of treatment with intralesional gold and bismuth, radiotherapy, isoniazid, potassium arsenite, testosterone, and antimalarials, but within the past 30 years there have been no reports of successful response to these agents. A report of adalimumab treatment for 6 months in one patient did not lead to improvement.

Granuloma inguinale

Ted Rosen



Granuloma inguinale, or donovanosis, is an infection causing granulomatous and destructive ulceration of genital, inguinal, and perineal skin. Cervical lesions are rare but may clinically mimic carcinoma. Extragenital lesions occur in about 6% of cases. This disorder is extremely rare in Western Europe and the United States, but is still endemic or epidemic in India, Brazil, and Papua New Guinea, and uncommonly in South Africa and very rarely among the Aboriginal people in Australia. Diagnosis can be made clinically by an experienced physician in endemic regions, but this may be difficult in other areas of the world. The causative organism is *Klebsiella granulomatis*, an intracellular, encapsulated, Gram-negative coccobacillus.

The disease presents with a subcutaneous granuloma or nodule that develops into characteristically painless, progressive ulcerative lesions without regional lymphadenopathy. Lesions are ulcerogranulomatous, highly vascular (i.e., a beefy red appearance), and friable (bleed easily on contact).

MANAGEMENT STRATEGY

Patients with donovanosis should be treated to prevent the gradual worsening of the disease leading to genital deformity or (very rarely) life-threatening disseminated infection, to prevent transmission, and to prevent the risk of concomitant transmission of human immunodeficiency virus (HIV) infection.

In the absence of evidence from randomized, placebo-controlled trials, antibiotic treatment of donovanosis is based on the results of local clinical experience and individual case reports, typically involving relatively small numbers of patients.

The U.S. Centers for Disease Control and Prevention (CDC) (2015) currently recommends *azithromycin*, with many alternative regimens (e.g., *doxycycline*, *ciprofloxacin*, *erythromycin*, *trimethoprim-sulfamethoxazole*). Azithromycin is also recommended in the 2016 European Guideline on donovanosis. The addition of an aminoglycoside, such as *gentamicin*, is recommended by the CDC if lesions do not respond within the first few days.

Therapy should be continued for a minimum of 3 weeks and until all lesions have healed completely. This typically starts at the outside margins and progresses inward. Despite seemingly effective initial therapy, a relapse can occur 6–18 months later. *Surgical excision* may be necessary for extensive disease that is unresponsive to antibiotic therapy. It should be noted that squamous cell carcinoma has been reported concurrent with active donovanosis, complicating longstanding cases, and developing at sites of healed lesions.

Sexual partners of patients who have granuloma inguinale should be examined and treated if they had sexual contact with the patient during the 60 days preceding the onset of symptoms in the patient or have clinical signs and symptoms of the disease.

Specific Investigations

- Tissue smear or biopsy with Wright or Giemsa stains
- Screen for other sexually transmitted infections (e.g., HIV, syphilis)
- Culture (not readily available)
- Polymerase chain reaction (PCR; not readily available)
- Serologic testing (not readily available, and not sufficiently reliable)

Genital ulcer disease: accuracy of clinical diagnosis and strategies to improve control in Durban, South Africa. O'Farrell N, Hoosen AA, Coetzee KD, et al. *Genitourin Med* 1994; 70: 7–11.

The clinical diagnostic accuracy for donovanosis was relatively high (63% in men, 83% in women). Donovanosis ulcers bled on touch and were not usually associated with inguinal lymphadenopathy.

The changing epidemiology of genital ulcer disease in South Africa: has donovanosis been eliminated? Muller EE, Kularatne R. *Sex Transm Infect* 2020. doi: 10.1136/sextrans-2019-054316 [Epub ahead of print].

Recent research using molecular techniques indicates that donovanosis is now rare as a cause of genital ulcer disease in South Africa due to specific elimination programs. This parallels similar results of public health programs in Australia.

Donovanosis. Hart G. *Clin Infect Dis* 1997; 25: 24–32.

Confirmation involves demonstration of typical intracellular Donovan bodies within large mononuclear cells visualized in smears prepared from lesions or biopsy specimens. The large mononuclear cells are 25–90 mcg in diameter with a vesicular or pyknotic nucleus.

Sexually transmitted disease surveillance 2010. Centers for Disease Control and Prevention. US Department of Health and Human Services, Atlanta; 2011.

Cases are confirmed by demonstration of intracytoplasmic Donovan bodies in Wright- or Giemsa-stained smears or biopsies of granulation tissue in a clinically compatible case (one or more painless or minimally painful granulomatous lesions in the anogenital area).

A colorimetric detection system for *Calymmatobacterium granulomatis*. Carter JS, Kemp DJ. *Sex Transm Infect* 2000; 76: 134–6.

A PCR test that could be used by well-equipped laboratories; largely a research tool.

Squamous cell carcinoma complicating donovanosis not a thing of the past! Sethi S, Sarkar R, Garg V, et al. *Int J STD AIDS* 2014; 25: 894–7.

A reminder that squamous cell carcinoma has been associated with active and healed donovanosis.

First-Line Therapy

- Azithromycin

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Donovanosis: treatment with azithromycin. Bowden FJ, Savage J. *Int J STD AIDS* 1998; 9: 61.

An Australian report of over 100 patients treated with azithromycin with no primary treatment failures. Regimens employed were 500 mg orally daily for 7 days or 1 g orally weekly for 4 weeks. The 1996–1997 edition of the Australian Antibiotic Guidelines lists azithromycin as the first-line agent for donovanosis. The drug is listed as a B1 agent in pregnancy, meaning that it can be used for the treatment of antenatal patients with the disease.

2016 European guideline on donovanosis. O'Farrell N, Moi H. *Int J STD AIDS* 2016; 27: 605–7.

Azithromycin 1 g orally weekly or 500 mg orally daily, for a minimum of 3 weeks and until complete healing is achieved, is recommended as first-line therapy. Second-line therapeutic recommendations parallel those enumerated by the CDC (see the next citation). Patients should be closely monitored for relapse up to 1.5 years after clinical resolution.

2018 UK national guideline for the management of donovanosis. O'Farrell N, Hoosen A, Kingston M. *Int J STD AIDS* 2018; 29: 946–8.

The British treatment guidelines precisely mimic the European guidelines of 2 years prior. The guidelines also point out the worldwide decrease in disease prevalence.

Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines, 2015. Workowski KA. *Clin Infect Dis* 2015; 61(Suppl 8): S759–62.

The treatment of choice is azithromycin 1 g orally once per week or 500 mg daily for at least 3 weeks and until all lesions have completely healed. Alternative (second-line) therapies include doxycycline 100 mg orally twice a day for at least 3 weeks and until all lesions have completely healed, ciprofloxacin 750 mg orally twice a day for at least 3 weeks and until all lesions have completely healed, erythromycin base 500 mg orally four times a day for at least 3 weeks and until all lesions have completely healed, and trimethoprim-sulfamethoxazole one double-strength (160 mg/800 mg) tablet orally twice a day for at least 3 weeks and until all lesions have completely healed.

Second-Line Therapies

- Doxycycline
- Erythromycin
- Trimethoprim-sulfamethoxazole
- Ciprofloxacin

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Clinico-epidemiologic features of granuloma inguinale in the era of acquired immune deficiency syndrome. Jamkhedkar PP, Hira SK, Shroff HJ, et al. *Sex Transm Dis* 1998; 25: 196–200.

Fifty patients (21 HIV positive and 29 HIV negative) treated with erythromycin 2 g orally daily. Healing took longer in the seropositive group (mean 25.7 vs. 16.8 days).

Granuloma inguinale. Rosen T, Tschen JA, Ramsdell W, et al. *J Am Acad Dermatol* 1984; 11: 433–7.

Twenty patients were safely and effectively treated with trimethoprim-sulfamethoxazole. It has been used extensively in India with consistently good results.

Third-Line Therapies

- Ceftriaxone
- Gentamicin
- Surgical treatment
- Norfloxacin
- Trovafloxacin
- Ampicillin
- Chloramphenicol
- Thiamphenicol

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Ceftriaxone in the treatment of chronic donovanosis in Central Australia. Merianos A, Gilles M, Chuah J. *Genitourin Med* 1994; 70: 84–9.

Eight women and four men treated with daily injections of 1 g ceftriaxone diluted in 2 mL of 1% lidocaine. Clinical improvement was dramatic in most lesions, and four patients healed completely without recurrence after a total 7–10 g of ceftriaxone.

1998 guidelines for treatment of sexually transmitted diseases. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 1998; 47: 1–116.

The CDC recommends the addition of gentamicin (1 mg/kg IV every 8 hours) if lesions do not respond within the first few days of therapy.

Surgical treatment of granuloma inguinale. Bozbor A, Erbil Y, Berber E, et al. *Br J Dermatol* 1998; 138: 1079–81.

Fistulas and abscesses unresponsive to antibiotics may require surgical treatment.

Treatment of donovanosis with norfloxacin. Ramanan CR, Sarma PSA, Ghorpade A, et al. *Int J Dermatol* 1990; 29: 298–9.

Ten patients treated with oral norfloxacin 400 mg twice daily showed complete healing in 2–11 days.

Trovafloxacin for the treatment of chronic granuloma inguinale. Hsu SL, Chia JK. *Sex Transm Infect* 2001; 77: 137.

One patient had complete resolution of lesions after 2 months of trovafloxacin 200 mg daily after previously failing doxycycline, ampicillin, erythromycin, trimethoprim-sulfamethoxazole, ceftriaxone, gentamicin, and chloramphenicol.

The diagnosis and treatment of donovanosis (granuloma inguinale). Richens J. *Genitourin Med* 1991; 67: 441–52.

Ampicillin is unreliable and not recommended as first-line therapy.

Donovanosis in Papua New Guinea. Maddocks I, Anders EM, Dennis E. *Br J Vener Dis* 1976; 52: 190–6.

Fifty cases treated with chloramphenicol 500 mg four times daily. Forty-three had complete or near-complete clinical and bacteriologic healing.

Chloramphenicol is effective, but risk of aplastic anemia limits its use to life-threatening disease.

Donovanosis treated with thiamphenicol. Belda W, Velho PE, Arnone M, et al. Braz J Infect Dis 2007; 11: 388–9.

Ten patients with donovanosis of the penis were treated with thiamphenicol 2.5 g orally on day 1 followed by 1 g daily for the next 14 days. In eight, including two HIV-positive patients, their lesions healed without recurrence.

Thiamphenicol is advantageous over chloramphenicol because of its once-daily administration and lack of reports of serious marrow toxicity.

SPECIAL CONSIDERATIONS

Pregnancy: Pregnant and lactating women should be treated with erythromycin with consideration for the addition of a parenteral

aminoglycoside. Azithromycin may also be safe and effective. Doxycycline should be avoided in the second and third trimesters of pregnancy because of the risk for discoloration of teeth and bones, but is compatible with breastfeeding. Ciprofloxacin presents a low risk to the fetus during pregnancy, but sulfonamides are associated with rare but serious kernicterus in those with G6PD deficiency and should be avoided in the third trimester and during breastfeeding.

HIV infection: Patients often require prolonged antibiotic treatment after the regimens cited earlier. The addition of gentamicin should be strongly considered.

Children: All guidelines agree that children should be treated with a short course of azithromycin dosed at 20 mg/kg. Infants born to mothers with donovanosis should be treated prophylactically with 3 days of azithromycin dosed at 20 mg/kg once daily.

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Granulomatous cheilitis

Charlene Lam, Bryan E. Anderson



Granulomatous cheilitis is characterized by chronic, painless swelling of one or both lips, with histologic evidence of non-caseating granulomatous inflammation. Granulomatous cheilitis exists along the spectrum of orofacial granulomatosis, which encompasses localized disease (cheilitis granulomatosa, Miescher cheilitis) to multisystem disease (Melkersson–Rosenthal syndrome). Melkersson–Rosenthal syndrome describes the triad of recurrent orofacial edema, recurrent facial nerve palsy, and lingua plicata (fissured tongue). Many investigators consider isolated granulomatous cheilitis to be a monosymptomatic form of Melkersson–Rosenthal syndrome.

MANAGEMENT STRATEGY

The treatment of granulomatous cheilitis is very challenging. Because the etiology is unknown, a variety of therapeutic strategies with varying degrees of success have been attempted. No randomized clinical trials or comparative studies have been performed. Given the evanescent nature of the condition, treatment outcomes are difficult to assess. Spontaneous remission of granulomatous cheilitis rarely occurs, further confounding assessment of therapies. Furthermore, a recent retrospective study demonstrated long-term treatment with topical medications and/or combination therapy may be required.

The aim of treatment is to prevent permanent labial deformity. Conservative measures for acute granulomatous cheilitis involve symptomatic relief, including *cold compresses* and *oral antihistamines* to reduce erythema and *ointments* to protect against fissuring of the lips. Initial therapy frequently includes *corticosteroids*, either topical, intralesional, or systemic. Initial topical therapy may include either *triamcinolone* or *clobetasol* (compounded into Orabase). Intralesional steroids may be used in doses ranging from 10 to 40 mg/kg. Nerve blocks may reduce patient discomfort in cases where large volumes

at low concentrations are needed. Although short courses of prednisone (25–50 mg/day) will frequently improve tissue swelling, flares are often noted on cessation.

Clofazimine has been reported to treat granulomatous cheilitis successfully. Response to therapy has been variable. Possible side effects include transient orange-pink discoloration of the skin, nausea, and vomiting. Fatal enteropathy may occur but only at higher doses than those recommended for granulomatous cheilitis treatment. *Thalidomide* can also be considered, especially in refractory cases. Patients must be monitored for the development of peripheral neuropathy and warned of its teratogenicity. Monotherapy with *metronidazole*, *tetracyclines*, *azithromycin*, *hydroxychloroquine*, or *sulfasalazine*, although less well substantiated, may be attempted. These medications may be used with corticosteroids. The addition of *minocycline* 100 mg twice daily or *tetracycline* 500 mg daily may prevent rebound after prednisone discontinuation. The value of *dapsone* and topical *tacrolimus* in the treatment of granulomatous cheilitis is unclear. Biologics, including *infliximab* and *adalimumab*, have also been successful treatments.

Granulomatous cheilitis may become persistent. Patients who suffer from permanent esthetic deformity or functional impairment may benefit from cheiloplasty. Surgical intervention should be performed only when more conservative approaches have failed and when inflammation is quiescent. An important consideration for Melkersson–Rosenthal syndrome patients undergoing anesthesia for surgical intervention or any surgical procedures is the risk of urticarial reaction due to anesthetic triggers during the procedure. In the past, remission was maintained with the use of postoperative corticosteroid injections. More recent reports, however, have described long remissions after surgery, with no additional treatment needed.

Granulomatous cheilitis has characteristics that are associated with several conditions that may require evaluation, including Crohn disease, sarcoidosis, infections (tuberculosis, leprosy, deep fungal, human immunodeficiency virus (HIV), and syphilis), acquired or hereditary angioedema, cheilitis glandularis, and leukemic infiltrates. It is also important to rule out any provocative cause such as odontogenic infections or allergenic sensitizers. Orofacial granulomatosis is associated with Crohn disease, especially in children, and may precede even minimal gastrointestinal symptoms.

Initial biopsies of granulomatous cheilitis may reveal dilated lymphatic channels, non-specific inflammatory infiltrates, and edema. In the later stages, the classic non-caseating granulomas are found. Absence of granulomata on biopsy does *not* exclude the diagnosis of granulomatous cheilitis. Granulomatous cheilitis is primarily a clinical diagnosis.

Specific Investigations

- Biopsy for histopathologic examination: polarization and stains/cultures for fungi and acid-fast bacilli
- Complete blood count and chemistry profile, including serum calcium
- Angiotensin-converting enzyme level
- Chest radiograph
- C1-esterase inhibitor; C1-esterase inhibitor functional assays; C1, C2, and C4 levels
- Consultation with dental professional if odontogenic infection suspected
- Consultation with gastroenterologist if there are any gastrointestinal complaints
- Standard patch testing (metal, bakery, dental, and other specialized patch series may be required) and food allergy testing to determine whether an allergen is causative

Cheilitis granulomatosa (Miescher Melkersson Rosenthal Syndrome). Gossman W, Agrawal M, Jamil RT, et al. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK470396/>.

Orofacial granulomatosis. Miest R, Bruce A, Rogers RS. Clin Dermatol 2016; 34: 505–13.

This article reviews orofacial granulomatosis and provocative factors and discusses possible etiologies and differential diagnoses.

Characteristics of patients with orofacial granulomatosis. McCartan BE, Healy CM, McCreary CE, et al. Oral Dis 2011; 17: 696–704.

The largest review of clinical and laboratory findings in 119 patients with orofacial granulomatosis. Mean age of 28, with an equal male-to-female ratio. Almost all patients had clinical evidence of lip and/or facial swelling. Over 50% of biopsies showed granulomatous inflammation.

Melkersson–Rosenthal syndrome: a review of 36 patients. Greene RM, Rogers RS 3rd. J Am Acad Dermatol 1989; 21: 1263–70.

Cheilitis granulomatosa: overview of 13 patients with long-term follow-up: results of management. Int J Dermatol 2002; 41: 225–9.

Orofacial granulomatosis: clinical features and long-term outcome of therapy. Al Johani KA, Moles DR, Hodgson TA, et al. J Am Acad Dermatol 2010; 62: 611–20.

Anesthetic management of patients with Melkersson–Rosenthal syndrome. Tekin M, Kati I. J Anesth 2008; 22: 294–6.

Is orofacial granulomatosis in children a feature of Crohn’s disease? Khouri JM, Bohane TD, Say AS. Acta Paediatr 2005; 94: 501–4.

Orofacial granulomatosis as the initial presentation of Crohn’s disease in an adolescent. Bogenrieder T, Lehn N, Landthaler M, et al. Dermatology 2003; 206: 273–8.

Cutaneous Crohn’s disease mimicking Melkersson–Rosenthal syndrome: treatment with methotrexate. Tonkovic-Capin V, Galbraith SS, Rogers RS III, et al. J Eur Acad Dermatol Venereol 2006; 20: 449–52.

Asymptomatic granulomatous vulvitis and granulomatous cheilitis in childhood: the need for Crohn disease workup. Nabatian AS, Shah KN, Iofel E, et al. J Pediatr Gastroenterol Nutr 2011; 53: 100–1.

Orofacial granulomatosis: three case reports illustrating the spectrum of disease and overlap with Crohn’s disease. Smith VM, Murphy R. Clin Exp Dermatol 2013; 38: 33–5.

These articles highlight the possibility of Crohn disease presenting with, or subsequent to, the diagnosis of granulomatous cheilitis. Narbutt et al. note that although the treatment of granulomatous cheilitis can be mostly cosmetic, Crohn disease is a systemic illness with multiple potential complications.

Although there are many similar clinical and histologic features between oral Crohn disease and orofacial granulomatosis, its relationship

is controversial. Some contend that adolescent granulomatous cheilitis is a predictor of future Crohn disease. It is unknown what percentage of patients with granulomatous cheilitis will develop Crohn disease, but it may be prudent to discuss this issue with granulomatous cheilitis patients.

Melkersson–Rosenthal syndrome and cheilitis granulomatosa. A clinicopathologic study of thirty-three patients with special reference to their oral lesions. Worsaae N, Christensen KC, Schiødt M, et al. Oral Surg Oral Med Oral Pathol 1982; 54: 404–13.

The elimination of odontogenic infections led to inactivity of orofacial edema in 11 of 18 patients.

Contact hypersensitivity in patients with orofacial granulomatosis. Armstrong DKB, Biagonia P, Lamey PJ, et al. Am J Contact Dermatol 1997; 1: 35–8.

Ten of 48 patients showed positive reactions to an oral battery on standard patch testing. Of these 10, seven showed an improvement on an elimination diet. In most cases this was not a complete result.

Patch testing for food-associated allergies in orofacial granulomatosis. Fitzpatrick L, Healy CM, McCartan BE, et al. J Oral Pathol Med 2011; 40: 10–3.

Orofacial granulomatosis associated with hypersensitivity to dental amalgam. Tomka M, Machovcova A, Peldova D, et al. Oral Surg Oral Med Oral Pathol 2011; 112: 335–41.

First-Line Therapies

• Intralesional corticosteroids ± topical immunomodulators	C
• Oral corticosteroids	C

Long-term effectiveness of intralesional triamcinolone acetonide therapy in orofacial granulomatosis: an observational cohort study. Fedele S, Fung PPL, Bamashmous N, et al. Brit J Dermatol 2014; 170: 794–801.

This is the first retrospective observational cohort ($n = 22$) study demonstrating the long-term effectiveness of intralesional triamcinolone acetonide 40 mg/mL. Doses of 0.1 mL were injected into four equally distanced sites (left labial corner and next to median line, right corner and next to median line) per lip once a week for 3 weeks (one treatment course). The majority (14/22) of the patients were treated with one course and did not experience recurrence. There were no adverse effects.

Clinical behavior and long-term therapeutic response in orofacial granulomatosis patients treated with intralesional triamcinolone acetonide injections alone or in combination with topical pimecrolimus 1%. Mignogna MD, Pollio A, Leuci S, et al. J Oral Pathol Med 2013; 42: 763–81.

Triamcinolone acetonide 40 mg/mL diluted to 2:1 with saline (25 mg/mL) was injected every 2 weeks for a maximum of 3 months (six sessions). The majority (11/19) responded. The eight partial responders who were then administered topical pimecrolimus 1% twice daily achieved clinical remission.

Effectiveness of small-volume, intralesional, delayed-release triamcinolone injections in orofacial granulomatosis: a pilot study. Mignogna MD, Fedele S, Lo Russo L, et al. J Am Acad Dermatol; 2004; 51: 265–8.

In this pilot study, triamcinolone 40 mg/mL, with each injection amounting to 0.1 mL, was used weekly for two to three sessions. The needle was injected between the prolabium and labia mucosa, and directed to the oral mucosa to avoid atrophy and hypopigmentation of the labial skin.

With the growing evidence demonstrating the safety and efficacy of high-concentration, low volumes of intralesional steroids, the necessity of nerve blocks for low-concentration, large volumes of intralesional steroids is limited.

Melkersson–Rosenthal syndrome and orofacial granulomatosis. Rogers RS III. *Dermatol Clin* 1996; 14: 371–9.

Oral prednisone 1–1.5 mg/kg daily tapered over 3–6 weeks may be effective for more severe and symptomatic episodes of granulomatous cheilitis.

Second-Line Therapies

• Clofazimine	C
• Biologics, including infliximab, adalimumab	C
• Azithromycin/roxithromycin	D
• Minocycline/tetracycline ± oral corticosteroids	E
• Metronidazole ± intralesional corticosteroids	E
• Mycophenolate mofetil ± topical corticosteroids	E

Clofazimine as elective treatment for granulomatous cheilitis. Fernandez-Freire LF, Gotarredona AS, Wittel JB, et al. *J Drugs Dermatol* 2005; 4: 374–7.

Three patients with granulomatous cheilitis treated with clofazimine 200–300 mg daily for 3–6 months obtained regression. Side effects included hyperpigmentation of the skin and elevation of liver enzymes.

Cheilitis granulomatosa Miescher: treatment with clofazimine and review of the literature. Ridder GJ, Fradis M, Löhle E. *Ann Otol Rhinol Laryngol* 2001; 110: 964–7.

A 15-year-old girl's granulomatous cheilitis was treated with clofazimine 100 mg daily. Regression was noted after 30 days of treatment. Thereafter, 100 mg of clofazimine three times a week was given for 3 months. Her lip eventually returned to normal size. Follow-up for 6 years revealed no recurrence.

This article reviews several case reports and a case series of clofazimine therapy and discusses the great variability in response to therapy.

Melkersson–Rosenthal syndrome: clinical, pathologic, and therapeutic considerations. Sussman GL, Yang WH, Steinberg S. *Ann Allergy* 1992; 69: 187–94.

Clofazimine 100 mg four times weekly for 3–11 months was used to treat 10 patients with granulomatous cheilitis/Melkersson–Rosenthal syndrome. Complete remission occurred in five, partial clinical responses occurred in three, and two patients had no clinical response.

Other studies have reported efficacy with a regimen consisting of clofazimine 100 mg daily for 10 days, followed by 200–400 mg weekly for 3–6 months.

Experience with anti-TNF- α therapy for orofacial granulomatosis. Elliot T, Campbell H, Esudier M, et al. *J Oral Pathol Med* 2011; 40: 14–9.

A retrospective review of 14 patients treated with infliximab and adalimumab for orofacial granulomatosis with and without Crohn disease. Short-term remission was achieved with infliximab

in 10 of the patients. Of those patients, 8 and 4 of them remained responsive at 1 and 2 years, respectively. Two of the patients who failed infliximab responded to adalimumab.

Treatment of granulomatous cheilitis with infliximab. Barry O, Barry J, Langan S. *Arch Dermatol* 2005; 141: 1081–3.

A 24-year-old woman with recalcitrant granulomatous cheilitis was treated with infliximab. In order to reduce the risk of infusion reactions, hydrocortisone (200 mg) was administered intravenously before treatment. The patient had restoration of normal lip architecture. Infliximab infusions were continued to maintain remission.

Melkersson–Rosenthal syndrome: a form of pseudoangioedema. Kakimoto C, Sparks C, White AA. *Ann Allergy Asthma Immunol* 2007; 99: 185–9.

A 19-year-old woman with recalcitrant granulomatous cheilitis was treated with infliximab infusions. The patient improved after the second infusion and had complete resolution after the third. Because adverse effects developed, therapy was changed to adalimumab (40 mg subcutaneously [SC] weekly), with no evidence of relapse noted.

Successful treatment of granulomatous cheilitis with adalimumab. Ruiz Villaverde R, Sanchez Cano D. *Int J Dermatol* 2012; 51: 118–20.

A 46-year-old woman with recalcitrant granulomatous cheilitis was treated with adalimumab at 80 mg SC for the first week, 40 mg the second week, and then every 2 weeks. After the third dose, clinical improvement was noticed, and no relapse occurred after completing 6 months of treatment.

Orofacial granulomatosis responding to weekly azithromycin pulse therapy. Yadav S, Dogra S, De D, et al. *JAMA Dermatol* 2015; 151: 219–20.

A case series of five patients with idiopathic orofacial granulomatosis on azithromycin 500 mg PO daily for 3 consecutive days weekly demonstrated improvement after 1 month and significant improvement in 3 months.

Granulomatous cheilitis successfully treated with roxithromycin. Inui S, Itami S, Katayama I. *J Dermatol* 2008; 35: 244–5.

A 37-year-old man with granulomatous cheilitis was treated with 300 mg/day of roxithromycin. Swelling resolved in 6 weeks. Roxithromycin was tapered, and remission was achieved at 1-year follow-up.

Successful treatment of granulomatous cheilitis with roxithromycin. Ishiguro E, Hatamochi A, Hamasaki Y, et al. *J Dermatol* 2008; 35: 598–600.

A 13-year-old male with granulomatous cheilitis treated with roxithromycin 150 mg/day. No relapse was noticed after 6 months of follow-up.

Melkersson–Rosenthal syndrome in childhood: successful management with combination steroid and minocycline therapy. Stein SL, Mancini AJ. *J Am Acad Dermatol* 1999; 41: 746–8.

Two children with Melkersson–Rosenthal syndrome were treated successfully with minocycline and prednisone.

Tetracyclines would usually be contraindicated until the permanent dentition has erupted.

Minocycline in granulomatous cheilitis: experience with 6 cases. Veller Fornasa C, Catalano P, Peserico A. *Dermatology* 1992; 185: 220.

Six case reports of patients with granulomatous cheilitis treated with minocycline after failing other oral therapies (steroids, clofazimine, hydroxychloroquine, and surgery). Only one of the six patients responded to minocycline. The sole responder was later found to have chronic granulomatous disease.

Treatment and follow-up of persistent granulomatous cheilitis with intralesional steroid and metronidazole. Coskun B, Saral Y, Cicek D, et al. *J Dermatol Treat* 2004; 15: 333–5.

Cheilitis granulomatosa treated with metronidazole. Miralles J, Barnadas MA, de Moragas JM. *Dermatology* 1995; 191: 252–3.

A 30-year-old woman with monosymptomatic Melkersson–Rosenthal syndrome was successfully treated with metronidazole 750–1000 mg daily for an 8-month tapering course.

Metronidazole has also been useful in two patients with granulomatous cheilitis associated with Crohn disease. Treatment failures are also reported.

Orofacial granulomatosis successfully treated with mycophenolate mofetil. Antonyan AS, Pena-Robichaux V, McHargue CA. *J Am Acad Dermatol* 2014; 70: 137–9.

A 59-year-old woman with orofacial granulomatosis was successfully treated with mycophenolate mofetil 500 mg twice a day (BID) with significant improvement after 1 month and near-complete remission after 6 months of therapy.

Third-Line Therapies	
• Cheiloplasty ± postoperative intralesional corticosteroids	C
• Thalidomide	E
• Hydroxychloroquine	E

Plastic surgical solutions for Melkersson–Rosenthal syndrome: facial liposuction and cheiloplasty procedures. Tan O, Atik B, Calka O. *Ann Plast Surg* 2006; 56: 268–73.

This article discusses surgical procedures in four patients, including reduction cheiloplasty consisting of mucosa, submucosa, and tangential muscle resection; crescent-shaped commissuroplasty; and facial liposuction. Mean follow-up duration was 13.7 months. No postoperative steroids were given, and there was no evidence of relapse in the follow-up period.

Cheilitis granulomatosa: successful treatment with combined local triamcinolone injections and surgery. Krutchkoff D, James R. *Arch Dermatol* 1978; 114: 1203–6.

A man with granulomatous cheilitis was treated with triamcinolone injections, followed by upper and lower cheiloplasty. Four months later, repeat cheiloplasty of the upper lip revealed granulomas were more numerous and larger than those observed initially. Postoperative corticosteroid injections maintained remission. The authors recommend postoperative corticosteroid injections to prevent exaggerated recurrences.

Long-term results after surgical reduction cheiloplasty in patients with Melkersson–Rosenthal syndrome and cheilitis granulomatosa. Ellitsgaard N, Andersson AP, Worsaae N, et al. *Ann Plast Surg* 1993; 31: 413–20.

A reduction cheiloplasty was performed on 13 patients. All were satisfied with their results, despite postoperative disease activity in six patients.

Lip reduction cheiloplasty for Miescher’s granulomatous macrocheilitis (cheilitis granulomatosa) in childhood. Oliver DW, Scott MJL. *Clin Exp Dermatol* 2002; 27: 129–31.

Lip reduction cheiloplasty provided successful treatment of granulomatous cheilitis in an 11-year-old boy, suggesting surgery can be safely undertaken in young children.

Effectiveness of surgical treatment of severe macrocheilia in a patient with orofacial granulomatosis. Vassallo C, Rivetti MM, Birroni V. *Clin Exp Dermatol* 2017; 42: 887–9.

After minimal improvement with diaminodiphenyl sulfone and slight improvement with oral clofazimine (discontinued due to elevated liver enzymes) and a lip twice the normal size with associated functional difficulties, cheiloplasty was undertaken and doxycycline was continued for 3 months with no recurrence at 3-year follow-up.

Treatment of Miescher’s cheilitis granulomatosa in Melkersson–Rosenthal syndrome. Camacho F, Garcia-Bravo B, Carriosa A. *J Eur Acad Dermatol Venereol* 2001; 15: 546–9.

The authors conclude the best treatment for resistant granulomatous cheilitis is surgery with immediate injection of triamcinolone, followed by a course of oral tetracycline.

Typically, cheiloplasty reduction procedures are possible when lesions are fixed and indurated without active disease with the exception of functional difficulties.

Successful treatment of granulomatous cheilitis with thalidomide. Thomas P, Walchner M, Ghoreschi K, et al. *Arch Dermatol* 2003; 139: 136–8.

A 39-year-old woman was treated with thalidomide 100 mg daily for 6 months. Lip swelling almost completely resolved. Thalidomide was reduced to 100 mg every other day for 2 months and then stopped. One year later, the patient’s condition was stable with no signs of relapse.

Baseline and follow-up neurologic assessments need to be done with thalidomide.

Thalidomide in treatment of refractory orofacial granulomatosis. Eustace K, Clowry J, Kirby B, et al. *Br J Dermatol* 2014; 171: 423–5.

Cheilitis granulomatosa: report of six cases and review of the literature. Allen CM, Camisa C, Hamzeh S, et al. *J Am Acad Dermatol* 1990; 23: 444–50.

Hydroxychloroquine 200–400 mg daily has been reported to be efficacious in granulomatous cheilitis. Chloroquine therapy has not been successful in Melkersson–Rosenthal syndrome.

Hailey–Hailey disease

Tabrez Sheriff, Benjamin S. Daniel,
Dedee F. Murrell



Hailey–Hailey disease (HHD; benign familial pemphigus) is a rare genodermatosis first described by the Hailey brothers in 1939. It is characterized by recurrent flares of vesicles, painful blistering, erosions, and weeping plaques, particularly involving the flexural areas. Frequent secondary infections are common. Symptoms usually begin in the second to fourth decades. The disease is generally localized, although widespread and severe involvement can occur. The most commonly affected sites are intertriginous areas like the axillae, groin, neck, and inframammary folds. The disease can exhibit an isomorphic response and affect areas of trauma or sites of inflammation from other diseases.

HHD is an autosomal dominant condition caused by loss of function mutations in the *ATP2C1* gene at 3q22.1. The gene encodes the adenosine triphosphate (ATP)-powered, magnesium-dependent calcium pump protein hSPCA1 on the Golgi membrane, which sequesters Ca^{2+} intracellularly into the Golgi apparatus. Calcium transport disruption can impair epidermal differentiation, barrier repair, cell–cell adhesion, and keratinocyte motility. The clinical and histopathologic picture can be similar to Darier disease and Grover disease.

MANAGEMENT STRATEGY

The management of HHD is accomplished through a combination of lifestyle modifications and medical and/or surgical therapy.

General measures – because friction, heat, and moisture can often exacerbate lesions of HHD, patients can adopt lifestyle changes aimed at reducing sweat, friction, and bacterial colonization by wearing loose clothing, avoiding excessively hot

environments, or using absorbent pads in skin folds to reduce moisture.

First-line treatments for mild disease include topical antimicrobials, topical corticosteroids, or topical calcineurin inhibitors aimed at reducing inflammation and treating opportunistic infections. Polymicrobial infections with bacteria, yeasts, and viruses also appear to be exacerbating factors, and secondary infection with these organisms can significantly worsen the disease, causing a pungent odor. Options for topical antimicrobials include clindamycin 1% cream, gentamicin 0.1% cream, mupirocin 2% cream, or antifungals such as ketoconazole 2%. If secondary infection with herpes simplex is suspected, *appropriate oral antiviral therapy* should be instituted.

Moderate-to-high potency topical corticosteroids can be used up to twice daily, although caution must be exercised with long-term use, particularly in intertriginous folds, due to the higher risk of skin atrophy in these areas. Combining antiinfective therapy with *topical corticosteroids* seems to be particularly helpful, but corticosteroids alone may reduce the severity of lesions. Topical calcineurin inhibitors such as tacrolimus 0.1% can be applied twice daily as an alternative for long-term use both as monotherapy or adjunctive therapy to topical corticosteroids. Some success has also been recorded with topical *calcitriol* and *topical fluorouracil*. Intralesional injection of botulinum toxin type A into the axillae or inguinal folds has also demonstrated efficacy as adjunctive therapy in reducing sweating and maceration. If there is not an expected response to topical therapy, clinicians should consider patch testing, as these patients commonly develop allergic contact dermatitis.

Second-line treatments for more severe cases include oral antibiotics, systemic therapies, and surgical or destructive methods. Antibiotic selection is based on culture sensitivities but intermittent courses of oral tetracyclines have proven beneficial due to their additional antiinflammatory property.

Systemic therapies have demonstrated efficacy in case reports. Options include dapsone, ciclosporin 2.5–3.5 mg/kg/day, methotrexate 15 mg/week, acitretin 25 mg/day, glycopyrrolate 1 mg/day, oral tacrolimus, and afamelanotide 16 mg sustained release subcutaneously. Short courses of oral prednisone should be administered with caution due to the potential of rebound of the disease activity upon withdrawal and risk for long-term dependence.

Surgical modalities including *cryotherapy*, *excision with grafting*, *dermabrasion*, and CO_2 and other lasers may also be beneficial in some patients, specifically for localized disease. *Electron beam therapy* has been reported for recalcitrant disease. There are few reports of treatment with biologic agents with limited benefit.

The chronic, relapsing nature of HHD has led to emerging treatments such as *oral magnesium* supplementation and *oral low-dose naltrexone*. Both are demonstrating increasing efficacy in refractory cases of Hailey–Hailey disease.

Low-dose naltrexone 1.5 mg–4.5 mg daily has demonstrated disease clearance and tolerability in multiple small case series within a 4-month period. The mechanism of action in Hailey–Hailey disease has not been validated; however, one hypothesis suggests some influence on intracellular calcium homeostasis and an antiinflammatory response. Similarly, magnesium supplementation of up to 300 mg daily has evidence of rapid disease clearance within a 4-week period.

Specific Investigations

- Biopsy
- Microbiologic cultures for bacteria, yeast, and herpesvirus
- Consider patch testing to topical preparations

First-Line Therapies

- Topical antimicrobials and systemic antibiotics **C**
- Topical corticosteroids **C**

Hailey–Hailey disease: the clinical features, response to treatment and prognosis. Burge SM. Br J Dermatol 1992; 126: 275–82.

In this series of 58 patients, 86% of patients found combinations of topical corticosteroids and antimicrobial agents helpful at the first sign of a flare.

Familial benign chronic pemphigus and doxycycline: a review of 6 cases. Le Saché-de Peufeilhoux L, Raynaud E, Bouchardeau A, et al. J Eur Acad Dermatol Venereol 2014; 28: 370–3.

This is a review of six patients who received oral doxycycline 50–100 mg/day. Two patients had complete remission, and two patients had significant improvement with mild flares during 4 years of follow-up.

The first article remains a key review of clinical and therapeutic aspects of this disease. We recommend that patients who are failing topical therapies are started on doxycycline as first-line systemic therapy.

Second-Line Therapies

- Topical calcineurin inhibitors **E**
- Calcitriol **E**
- Systemic corticosteroids **E**
- Naltrexone **C**
- Dapsone **E**
- Magnesium **E**
- Ciclosporin **E**
- Botulinum toxin **E**
- Carbon dioxide laser **E**

Topical tacrolimus ointment is an effective therapy for Hailey–Hailey disease. Sand C, Thomsen HK. Arch Dermatol 2003; 139: 1401–2.

A 67-year-old man was cleared with once-daily tacrolimus 0.1% within 1 month and was maintained with as-needed use.

Familial benign chronic pemphigus (Hailey–Hailey disease): use of topical immunomodulators as a modern treatment option. Tchernev G, Cardoso JC. Rev Med Chil 2011; 139: 633–7.

This is a report of a 51-year-old male responding well to pimecrolimus 1% cream twice daily.

Treatment of Hailey–Hailey disease with topical calcitriol. Bianchi L, Chimenti M, Giunta A. J Am Acad Dermatol 2004; 51: 475–6.

This report showed complete clearance of lesions for 3 months after completing 1 month of twice-daily calcitriol 3 mcg/g ointment.

Generalized Hailey–Hailey disease. Marsch WC, Stüttgen G. Br J Dermatol 1978; 99: 553.

The use of systemic corticosteroids was successful in controlling extensive disease, but cessation of therapy resulted in significant rebound.

Benign familial chronic pemphigus treated with dapsone. Sire DJ, Johnson BL. Arch Dermatol 1971; 103: 262.

Three 21- to 64-year-old patients were cleared with 100–200 mg of dapsone daily and one was maintained on 50 mg every other day.

Benign familial pemphigus (Hailey–Hailey disease) responsive to low dose ciclosporin. Nanda A, Khawaja F, Harbi R, et al. Indian J Dermatol Venereol Leprol 2010; 76: 422–4.

The reported patient was treated with 2.5 mg/kg/day and achieved a lasting remission with topical tacrolimus for maintenance.

Remission of refractory benign familial chronic pemphigus (Hailey–Hailey disease) with the addition of systemic ciclosporin. Varada S, Ramirez-FORT MK, Argobi Y, et al. J Cutan Med Surg 2015; 19: 163–6.

This patient had improvement on 2.8 mg/kg/day but nearly cleared on 3.8 mg/kg/day and had significant improvement in pain and pruritus.

Botulinum toxin type A as an adjuvant treatment modality for extensive Hailey–Hailey disease. Koeysers WJ, Van Der Geer S, Krekels G. J Dermatolog Treat 2008; 19: 251–4.

Diminution of the hyperhidrosis that exacerbates Hailey–Hailey disease may also be accomplished by utilizing oral glycopyrrolate.

Carbon dioxide laser treatment for Hailey–Hailey disease: a retrospective chart review with patient-reported outcomes. Hochwalt PC, Christensen KN, Cantwell SR, et al. Int J Dermatol 2015; 54: 1309–14.

Thirteen patients with refractory disease were treated with CO₂ laser, and all patients had no recurrence in the treated areas. Seventy percent had new disease outside of treated sites that responded to additional treatments.

Tacrolimus, pimecrolimus, and calcitriol are at least safe and good options for steroid-sparing maintenance therapy. Dapsone is generally safe and may work in certain patients. Ciclosporin can be used safely if doses do not exceed 5 mg/kg and patients are properly monitored. There are now a number of reports suggesting that botulinum toxin and CO₂ laser may be less invasive and efficacious options for refractory local disease.

Third-Line Therapies

- Surgical excision (with healing by secondary intention or by grafting) **E**
- Dermabrasion **E**
- Laser therapy (excluding CO₂ laser – see earlier) **E**
- Superficial irradiation (grenz rays or electron beam) **E**
- Methotrexate **E**
- Oral retinoids **E**
- Topical 5-fluorouracil **E**
- Biologics **E**
- Photodynamic therapy **E**
- Narrowband ultraviolet B therapy **E**
- Low-dose naltrexone **E**
- Oral magnesium chloride **E**

Surgical treatment of familial benign chronic pemphigus. Crotty CP, Scheen SR, Masson JK, et al. Arch Dermatol 1981; 117: 540–2.

This is a report of five patients who had excision followed by split-thickness skin grafting. Three patients had no recurrence in treated areas, and one patient had mild recurrence after 8 years.

Refractory Hailey-Hailey disease successfully treated with sandpaper dermabrasion. LeBlanc KG Jr, Wharton JB, Sheehan DJ. *Skinmed* 2011; 9: 263-4.

A 53-year-old female had a lasting improvement on the neck and popliteal fossae after fine sandpaper dermabrasion down to the superficial dermis; however, she did have recurrence in the axillae.

Successful treatment of refractory Hailey-Hailey disease with a 595-nm pulsed dye laser: a series of 7 cases. Hunt KM, Jensen JD, Walsh SB, et al. *J Am Acad Dermatol* 2015; 72: 735-7.

This report showed varying amounts of improvement of clinical lesions in six of seven patients treated with 595-nm pulsed dye laser.

Effective treatment of Hailey-Hailey disease with a long-pulsed (5 ms) alexandrite laser. Awadalla F, Rosenbach A. *J Cosmet Laser Ther* 2011; 13: 191-2.

A 35-year-old male had complete clearance after 13 treatments with long-pulsed alexandrite laser for 1 year with occasional short courses of topical hydrocortisone. The fluences ranged from 12 to 20 J/cm² with 10- to 15-mm spot sizes.

Persistent improvement of previously recalcitrant Hailey-Hailey disease with electron beam therapy. Narbutt J, Chrusciel A, Rychter A, et al. *Acta Derm Venereol* 2010; 90: 179-82.

Three patients had improvement of lesions after 20 Gy in 10 fractions to 90% isodose to each axilla without recurrence in 38 months of follow-up.

Methotrexate for refractory Hailey-Hailey disease. Vilarinho C, Ventura F, Brito C. *J Eur Acad Dermatol Venereol* 2010; 24: 106.

A 42-year-old woman showed near clearance after 3 months of oral methotrexate 15 mg weekly and had no recurrence in 2 years of follow-up.

Vesiculobullous Hailey-Hailey disease: successful treatment with oral retinoids. Hunt MJ, Salisbury EL, Painter DM, et al. *Australas J Dermatol* 1996; 37: 196-8.

A 56-year-old male had significant improvement after 6 weeks of 25 mg of daily etretinate. The patient was recurrence free 2 months after completing a 6-month course.

Successful treatment of Hailey-Hailey disease with acitretin. Berger EM, Galadari HI, Gottlieb AB. *J Drugs Dermatol* 2007; 6: 734-6.

A 64-year-old male had significant improvement after 6 months of 25 mg of daily acitretin.

Successful treatment of Hailey-Hailey disease with topical 5-fluorouracil. Dammak A, Camus M, Anyfantakis V, et al. *Br J Dermatol* 2009; 161: 967-8.

A 43-year-old male was treated with 5-fluorouracil 5% cream three times weekly for 3 months, followed by weekly applications

for 3 months, and showed near clearance for 6 months after completion of therapy.

Case reports of etanercept in inflammatory dermatoses. Norman R, Greenberg RG, Jackson JM. *J Am Acad Dermatol* 2006; 54 (Suppl 2): S139-42.

A 47-year-old woman was treated with subcutaneous etanercept 25 mg weekly for 1 month, then increased to 50 mg for 6 months, and then to 75 mg weekly to improve response. She showed dramatic improvement in 10 months and continued to improve.

Experience with photodynamic therapy in Hailey-Hailey disease. Fernandez Guarino M, Ryan AM, Perez-Garcia B, et al. *J Dermatol Treat* 2008; 19: 288.

Three patients were treated with methyl aminolevulinic acid for 3 hours and then exposed to 7.5 min of 630 nm red light. The patients had a lot of pain and did not have significant improvement.

Successful therapeutic use of targeted narrow-band ultraviolet B therapy for refractory Hailey-Hailey disease. Hamada T, Umemura H, Aoyama Y, et al. *Acta Derm Venereol* 2013; 93: 110-1.

This report showed efficacy of narrowband ultraviolet B (NB-UVB) therapy conflicting with previous reports of exacerbation with UV light.

Surgery can be definitive and should be considered for refractory localized disease. Many authors report some recurrences, either around the edges of the treated areas or on further friction or trauma. Treatment is invasive, and the trauma of dressings may exacerbate the disease, so proper patient selection is important. The rest of the modalities in this section have few reports demonstrating their efficacy. They should be reserved for very recalcitrant disease in appropriate patients.

Treatment of Hailey-Hailey disease with low-dose naltrexone. Albers LN, Arbiser JL, Feldman RJ. *JAMA Dermatol* 2017; 153(10): 1018-20. doi:10.1001/jamadermatol.2017.2446.

Three patients with severe Hailey-Hailey disease recalcitrant to multiple therapies, treatment with low-dose naltrexone at 3 mg and, in two of the patients, titrated to 4.5 mg nightly, was attempted and resulted in clinical resolution within 2 months. Lesions flared when stopping low-dose naltrexone and cleared within a few days on rechallenge.

Oral magnesium chloride: a novel approach in the management of Hailey-Hailey disease. Barde NG, Mishra DB, Ingole SO. *Indian J Dermatol Venereol Leprol* 2017; 83: 259.

A 34-year-old woman was treated with 70 mL of oral magnesium chloride containing 300 mg of elemental magnesium. A significant improvement in the skin lesions was noted after 15 days of treatment and an almost complete remission of signs and symptoms was obtained after 4 weeks. No side effects were reported by the patient, except for the unpleasant taste of the solution. The patient's quality of life significantly improved. The pre- and post-treatment serum levels of electrolytes, in particular, calcium, magnesium, and zinc, were within normal limits. The patient is still on treatment for 4 months, with sustained remission.

Hand and foot eczema (endogenous, dyshidrotic eczema, pompholyx)

Surina Frey, Margaret L. Snyder,
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The hands and feet are essential tools in daily activities. The bipedal gait and manual activity of *homo sapiens* result in high exposure of these areas to numerous allergens and irritants. The palmar and plantar skin have a similar skin structure with a thick corneal layer, thus creating a special situation regarding penetration characteristics of topical therapies.

Cases of hand and foot eczema can be classified regarding their etiology, clinical presentation, and chronicity. Hand and foot eczema can be triggered by endogenous factors, such as atopy or contact to exogenous factors, such as irritants or allergens.

A clinical classification of the disease is most commonly based on morphology, ranging from pompholyx and dyshidrotic eczema to hyperkeratotic and fissured skin lesions. The clinical presentation is quite variable, and transitional as well as overlapping forms are often present. Pruritus and pain are frequent symptoms, especially if fissures are present. Secondary infection is common.

The acute, recurrent, and persistent course of the hand and foot eczema will largely determine the choice of treatment modalities.

MANAGEMENT STRATEGY

Diagnostic procedures should be performed either to exclude the common differential diagnoses of hand and foot dermatitis such as dermatomycoses and psoriasis, or to reveal potential trigger factors of irritant and allergic contact eczema. The presence of lesions on both hands and feet is associated with chronic and more severe hand eczema, as well as a hyperkeratotic subtype of hand eczema.

Before starting any treatment, avoidance strategies and measures for known irritants and allergens should be employed. This

may include a nickel-free diet and complete cessation of smoking for nickel-sensitized patients. Moreover, patient education programs and adherence improving techniques are helpful components of an effective management system.

Possible treatment options include topical agents, ultraviolet (UV) phototherapy, and systemic therapy. Dry and fissured skin lesions are best treated with highly lipophilic ointments, possibly combined with occlusive or semi-occlusive dressings to increase penetration. Keratolytic agents such as urea or salicylic acid are helpful in hyperkeratotic eczema, whereas moist and oozing skin may benefit from hydrophilic creams or gels. Desiccative agents have shown value in dyshidrotic forms of eczema. Antiseptics should be considered to avoid superinfection, especially in erosive or fissured lesions.

Topical corticosteroids of medium to high potency are the mainstay of all topical therapies of hand eczema. The topical *calcineurin inhibitor* *tacrolimus* may also be effective, especially for long-term treatment, but should not be combined with UV therapy. *Pimecrolimus* has shown less efficacy.

Calcipotriol ointment may show beneficial effects in chronic hand eczema, especially in the hyperkeratotic subtype, and may reflect a topical steroid-sparing alternative.

Adjuvant use of oral *antihistamines* has demonstrated only a slight effect on pruritus. Oral *antibiotics*, such as first generation cephalosporins, may be added in case of severe bacterial infection.

Psoralen-UVA (PUVA) therapy is the most effective UV-light treatment option for chronic, recurrent hand and foot eczema. *UVA phototherapy* or *narrowband UVB (NB-UVB) phototherapy* may also be useful.

Systemic treatment is frequently required in severe, refractory, or persistent hand and foot eczema. Systemic corticosteroids are recommended for short-term use only. *Prednisone* 0.5–1.0 mg/kg/day tapered over 2 weeks is a typical regimen. Systemic retinoids such as *alitretinoin* or *acitretin* are helpful if pregnancy prevention programs are followed strictly. Classic immunosuppressants such as *methotrexate*, *azathioprine*, and *mycophenolate mofetil* have been tried successfully. *Ciclosporin* may be especially useful in atopic hand eczema, and is approved in many countries for severe atopic dermatitis. Interestingly, a case has also been reported of improvement with oral apremilast.

New emerging therapies include *dupilumab*, a monoclonal antibody blocking the IL-4/IL-13 pathway. Topical Janus kinase (JAK) inhibitors such as *delgocitinib* may improve chronic hand eczema despite its subtype, and should be useful in therapy-refractory chronic hand eczema. Oral JAK inhibitors will undoubtedly be useful for hand eczema in the future.

Intradermal localized *botulinum toxin A* will reduce sweating and may therefore be helpful as adjuvant therapies in dyshidrotic forms.

Specific Investigations

- Patch testing
- Skin prick testing
- Bacterial and mycological diagnostics

Factors associated with combined hand and foot eczema.

Agner T, Aalto-Korte K, Andersen KE, et al. *J Eur Acad Dermatol Venereol* 2017; 31: 828–32.

About 30% of all hand eczema patients presented with concomitant foot eczema. Hyperkeratotic lesions, a long duration, and high severity of the hand eczema were associated with combined foot involvement.

Patch test results of hand eczema patients: relation to clinical types. Boonstra MB, Christoffers WA, Coenraads PJ, et al. *J Eur Acad Dermatol Venereol* 2015; 29: 940–7.

The retrospective study including 1571 patients revealed nickel sulfate, cobalt, fragrances, and preservatives as the most common causative allergens in hand eczema. Contact allergy was more prevalent in patients with recurrent vesicular hand eczema.

First-Line Therapies

• Topical corticosteroids	A
• Topical JAK inhibitors	A
• Topical calcineurin inhibitors	B
• Emollients	B
• Keratolytics (if hyperkeratotic)	D
• Oral antibiotics (if infected)	D

Hand eczema: treatment. Elsner P, Agner T. *J Eur Acad Dermatol Venereol* 2020; 34 (Suppl 1): 13–21.

Broad review on the treatment of hand eczema and new emerging therapeutic targets.

Efficacy and safety of topical delgocitinib in patients with chronic hand eczema: data from a randomized, double-blind, vehicle-controlled phase IIa study. Worm M, Bauer A, Elsner P, et al. *Br J Dermatol* 2020; 182(5): 1103–10.

A total of 91 patients with chronic hand eczema were randomized to receive delgocitinib ointment or vehicle for 8 weeks. Of the patients receiving delgocitinib, 46% achieved a Physician's Global Assessment of disease severity (PGA) of clear or almost clear with 2-point reduction from baseline compared with 15% receiving placebo ($p=0.0009$). Additionally, mean Hand Eczema Severity Index (HECSI) score was lower with delgocitinib than with placebo (13.0 vs. 25.8; $p=0.0003$).

Topical tacrolimus (FK 506) and mometasone furoate in treatment of dyshidrotic palmar eczema: a randomized, observer-blinded trial. Schnopp C, Remling R, Mohrenschlager M, et al. *J Am Acad Dermatol* 2002; 46: 73–7.

In 16 patients with dyshidrotic hand eczema, topical tacrolimus 0.1% ointment applied twice daily showed an efficacy comparable to 0.1% mometasone furoate ointment after 4 weeks.

Efficacy and safety of pimecrolimus cream 1% in mild-to-moderate chronic hand dermatitis: a randomized, double-blind trial. Hordinsky M, Fleischer A, Rivers JK, et al. *Dermatology* 2010; 221: 71–7.

Less than 30% of 652 patients showed improved skin and reduced itch upon topical therapy with pimecrolimus 1% cream applied twice daily with overnight occlusion over 6 weeks.

Second-Line Therapies

• Alitretinoin	A
• Acitretin	B
• Topical PUVA (cream or bath)	B
• UVA and NB-UVB	B
• Intradermal botulinum A toxin	C

Efficacy and safety of oral alitretinoin (9-*cis* retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind,

placebo-controlled, multicentre trial. Ruzicka T, Lynde CW, Jemec GB, et al. *Br J Dermatol* 2008; 158: 808–17.

Alitretinoin 30 mg administered daily for 12–24 weeks improved skin lesions and subjective symptoms in 48% of 409 patients with chronic hand eczema.

Alitretinoin and acitretin in severe chronic hand eczema: results from a retrospective daily practice study. Politiek K, Christoffers WA, Coenraads PJ, et al. *Dermatol Ther* 2016; 29: 364–71.

Acitretin is effective as well, but more difficult to maintain, and patients discontinue more frequently due to side effects.

An observer-blinded randomized controlled pilot trial comparing localized immersion psoralen-ultraviolet A with localized narrowband ultraviolet B for the treatment of palmar hand eczema. Brass D, Fouweather T, Stocken DD, et al. *Br J Dermatol* 2018; 179: 63–71.

Both immersion PUVA and NB-UVB therapy applied twice weekly over 12 weeks resulted in improvement of skin lesions in 23 patients with hand eczema, but more patients in the PUVA group reached the primary outcome of a clear or almost clear PGA.

Comparison of localized high-dose UVA1 irradiation versus topical cream psoralen-UVA for treatment of chronic vesicular dyshidrotic eczema. Petering H, Breuer C, Herbst R, et al. *J Am Acad Dermatol* 2004; 50: 68–72.

Twenty-four of 27 patients treated with UVA1 irradiation and cream PUVA on one hand, respectively, showed a comparable improvement in chronic dyshidrotic eczema after 3 weeks of treatment.

Treatment of dyshidrotic hand dermatitis with intradermal botulinum toxin. Swartling C, Naver H, Lindberg M, et al. *J Am Acad Dermatol* 2002; 47: 667–71.

Seven of 10 patients treated with intradermal botulinum toxin A showed improved skin and reduced itch.

Third-Line Therapies

• Ciclosporin	A
• Methotrexate	D
• Azathioprine	C
• Mycophenolate mofetil	E
• Topical calcipotriol	C
• Dupilumab	B
• Apremilast	E

Drug survival of cyclosporine in the treatment of hand eczema: a multicentre, daily use study. Christoffers WA, Politiek K, Coenraads PJ, et al. *J Eur Acad Dermatol Venereol* 2016; 30: 63–6.

In this study, 62.9% of 102 patients presented good improvement after 3 months of cyclosporin (max. dosage 5 mg/kg/day) in different up- and down-dosing regimens. Patients with vesicular hand eczema responded best.

Low-dose oral methotrexate treatment for recalcitrant palmo-plantar pompholyx. Egan CA, Rallis TM, Meadows KP, et al. *J Am Acad Dermatol* 1999; 40: 612–4.

Five patients with refractory pompholyx received methotrexate (12.5–22.5 mg) weekly, resulting in a reduction or discontinuation of concomitant systemic prednisone use.

Azathioprine treatment and drug survival in patients with chronic hand eczema – results from daily practice. Oosterhaven JAF, Politiek K, Schuttelaar M-LA. *Contact Dermatitis* 2017; 76: 304–7.

A retrospective analysis on 30 patients with chronic hand eczema showed that azathioprine therapy can be effective, but side effects led to discontinuation of 15 out of 30 patients during the first 3 months.

Dyshidrotic eczema treated with mycophenolate mofetil. Pickenacker A, Luger TA, Schwarz T. *Arch Dermatol* 1998; 134: 378–9.

Single case report of a patient with refractory dyshidrotic eczema and complete resolution after initiation of mycophenolate mofetil at a dose of 1.5 g twice daily followed by 1 g/day for 1 year.

Calcipotriol ointment shows comparable efficacy to topical steroids in chronic hand eczema. Juntongjin P, Pongprasert R. *Dermatol Ther* 2019; 32: e12956.

Topical calcipotriol ointment (0.005%) showed comparable effects on chronic hand eczema as desoximetasone ointment with up to 75% reduction of skin lesions.

Chronic hand eczema and hepatogenic pruritus with good response to apremilast. Navarro-Trivino FJ, Cuenca-Barrales C, Vega-Castillo JJ, et al. *Dermatol Ther* 2019 Apr 1; 32(3): e12879. doi: 10.1111/dth.12879 [Epub ahead of print].

A 65-year-old man with chronic hand eczema for 5 years and concomitant non-alcoholic hepatic steatosis who could not tolerate alitretinoin due to elevation in transaminases had complete clearance of skin lesions after 1 month of treatment with apremilast 30 mg Q12HR.

A retrospective review of dupilumab for hand dermatitis. Lee N, Chipalkatti N, Zancanaro P, et al. *Dermatology* 2019; 235: 187–8.

A reevaluation of 66 AD patients with and without hand involvement on dupilumab; both groups showed improvement of symptoms.

Effect of dupilumab on hand eczema in patients with atopic dermatitis: an observational study. Oosterhaven JAF, Voorberg AN, Romeijn GLE, et al. *J Dermatol* 2019; 46: 680–5.

Forty-seven AD patients with concomitant chronic hand eczema and dupilumab therapy showed improvement of skin lesions over a period of 16 weeks with 60% reaching a 75% improvement of the Hand Eczema Severity Score. Concomitant use of topical corticosteroids and calcineurin inhibitors was allowed throughout the study.

Dupilumab for the treatment of dyshidrotic eczema in 15 consecutive patients. Waldman RA, DeWane ME, Sloan B, et al. *J Am Acad Dermatol* 2020; 82: 1251–2.

Fifteen non-AD patients with refractory dyshidrotic hand eczema received dupilumab. All reached partial and 40% reached complete response to treatment.

Dyshidrotic eczema treated with dupilumab: report of 2 cases. Weston G, Strober B. *J Am Acad Dermatol* 2018; 79(3): AB114.

Two adults with dyshidrotic eczema refractory to various combinations of topical and systemic treatments with complete clearance of lesions after 8–16 weeks of dupilumab (600 mg loading dose followed by 300 mg every other week).

Hemangiomas

Yamila Goenaga-Vázquez, Adelaide A. Hebert



Hemangiomas are a neoplastic proliferation of endothelial cells that are generally benign but have been associated with local tissue damage, functional impact, and ulceration. The true incidence is unknown but is reported as approximately 5% in Caucasian infants. Hemangiomas occur more frequently in Caucasian female infants with a predilection for premature infants, especially of low birth weight or multiple gestations. Most hemangiomas arise spontaneously during infancy, but an autosomal-dominant pattern of inheritance has rarely been reported.

MANAGEMENT STRATEGY

Cutaneous hemangiomas appear in the first few weeks of life and reach 80% of size by 3 months, with spontaneous involution in most cases by age 10. Early evaluation and treatment are critical to limit the patient's functional impairment and disfigurement. About half of children with hemangiomas have normal skin after involution, but the rest may have residual changes, including telangiectasias, atrophy, fibrofatty residuum, and scarring.

Differentiating benign common hemangiomas from other vascular anomalies is essential, as the pathophysiology, treatment modalities, and prognoses are significantly different. Vascular malformations and tumors, such as the kaposiform hemangioendothelioma (KE) and tufted angioma (TA), differ from hemangiomas in both clinical and histologic appearance as well as growth rate and involutional tendencies. In particular, KE and TA are associated with Kasabach–Merritt syndrome and the accompanying coagulopathy, whereas common hemangiomas are not. The majority of common hemangiomas occur as solitary lesions but

can be a sign of multisystem involvement such as diffuse neonatal hemangiomatosis, LUMBAR syndrome (lower body congenital infantile hemangiomas (IHs) and other skin defects, urogenital anomalies and ulceration, myelopathy, bony deformities, anorectal malformations and arterial anomalies, and rectal anomalies), and PHACES syndrome (posterior fossa malformation, large segmental hemangiomas, arterial lesions, cardiac anomalies, eye abnormalities, and sternal cleft/supraumbilical raphe).

Although the natural course of hemangiomas is self-limited, pharmaceutical intervention is indicated for most hemangiomas due to the potential for rapid growth and potential ulceration and scarring, disfigurement or functional impairment (e.g., compress or obstruct vital structures such as the larynx, eyes, ears, and nose). IHs associated with structural anomalies (e.g., in PHACES or LUMBAR syndromes) also warrant therapy. After identifying an IH, the clinician should facilitate evaluation by a hemangioma specialist within weeks 3–8 of the newborn's life as the most rapid growth of superficial hemangiomas typically occurs between 5.5 and 7.5 weeks of age (termed the proliferative phase).

Topical and systemic β -blockers have become the preferred first-line therapy in very early or small hemangiomas. Oral propranolol hydrochloride solution was approved by the US Food and Drug Administration (FDA) in 2014 for use in infants with an escalating starting dose of 1.2 mg/kg/day to a target dose of 3.4 mg/kg/day divided into two daily doses. Treatment typically is continued for at least 6 months and often is maintained until 12 months of age or longer. Adverse events are rare but may include the masking of hypoglycemia, hypotension, and bradycardia. Administering the medication after feeding and monitoring the heart rate and blood pressure after dose increases can help reduce these seldom-encountered side effects. Bronchial hyperreactivity is another rare but possible side effect, especially in susceptible individuals. Other β -blockers, such as atenolol and nadolol, have been shown to be effective for the treatment of IHs in small clinical trials, and are probably associated with fewer side effects in comparison to propranolol. Timolol, available as a solution or a gel, has been shown in small randomized clinical trials to be safe and effective for superficial, small, thin non-ulcerated IHs with twice-daily topical application.

Surgical excision, either alone or in combination with corticosteroids or β -blockers, may also be employed in certain cases such as large IHs located periorbitally or on the nasal tip, or for the treatment of residual skin changes after involution. Cyclophosphamide, vincristine, bleomycin, and interferon are considered obsolete therapies since the advent of propranolol.

Specific Investigations

- Ultrasound with Doppler
- Magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA)
- Biopsy with immunohistochemistry

The diagnosis of a hemangioma is made clinically but the following clinical scenarios warrant imaging: IHs ≥ 5 cm on the face may need to be imaged with contrast-enhanced MRI and with MR angiography of the head and neck to rule out PHACES syndrome. IHs ≥ 5 cm on the midline back and perineal region or with segmental morphology in children ≤ 3 months of age should be imaged with ultrasound of the spine and with color Doppler ultrasound of the abdomen and pelvis to rule out LUMBAR syndrome. Atypical lesions appearing after 6 months of age and ≥ 5 cutaneous IHs also warrant further imaging. IHs that are

segmental, especially if multiple, may raise suspicion for the presence of visceral hemangiomatosis. There is no defined approach for follow-up imaging intervals for superficial IHs; however, liver and visceral involvement might be followed with MR or ultrasound every 2–3 months to assess response to therapy.

The changing face of complicated infantile hemangioma treatment. Menapace D, Mitkov M, Towbin R, et al. *Pediatric Radiol* 2016; 46: 1494–1506.

This article reviews the 2014-updated International Society for the Study of Vascular Anomalies classification for vascular anomalies, focusing on the management of IHs with regard to indications for imaging. Imaging should only be performed if the diagnosis of IH is uncertain or associated anatomic abnormalities are suspected.

GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. North PE, Waner M, Mizeracki A, et al. *Hum Pathol* 2000; 31: 11–22.

Immunohistochemical staining can serve as a useful adjunct to distinguish between IHs and other common vascular malformations or vascular neoplasms that present during infancy. GLUT1 (glucose transporter 1) stain is shown to be highly specific and uniformly positive in the endothelial vasculature of IHs. Staining for placenta-associated vascular antigens Fc gamma RII, Lewis Y antigen (LeY), and merosin in IHs has shown a high specificity and holds promise for the development of an IH-specific immunohistochemical panel.

First-Line Therapies

• Systemic β -blockers	A
• Topical β -blockers	B
• Topical corticosteroids	D
• Intralesional corticosteroids	B
• Systemic corticosteroids	B

A randomized, controlled trial of oral propranolol in infantile hemangioma. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, et al. *N Engl J Med* 2015; 372: 735–46.

A randomized, double-blind, multicenter trial of 460 infants to assess the efficacy of oral propranolol in treating IHs. In the first stage, the infants were randomized to receive either a placebo or one of four propranolol regimens of either 1 mg/kg/day or 3 mg/kg/day of propranolol for a duration of 3 or 6 months. After an interim analysis, new infants were treated with either a placebo or 3 mg/kg/day of propranolol for 6 months. Sixty percent of all infants receiving this regimen had complete or nearly complete resolution of the target hemangioma.

Clinical practice guideline for the management of infantile hemangiomas. Krowchuk DP, Frieden IJ, Mancini AJ, et al. *Pediatrics* 2019; 143: 1.

This is a comparative effectiveness review of potential benefits and harms of diagnostic modalities and pharmacologic and surgical treatments for IHs.

Interventions for infantile haemangiomas of the skin. Novoa M, Baselga E, Beltran S, et al. *Cochrane Database Syst Rev* 2018; 4: CD006545.

This review updates the evidence on the effects of different interventions for the management of IHs. Twelve interventions, 28 studies, and 30 comparisons were included. Oral propranolol

and topical timolol maleate are more beneficial than placebo in terms of clearance or other measures of resolution, or both, without an increase in harm. The authors found no evidence of a difference between oral propranolol and topical timolol maleate with regard to reducing hemangioma size but are uncertain if there is a difference in safety.

Clinical management of IHs depends on the following risk factors, among others: the grade of complication, presence of comorbidities, clinician experience, and patient factors.

Pharmacologic interventions for infantile hemangioma: a meta-analysis. Chinnadurai S, Fonnesbeck C, Snyder KM, et al. *Pediatrics* 2016; 137: e2015389.

In this meta-analysis, 18 studies were included assessing relative expected rates of IH clearance associated with β -blockers and steroids. Oral propranolol had the largest mean estimate of expected clearance relative to oral corticosteroids and control. Corticosteroids demonstrated moderate effectiveness at reducing size/volume.

Efficacy of intralesional steroid injection in head and neck hemangioma: a systematic review. Prasetyono TO, Djoenaedi I. *Ann Plast Surg*. 2011; 66: 98–106.

This is a systematic review done during the period 1996–2008 evaluating the efficacy of intralesional steroid injections in head and neck hemangiomas. The study included 22 prospective and retrospective case reviews. From 749 patients, a total of 71% of patients demonstrated excellent clinical response, 23.4% good, 2.96% poor, 2% no response, and 0.6% were lost to follow-up. The authors concluded that this treatment modality is a good and safe alternative.

Topical timolol maleate treatment of infantile hemangiomas. Puttgen K, Lucky A, Adams D, et al. *Pediatrics* 2016; 138.

This multicenter retrospective cohort study of 731 patients evaluated the efficacy of topical timolol. At 6–9 months of treatment, 92.3% of patients had improved color and 76.6% had improvement in size, extent, and volume. The best response to therapy occurred in superficial hemangiomas <1 mm thick.

RCT of timolol maleate gel for superficial infantile hemangiomas in 5- to 24-week-olds. Chan H, McKay C, Adams S, et al. *Pediatrics* 2013; 131: e1739–47.

In this randomized control trial studying the efficacy of timolol compared with placebo, 41 infants with superficial IHs without ulceration not proximal to mucosal surfaces were recruited and randomly assigned to placebo and treatment (timolol maleate 0.5% gel) groups. A significantly higher proportion of treated IHs had reduced in size by >5% at weeks 20 and 24 ($p < 0.02$) than those in the placebo arm. Topical timolol maleate 0.5% gel with a maximum dose of 0.5 mg/day provided a safe and effective option for small superficial IHs that had not ulcerated and were not on or proximate to mucosal surfaces.

Comparison of efficacy and safety between propranolol and steroid for infantile hemangioma: a randomized clinical trial. Kim KH, Choi TH, Choi Y, et al. *JAMA Dermatol* 2017; 153:529–36.

In this small, non-inferiority RCT 34 children aged 0.3–8.2 months with hemangiomas located predominantly on the face were randomly assigned to treatment with propranolol 2 mg/kg/day in three divided doses or prednisolone 2 mg/kg/day in a single dose for 16 weeks. A response to treatment was achieved by 96% and 92% of patients in the propranolol and systemic

corticosteroid groups, respectively. Adverse effects were generally mild and occurred with equal frequency in both groups.

Atenolol treatment for infantile haemangioma. Tasani M, Glover M, Martinez AE, et al. *Br J Dermatol* 2017; 176: 1400–2.

This series of 19 patients with IHs were treated with atenolol following cessation of propranolol due to adverse effects. Eighty-nine percent of patients reported good response of the IH with atenolol treatment. Sleep disturbance disappeared within 48 h after starting treatment with atenolol in 93% of patients and 100% of patients who were converted to atenolol due to bronchial hyperreactivity reported reduction of at least 50% in the frequency of episodes requiring bronchodilator treatment.

Atenolol is a selective β -blocker that spares the β_2 -adrenergic receptors and does not cross the blood–brain barrier, which may account for fewer respiratory and central nervous system (CNS) side effects (e.g., sleep disturbances), respectively.

Topical timolol as adjunct therapy to shorten oral propranolol therapy for infantile hemangiomas. Mannschreck DB, Huang AH, Lie E, et al. *Pediatric Dermatology* 2019; 36: 283–9.

A retrospective chart review of 559 patients with IH seen at the pediatric dermatology clinic of a tertiary care center between December 2008 and January 2018. Children were grouped by treatment received: propranolol only, timolol only, propranolol to timolol, timolol to propranolol to timolol, and timolol to propranolol. Among all patients treated with propranolol, those who received propranolol followed by timolol received the shortest duration of oral propranolol and were the youngest at the time of propranolol completion.

Ultrapotent topical corticosteroid treatment of hemangiomas of infancy. Garzon MC, Lucky AW, Hawrot A, et al. *J Am Acad Dermatol* 2005; 52: 281–6.

A retrospective review of 34 patients with hemangiomas treated with class I topical steroids showed good response in 35%, partial response in 38%, and no response in 27%. Treatment protocols varied between patients.

Second-Line Therapies

• Surgical excision	D
• Pulsed-dye laser	B
• Becaplermin gel for ulcerated lesions	D

Surgical treatment of facial infantile hemangiomas: an analysis based on tumor characteristics and outcomes. Goldenberg DC, Hiraki PY, Marques TM, et al. *Plast Reconstr Surg* 2016; 137: 1221–31.

A retrospective case review of 74 patients treated surgically was analyzed to evaluate outcomes based on tumor-related clinical features. Surgery was performed during the proliferative phase in 58.1% of patients and growth-related deformity was the main indication. The best candidates for emergency surgery were non-responders to pharmacologic therapy with segmental periorbital hemangiomas, whereas those undergoing elective surgery were patients with localized lip, nasal, or eyelid hemangiomas in the proliferative phase. Although most patients with IHs should be managed with pharmacotherapy, surgery remains an option. The exact algorithm of when to operate remains controversial.

Response of ulcerated perineal hemangiomas of infancy to becaplermin gel, a recombinant human platelet-derived growth factor. Metz BJ, Rubenstein MC, Levy ML, et al. *Arch Dermatol* 2004; 140: 867–70.

Eight infants were treated with becaplermin gel 0.01% for ulcerated perineal hemangiomas of infancy. Rapid ulcer healing occurred in all patients within 3–21 days (average, 10.25 days). The rapid healing achieved with 0.01% becaplermin gel allows a reduction in the risk of secondary infection, pain, and the need for hospitalization, as well as in the costs that often accumulate from multiple follow-up visits and long-term therapy.

Third-Line Therapy

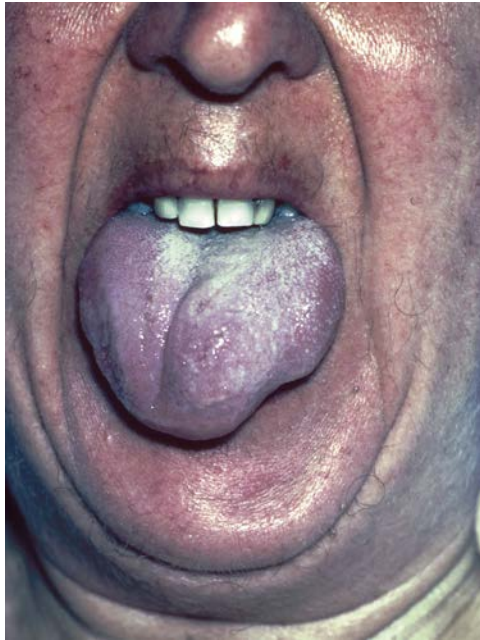
• Imiquimod	C

A phase II, open-label study of the efficacy and safety of imiquimod in the treatment of superficial and mixed infantile hemangioma. McCuaig CC, Dubois J, Powell J, et al. *Pediatr Dermatol* 2009; 26: 203–12.

This is a phase II, open-label, non-comparative study of imiquimod applied for 16 weeks, with posttherapy follow-up 16 weeks later (8 months total). Sixteen infants with a mean age at entry of 4.1 months were enrolled. At the 4-month posttreatment visit, 11 of 14 subjects had improvement in erythema. Treatment was generally well tolerated with low systemic exposure. Improvement was observed in hemangioma coloration, but not lesion size, suggesting effects were limited to the superficial component.

Hereditary angioedema

Tabi A. Leslie



Hereditary angioedema (HAE) is a rare genetic disorder characterized by debilitating, disfiguring, and potentially fatal attacks of edema. There are three types of HAE: type I HAE (HAE-1) and type II HAE (HAE-2), the most common forms, are autosomal dominantly inherited with a prevalence of 1:50,000 due to mutations in the C1-esterase inhibitor (C1-INH) gene on chromosome 11q12-q13.1. De novo mutations of the gene controlling C1-INH (*SERPING1*) can occur, accounting for approximately 25% of C1-INH-HAE cases. HAE-1 is characterized by a quantitative abnormality of the C1-INH (low antigen and low functional levels), which accounts for 85% of HAE patients. HAE-2 is due to a functional defect of the inhibitor of the C1-INH (with normal protein concentration); this comprises about 15% of patients. HAE-1/2 are mediated by the protease kallikrein and the nonapeptide bradykinin, acting on B₂ receptors and 98% of cases have low C4, rising to nearly 100% during attacks. The third type of HAE, previously known as HAE type III (or the estrogen-dependent type), is now referred to as *HAE with normal C1-INH* (HAE nC1-INH). Less prevalent than HAE-1/2, this type is associated with a positive family history, occurring predominantly in women, with no detectable abnormality of C1-INH or other complement components. A mutation in the gene encoding for factor 12 (*F12*), which encodes for the coagulation factor XII (FXII or Hageman factor), has been identified in some of these families. HAE attacks are characterized by sudden, unpredictable swellings of subcutaneous and submucosal tissues, including abdominal organs, genitals, face, and the upper airway. The angioedema is often asymmetrical and may sometimes be painful rather than pruritic. HAE is not associated with urticarial wheals, as it is not mast cell mediated, but a prodromal erythema marginatum rash

can occur. Acute abdominal pain simulating an 'acute abdomen' is an important presentation in any type of HAE, and fatalities are possible due to laryngeal obstruction.

MANAGEMENT STRATEGY

Therapy for HAE is dependent on three considerations:

- Relief of acute angioedema attacks especially preservation of the airway (also known as on-demand therapy)
- Long-term prophylaxis for minimizing overall frequency and/or severity of attacks
- Short-term prophylaxis for the prevention of relapse due to dental and surgical interventions

ACUTE ANGIOEDEMA

Acute presentations of HAE are treated optimally with intravenous (IV) *plasma-derived (pd) C1-INH concentrate* (Berinert, Cinryze). This treatment is safe, and no proven cases of viral transmission have been reported. Reduction in swelling is usually significant within minutes and substantial within 2–3 hours. A *recombinant C1-INH* preparation (Ruconest) is now available. Patients should be taught to self-administer for a more rapid resolution of symptoms and to prevent further progression of the attack. The kallikrein–bradykinin mediator pathway is the target of current approaches to treatment of acute HAE. The swellings of HAE are mediated by bradykinin, a product of the action of kallikrein on its substrate kininogen. Bradykinin acts on B₂ receptors, and its specific antagonist *icatibant* subcutaneously has been proven effective in acute attacks of HAE. Icatibant may be the preferred therapy because it is given subcutaneously, preferably in the abdominal area, and can be administered in a domiciliary setting by health care professionals or even by self-administration after appropriate training. *Ecallantide*, a kallikrein inhibitor administered as subcutaneous injections, has been proven to be safe and effective for acute attacks. *Fresh frozen plasma (FFP)*, which contains C1-INH, can be used in an emergency if concentrate is unavailable. However, FFP carries a higher risk of inadvertent viral transmission (HIV, hepatitis) and theoretically could exacerbate angioedema due to the presence of C1-esterase substrate. Laryngeal edema may require *tracheostomy*, *intubation*, and/or other life-support measures. Patients are routinely admitted for 24 hours after acute episodes, as life-threatening relapses are common.

LONG-TERM PROPHYLAXIS

Long-term prophylaxis should be considered in those patients with at least one or more attacks of angioedema per month and in those with severe symptoms. However, patients could have infrequent attacks and still present with laryngeal edema. Even first-episode angioedema can be fatal. Prophylactic treatment with IV pd C1-INH (Cinryze) is currently the first-line therapy and can lead to less severe symptoms and even attack prevention. Pd C1-INH is also now available as a subcutaneous therapy (Haegarda), which may be preferred as a more convenient method than IV with superior steady state plasma concentrations of C1-INH. Other treatments include the 17 α -alkylated 'attenuated' androgens (*danazol*) used as second-line prophylactic medications that may be effective in preventing angioedema in some patients with HAE-1/2. The lowest effective dose of androgen should be used to obtain clinical remission. Side effects include hirsutism, deepening of voice, and menorrhagia. These attenuated androgens are unsuitable for long-term treatment of HAE in children and pregnant women, or the treatment of acute attacks. However, they are safe

and effective in adults, provided they are closely supervised with clinical biochemical and radiologic assessments. Liver function tests and lipid levels should be monitored, with liver ultrasound scans performed every 2 years. Other less effective prophylactic therapies have included antifibrinolytics (*tranexamic acid*) but should be avoided in patients with a history of thrombotic diseases. They are useful for short-term prophylaxis, especially for those where C1-INH is not available or other therapies are contraindicated. In patients with mild infrequent attacks, *avoidance of provoking factors*, including estrogens and angiotensin-converting enzyme (ACE) inhibitors, may be sufficient.

Lanadelumab, a fully human monoclonal antibody that provides targeted inhibition of plasma kallikrein, is now approved for prevention of HAE attacks.

A newer treatment currently under review, berotralstat (BCX7353), is a potent synthetic small molecule inhibitor of plasma kallikrein that offers the distinct advantage of oral administration. It has been shown to lower rates of HAE attacks and would be the first targeted oral therapy licensed for prophylaxis of HAE, representing a major advance in therapy.

SHORT-TERM PROPHYLAXIS (STP) FOR PREVENTION OF RELAPSE DUE TO DENTAL AND SURGICAL INTERVENTIONS

In all patients, prior to elective surgical, dental, or other invasive procedures, prophylaxis with pdC1-INH concentrate before the procedure is recommended. Due to the possibility of breakthrough attacks, additional on-demand treatment should be available. Second-line STP could include short courses of attenuated androgens when C1-INH is not available. If an emergency procedure is necessary, C1-INH concentrate or FFP can be administered beforehand. Patients with HAE should all wear a *Medic-Alert disk* stating the diagnosis and emergency treatment.

Specific Investigations

- Complement C4 level
- C1-INH protein
- C1-INH function

Hereditary angioedema. Busse PJ, Christiansen SC. *N Engl J Med* 2020; 382(12): 1136–48.

Both types HAE-1/2 are characterized by low serum C4 levels from activation of the complement cascade. The C4 level is typically reduced between attacks, and nearly undetectable during an attack; therefore, all patients with suspected HAE-1/2 should have serum C4 measured as an initial screening test. However, normal or high C4 level cannot exclude HAE. To confirm the diagnosis, tests include C1 inhibitor antigen levels and C1 inhibitor function. In HAE-1 the C1-INH protein level is low, while in HAE-2, the C1-INH protein level can be normal while C1 inhibitor function is low. C1q plasma levels are characteristically normal in HAE.

ACUTE ANGIOEDEMA

First-Line Therapies

• C1-INH concentrate	A
• Icatibant	A
• Ecallantide	A

C1 esterase inhibitor concentrate in 1085 Hereditary Angioedema attacks – final results of the I.M.P.A.C.T.2 study. Craig TJ, Bewtra AK, Bahna SL, et al. *Allergy* 2011; 66(12): 1604–11.

A group of 57 patients were treated for a total of 1085 attacks in various areas of the body during a 24-month study period. The median time to onset of symptom relief was 0.46 hours (h) and the median time to complete resolution of symptoms was 15.5 h. No inhibitory anti-C1-INH antibodies were detected in patients, and no other treatment related safety concerns. The study concluded that 20 U/kg C1-INH is a consistent, reliable, and safe treatment of successive HAE attacks in any area of the body.

Recombinant human C1-esterase inhibitor relieves symptoms of hereditary angioedema attacks: phase 3, randomized, placebo-controlled trial. Riedl MA, Bernstein JA, Li H, et al. *Ann Allergy Asthma Immunol* 2014; 112(2): 163–9.

In this trial 75 patients undergoing acute laryngeal, abdominal, facial, or peripheral attacks were randomized to treatment with recombinant human C1-INH ($n=44$) or saline placebo ($n=31$). In the rhC1-INH-treated patients, median time to beginning of symptom relief was 75 min vs. 303 min in placebo-treated patients ($p=0.003$). The median time to minimal symptoms was 240 min in the rhC1-INH-treated group vs. 362 min in the placebo-treated group ($p=0.005$). RhC1-INH was well tolerated, with no thromboembolic events or observations of neutralizing antibodies or anaphylaxis.

An analysis of the teaching of intravenous self-administration in patients with hereditary angio-oedema. Mühlberg H, Ettl N, Magerl M. *Clin Exp Dermatol* 2016; 41(4): 366–71.

A group of 18 patients were trained to self-administer intravenous pdC1-INH for acute treatment (or routine prevention) of HAE attacks. The median number of training sessions that patients required was 5 (range 2–30). After self-administration training, the median time to acute treatment was 15 min by patients, reduced from 270 min time to treatment by medical professionals.

Icatibant for multiple hereditary angioedema attacks across the controlled and open-label extension phases of FAST-3. Lumry WR, Farkas H, Moldovan D, et al. *Int Arch Allergy Immunol* 2015; 168(1): 44–55.

Out of 88 patients undergoing between one and five HAE attacks that were treated with icatibant at any location, the median times for onset of symptom relief (1.9–2.1 h), onset of primary symptom relief (1.5–2 h), and almost complete symptom relief (3.5–19.7 h) were consistent across the multiple attacks. Similar outcomes (1.0–2.0 h, 1.0–2.0 h, and 1.5–8.1 h, respectively) were observed for laryngeal attacks ($n=25$). Two serious adverse events that were attributed to icatibant were arrhythmia and non-cardiac chest pain.

Ecallantide (DX-88) for acute hereditary angioedema attacks: integrated analysis of 2 double-blind, phase 3 studies. Sheffer AL, Campion M, Levy RJ, et al. *J Allergy Clin Immunol* 2011; 128(1): 153–9. e4.

Integrated analysis of data from 143 unique patients treated within 8 hours for a moderate-to-severe HAE attack at any location of the body was evaluated. Results showed that 30 mg subcutaneous ecallantide demonstrated significantly greater reduction in Mean Symptom Complex Severity scores than placebo from baseline to 4 h after treatment/administration/dosing, as well as significantly greater increase in Treatment Outcome Score. Similarly, after 24 h, ecallantide resulted in significantly greater

symptomatic improvement over placebo. Safety analysis of 183 unique patients found similar incidence of adverse events (AEs) between ecallantide-treated patients (36%) and placebo-treated patients (34.6%).

Efficacy of different medical therapies for the treatment of acute laryngeal attacks of hereditary angioedema due to C1-esterase inhibitor deficiency. Bork K, Bernstein JA, Machnig T, et al. *J Emerg Med* 2016; 50(4): 567–80. e1.

Data from clinical studies, in which a total of 881 acute laryngeal attacks treated with either pdC1-INH, rhC1-INH, icatibant, or ecallantide, were reviewed and compared. The authors concluded that a single body-weight-adjusted dose of pdC1-INH (20 U/kg) provided the most reliable treatment response.

Second-Line Therapies

- Solvent detergent-treated plasma (SDP) **C**
- Fresh frozen plasma (FFP) **C**

Fresh frozen plasma for on-demand hereditary angioedema treatment in South Africa and Iran. Wentzel N, Panieri A, Ayazi M, et al. *World Allergy Organ J* 2019; 12(9): 100049.

This study retrospectively reviewed 176 acute attacks in 43 HAE patients in two low- and middle-income countries where FFP is the only on-demand treatment available. In total, 98 attacks were treated with FFP (median 400 mL), leading to resolution of symptoms in all but two, with median 4 hours to resolution. Five adverse reactions occurred (5%), including one episode of anaphylaxis, and there were no deaths.

LONG-TERM PROPHYLAXIS

First-Line Therapy

- Plasma-derived C1-INH **A**

Long-term outcomes with subcutaneous C1-inhibitor replacement therapy for prevention of hereditary angioedema attacks. Craig T, Zuraw B, Longhurst H, et al. *J Allergy Clin Immunol Pract* 2019; 7(6): 1793–802. e2.

A total of 126 patients were treated with a highly concentrated human plasma-derived C1-INH for subcutaneous injection (Haegarda) for a mean of 1.5 years, including 44 patients that were treated for more than 2 years. A sizeable and continual prophylactic effect was observed. Median annualized attack rates were 1.3 and 1.0 for the 40 IU/kg and 60 IU/kg groups, respectively, and median rescue medication use was 0.2 and 0.0 occasions per year. The majority of patients became free from debilitating disease symptoms during the treatment period, with 19 of the 25 patients who received 60 IU/kg (83%) being attack free during months 25–30 of the trial.

Second-Line Therapy

- Attenuated androgen (danazol) **B**

Critical appraisal of androgen use in hereditary angioedema: a systematic review. Riedl MA. *Ann Allergy Asthma Immunol* 2015; 114(4): 281–8. e7.

An evaluation of 15 studies categorized as level of evidence (LOE) 2, and multiple LOE 4 reports, found a high level of prophylactic efficacy for androgen use in HAE. There were occasionally reports of poor prophylactic response and a range of common AEs, including weight gain, headaches, elevations in liver function test results, serum lipid level, and creatine phosphokinase level, which were often correlated with dosage and treatment duration.

Third-Line Therapy

- Antifibrinolytic (tranexamic acid) **C**

Hereditary angioedema: an update on causes, manifestations and treatment. Longhurst HJ, Bork K. *Br J Hosp Med (Lond)* 2019; 80(7): 391–8.

While tranexamic acid is not as effective as androgens for prophylaxis in HAE patients, it has fewer side effects and is more commonly used in children. Efficacy data are lacking, and therefore its use is confined to when C1-INH is not available and androgens are contraindicated.

New Therapies for Long-Term Prophylaxis

- Lanadelumab (subcutaneous plasma kallikrein inhibitor – monoclonal antibody) **A**
- Berostralstat (oral plasma kallikrein inhibitor – synthetic small molecule) **A**

Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. Banerji A, Riedl MA, Bernstein JA, et al. *JAMA* 2018; 320(20): 2108–21.

In this double-blind, parallel group, placebo-controlled clinical trial, 125 patients with HAE-1/2 completed a 26-week treatment period. Compared with placebo, the mean differences in attack rate per month were –1.49 in the 150 mg every 4 weeks group ($p < 0.001$), –1.44 in the 300 mg every 4 weeks group ($p < 0.001$), and –1.71 in the 300 mg every 2 weeks group ($p < 0.001$). The lanadelumab treatment group experienced greater frequency of injection site reactions (31.4% placebo vs. 52.4% lanadelumab) and dizziness (0% placebo vs. 6.0% lanadelumab).

Oral plasma kallikrein inhibitor for prophylaxis in hereditary angioedema. Aygören-Pürsün E, Bygum A, Grivcheva-Panovska V, et al. *N Engl J Med* 2018; 379(4): 352–62.

The Angioedema Prophylaxis 1 (APeX-1) trial was completed by 72 patients with type I or type II HAE and a history of at least two attacks per month. Patients were randomly assigned to treatment with BCX7353 (berotralstat) 62.5 mg, 125 mg, 250 mg, or 350 mg once daily or placebo, supplied as capsules for daily administration for 28 days. The number of HAE attacks during the effective dosing period (8–28 days) was significantly lower in the 125 mg treatment group vs. the placebo group, with a 73.8% difference ($p < 0.001$). There were significant improvements in quality-of-life scores in the 125 mg and 250 mg groups ($p < 0.05$). Common adverse effects were mild gastrointestinal symptoms.

SHORT-TERM PROPHYLAXIS

First-Line Therapy

- C1-INH concentrate **B**

Short-term prophylactic use of C1-inhibitor concentrate in hereditary angioedema: findings from an international patient registry. Magerl M, Frank M, Lumry W, et al. *Ann Allergy Asthma Immunol* 2017; 118(1): 110–2.

The Berinert Registry collected data on individuals using plasma-derived, pasteurized, nanofiltered C1-INH concentrate (pnfC1-INH) between 2010 and 2014 at 37 sites across the United States and Europe. Of the 318 patients in the registry, 79 used pnfC1-INH as STP at least once. The median dose per infusion was 14.6 IU/kg or 1000 IU. Analyses of dose response suggest higher efficacy with weight-based doses of at least 15 IU/kg and absolute doses of 1500 U and above. Regardless of dose, there were 0.4 HAE attacks within 1 day after STP infusion, and 0.6 attacks within 2 days. The data from this large registry indicate that pnfC1-INH is safe and effective as STP for HAE patients undergoing surgical procedures.

Second-Line Therapies

• Attenuated androgen (danazol)	B
• FFP	C

The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. Maurer M, Magerl M, Ansotegui I, et al. *Allergy* 2018; 73(8): 1575–96.

Attenuated androgen (danazol), used for 5 days prior to and 2–3 days after a surgical procedure, has previously been recommended for STP as an alternative to C1-INH concentrate. Their use is deemed to be safe in children; however, adverse effects are associated with long-term use, and frequent short courses may similarly lead to these side effects. FFP may be helpful. However, it is less safe than C1-INH concentrate, with increased risk of allo-sensitization, as well as transmission of bloodborne pathogens. While tranexamic acid has been previously used for STP, it is now not recommended.

TREATMENT IN CHILDREN

International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. Farkas H, Martinez-Saguer I, Bork K, et al. *Allergy* 2017; 72(2): 300–13.

Plasma-derived C1-INH (Berinert) is the first on-demand medication licensed for children of all ages with HAE. However, there are little data on its use in babies and very young children. Recombinant C1-INH (Ruconest) is currently licensed in the United

States for adolescents aged over 13 years, while its approval in Europe has been extended to include all children aged 2 years and over. Ecallantide (Kalbitor) is licensed in the United States for children 12 years and over. Icatibant (Firazyr) is approved in Europe for children and adolescents aged 2 years and over, but not yet in the United States.

For long-term prophylaxis in children with HAE-1/2, pdC1-INH may be the safest and therefore preferred approach. Cinryze is approved in United States and Europe for children aged 6 and over. Tranexamic acid (TA) is also favored in pediatrics because of its long-term safety profile. Attenuated androgens are not usually considered until after Tanner Stage 5, at which point they may be tried, aiming to achieve the minimum effective dose. Regular monitoring and follow-up are vital with all therapies. Lanadelumab (Takhzyro) has been approved in United States and Europe for children over 12 years.

HEREDITARY ANGIOEDEMA WITH NORMAL C1-INH

Hereditary angioedema with normal C1 inhibitor: update on evaluation and treatment. Magerl M, Garmeniz AE, Maas C, et al. *Immunol Allergy Clin North Am* 2017; 37(3): 571–84.

It is thought that swelling attacks in patients with HAE with normal C1-INH (HAE-nC1) are caused by bradykinin. ACE inhibitors, angiotensin II receptor antagonists, and estrogens, which are known to provoke attacks in affected women, should be avoided. So far there have been no prospective randomized controlled trials in HAE-nC1 patients and there are no licensed treatments. Antihistamine and corticosteroids are ineffective in acute attacks; however, on-demand treatment with C1-INH concentrate appears to be effective in many cases, to variable degrees. Icatibant has been reported to be effective in many patients, although there are also non-responders and delayed responders, and ecallantide has been used successfully for repeated on-demand treatment.

The effectiveness of STP therapies for HAE-nC1 is unclear, although C1-INH concentrate has been used repeatedly, mainly for deliveries. For long-term prophylaxis, TA seems to be more effective in patients with HAE-nC1 than those with HAE-1/2, for whom TA is unreliable. There have been excellent therapeutic responses to progestin reported in women with HAE-nC1. There are few data on attenuated androgens for long-term prophylaxis in HAE-nC1, perhaps because most patients are female. There is similarly little information on C1-INH concentrate, which has been reported to be effective, although more details on outcomes are needed.

Hereditary hemorrhagic telangiectasia

Mitchell S. Cappell, Oscar Lebwohl



From Lebwohl, MG. Atlas of the Skin and Systemic Disease Atlas of the Skin and Systemic Disease. © Churchill Livingstone 1995.

Hereditary hemorrhagic telangiectasia (HHT; or Osler-Weber-Rendu syndrome) is an autosomal dominant disease, producing a syndrome of multiple orocutaneous telangiectasias, especially on the face, lips, tongue, oral mucosa, and fingertips, together with multiple internal telangiectasias, especially on the mucosa of the nose and gastrointestinal (GI) tract. They generally slowly increase in size and number with age. GI lesions visible at endoscopy have similar characteristics as cutaneous lesions. The basic pathophysiology in HHT is a defect in the wall of small vessels that leads to direct arteriovenous communications without intervening capillaries. The prevalence of HHT is estimated at 1 per 6000 individuals. HHT is reliably diagnosed when three or more criteria are satisfied among a clinical tetrad (Curaçao criteria), listed in Table 102.1. HHT is possible or suspected when two criteria are satisfied. HHT is highly unlikely in adult patients satisfying only one or none of these criteria. About 90% of cases of HHT are due to underlying genetic mutations either in the gene encoding endoglin (ENG) that produces HHT1, or in the gene encoding activin receptor-like kinase (ACVRL1, previously called ALK-1) that produces HHT2. Three other genetic types of HHT have been described, including a rare type in which mutations of the SMAD4 gene cause an overlap syndrome of HHT and juvenile polyposis.

Patients with sporadic GI angiodysplasia are differentiated from patients with HHT by clinical presentation in old age, paucity of lesions, negative family history, and by exclusive GI involvement without epistaxis or intranasal telangiectasia.

MANAGEMENT STRATEGY

The two major clinical complications of HHT are frequent or severe epistaxis and GI bleeding from nasal and GI telangiectasias, respectively. The bleeding may be acute or chronic. Acute blood loss may cause hypovolemia and systemic hypotension, whereas chronic blood loss may cause iron-deficiency anemia. Vascular

Table 102.1 Clinical (Curaçao) criteria for diagnosis of hereditary hemorrhagic telangiectasia (HHT)

Organ or other parameter	Characteristic finding
Nose	Recurrent, spontaneous epistaxis
Mucocutaneous	Telangiectasias on lips, oral cavity, nasal mucosa, or fingers
Gastrointestinal	Mucosal telangiectasias (or visceral arteriovenous malformations)
Family history	One or more first-degree relatives with HHT

hemorrhage in HHT is related to the thin and fragile vessel walls of telangiectasia, and is unrelated to a hemorrhagic diathesis (e.g., abnormal international normalized ratio or thrombocytopenia). Internal shunts created by direct arteriovenous communications in HHT uncommonly cause clinical manifestations, including hypoxia or pulmonary hypertension from pulmonary arteriovenous shunts; cerebral ischemia, hemorrhage, or abscesses from intracerebral shunts; and portal hypertension, biliary tract disease, or high-output cardiac failure from intrahepatic shunts. Dermatologic telangiectasias are usually only a minor, cosmetic problem.

Severe bleeding requires hospitalization and insertion of two large-bore IV lines. Significant acute blood loss is treated with intravenous fluid resuscitation and transfusion of packed erythrocytes as needed. Chronic blood loss is treated with iron supplementation as needed.

Non-specific therapy for bleeding from HHT includes avoidance of aspirin, non-steroidal antiinflammatory drugs, other antiplatelet drugs, and anticoagulants; and administration of iron for patients with significant iron-deficiency anemia.

Nasal moisturizers and room humidification promote mucosal integrity and reduce nasal mucosal injury and epistaxis. Epistaxis is initially treated by non-specific local therapy such as nasal packing to tamponade the bleeding. Estrogen with progesterone is used to prevent or arrest chronic epistaxis by promoting vascular integrity. Mutations in the different forms of HHT result in highly elevated levels of vascular endothelial growth factor (VEGF) that can produce abnormal, immature vasculature containing telangiectasias. Bevacizumab, a recombinant humanized monoclonal antibody to VEGF, may reverse the telangiectasias occurring in HHT by inhibiting VEGF (antiangiogenesis). Several moderate-sized clinical trials have shown IV bevacizumab may significantly reduce epistaxis in patients with HHT. IV bevacizumab has rare risks, including hypertension, bleeding in other organs, and bowel perforation. Submucosal or topical intranasal administration of bevacizumab may avoid much of the systemic toxicity of IV therapy with similar efficacy.

Several studies have reported a markedly reduced incidence of chronic epistaxis from telangiectasias after instituting estrogen therapy, either alone or with progesterone, by promoting endothelial integrity. Despite controversy concerning efficacy, estrogen therapy should be considered before performing nasal surgery for chronic epistaxis because of its low risk and the risk of recurrent bleeding after surgery. Estrogen therapy is less desirable in males than in females because it can cause feminization.

Septal dermoplasty is indicated for severe, recurrent epistaxis, especially from the anterior nasal mucosa. Skin, removed from the upper thigh, is grafted on to the anterior nasal septum and floor to cover and protect the fragile mucosal telangiectasias from local trauma. The procedure is well tolerated using only local anesthesia, and complications, other than recurrent epistaxis, are rare. Septal dermoplasty is effective in >75% of cases. Failure results from inadequate graft coverage with bleeding from telangiectasias

at or beyond the border of the grafted area. Focal laser therapy can be used to ablate discrete bleeding intranasal lesions.

Chronic GI bleeding from telangiectasias may also be reduced by estrogen and progesterone therapy, as demonstrated in multiple individual case reports and small studies. Several studies have shown decreased GI bleeding from telangiectasia with *thalidomide* therapy. Several mechanisms have been proposed for this efficacy.

At endoscopy, actively bleeding, individual, GI telangiectasias are preferably treated with *endoscopic argon plasma coagulation* (APC), or alternatively with *endoscopic thermocoagulation* or *electrocoagulation*. APC is easier to apply endoscopically and is potentially safer due to more superficial tissue ablation. Nonetheless, all these endoscopic therapies are relatively safe and highly successful at achieving hemostasis when performed by experienced endoscopists. Non-bleeding lesions are generally not treated at endoscopy unless the lesions are particularly large and thus likely to bleed. However, patients with HHT often rebleed from other, untreated GI telangiectasias after an initial session of endoscopic therapy, and patients therefore require multiple sessions of endoscopic therapy to treat these other lesions.

Segmental bowel resection is reserved for severe active bleeding, localized to a single region and refractory to medical and endoscopic therapy. Where available, *angiographic embolization* can obviate the need for GI surgery. Surgery or angiographic embolization often provides only intermediate-term relief owing to formation of telangiectasias at other GI sites.

Some data support the use of *tamoxifen*, an estrogen antagonist, to prevent bleeding from telangiectasias in HHT. A few patients have responded to therapy with α -*interferon*, which has known antiangiogenic properties, but this therapy is currently experimental because of insufficient data.

Local non-specific therapy of *arterial ligation*, *cryosurgery*, *electrical cautery*, or *submucosal resection* provides temporary relief of epistaxis from HHT. However, these treatments can cause mucosal scarring, which diminishes the efficacy of subsequent septal dermoplasty. Topical intranasal therapy with vasoconstrictors or aminocaproic acid rarely produces scarring. Non-specific therapies are indicated only for temporary relief of acute bleeding. Life-threatening epistaxis refractory to septal dermoplasty is treated by surgical closure of one or both nostrils, depending on the bleeding source.

Aminocaproic acid promotes thrombosis and retards bleeding by inhibiting fibrinolysis. Oral aminocaproic acid therapy has had mixed success with HHT. This therapy rarely causes hypotension or rhabdomyolysis. Aminocaproic acid is a temporary, second-line therapy.

Specific Investigations for Epistaxis or GI Bleeding

For epistaxis or GI bleeding

- Serial hematocrit determinations – to assess severity of bleeding
- Serum iron, total iron binding capacity, and ferritin levels

For epistaxis

- Flexible nasal endoscopy
- Nasal examination using fine-caliber, rigid, nasal endoscope

For GI bleeding

- Esophagogastroduodenoscopy (EGD)
- Colonoscopy
- Capsule endoscopy or double-balloon enteroscopy
- Angiography – for ongoing bleeding after non-diagnostic endoscopic examinations

For epistaxis, bleeding severity is determined by inspection, vital signs, and laboratory tests. The bleeding site is precisely localized by nasal examination with a fine-caliber rigid tube (endoscope) using spot suction, and bright, shadow-free illumination with a headlight, head mirror, or cold fiberoptic illumination. Flexible nasal endoscopy is a recently popular alternative technique. For GI bleeding, the bleeding severity is indicated by patient history, vital signs, physical findings, rectal examination, and nasogastric aspiration. Serial hematocrit determinations guide requirements for transfusions of packed erythrocytes. The bleeding site and source are conclusively diagnosed by GI endoscopy. Iron studies will determine the need for iron supplementation.

Upper GI bleeding, usually manifested by hematemesis or melena, should be investigated by esophagogastroduodenoscopy (EGD). Lower GI bleeding, usually manifested by hematochezia or fecal occult blood, and occasionally by melena, should be investigated by colonoscopy. Barium contrast radiography or virtual colonoscopy are not helpful due to the macular nature of telangiectases. Small intestinal bleeding, usually manifested by hematochezia, melena, or fecal occult blood, can be investigated by capsule endoscopy after exclusion of upper and lower GI bleeding by EGD and colonoscopy, respectively. Double-balloon enteroscopy is often used at tertiary medical centers instead of capsule endoscopy to investigate small intestinal bleeding because of its greater diagnostic sensitivity and ability to perform therapy, despite its greater costs.

Telangiectasias are distinguished from lesions due to endoscopic trauma by identification during endoscopic intubation, as opposed to identification during endoscopic extubation with trauma; by a finely reticular (fern-like) internal structure due to a vascular tuft; by an irregular (fern-like) border as opposed to a round border with trauma, by an abrupt lesion margin as opposed to an indistinct margin with trauma; and by lesions lying flush (coplanar) with mucosa. Additionally, colonic lesions from endoscopic trauma usually occur at sharp colonic turns, during endoscopic looping, or after endoscopic suctioning.

Angiography is indicated for active GI bleeding if EGD and colonoscopy fail to diagnose the source of bleeding. The angiographic hallmarks of telangiectasias are a vascular tuft or tangle resulting from the local aggregation of irregular vessels; an early and intensely filling vein resulting from direct arteriovenous connection without intervening capillaries; and persistent opacification beyond the normal venous phase (slowly emptying vein), attributed to vascular tortuosity. Telangiectasias bleed only intermittently, and extravasation of contrast material from telangiectasias is infrequently detected at angiography.

Systematic screening in hereditary hemorrhagic telangiectasia: a review. Kroon S, Snijder RJ, Faughnan ME, et al. *Curr Opin Pulm Med* 2018; 24: 260–8.

Clinically oriented review of the genetics, pathophysiology, clinical presentation, and diagnosis of HHT.

Liver disease in patients with hereditary hemorrhagic telangiectasia. Garcia-Tsao G, Korzenik JR, Young L, et al. *N Engl J Med* 2000; 343: 931–6.

Review of clinical findings caused by intrahepatic shunts with HHT, including eight patients with high-output cardiac failure, six patients with portal hypertension, and five patients with biliary tract disease.

Diagnostic yield of capsule endoscopy for small bowel arteriovenous malformations in patients with hereditary

hemorrhagic telangiectasia: a systematic review and meta-analysis. Singh K, Ayla Zubair A, Prindle A, et al. *Endosc Int Open* 2019; 7: E282–9.

Recently published meta-analysis and systematic literature review, encompassing five studies and 124 patients with HHT, revealed capsule endoscopy had a diagnostic yield of 77.0% (95%; confidence interval of 65.8%–85.4%) for small bowel arteriovenous malformations (AVMs). Although capsule endoscopy, a minimally invasive test, has a superior diagnostic yield, it lacks therapeutic capabilities for treating AVMs to achieve hemostasis.

Evaluation of patients with hereditary hemorrhagic telangiectasia with video capsule endoscopy: a single-center prospective study. Chamberlain SM, Patel J, Carter Balart J, et al. *Endoscopy* 2007; 39: 516–20.

In a prospective study of 80 patients evaluated by capsule endoscopy for small intestinal bleeding, the 32 patients with known HHT had significantly more GI telangiectasias than the 48 control patients without HHT (75% vs. 8.3% of patients had ≥five telangiectasias). This study demonstrates the high sensitivity of capsule endoscopy in diagnosing small intestinal telangiectasias in patients who have HHT.

First-Line Therapies

For epistaxis or GI bleeding

- Transfuse packed erythrocytes for significant, acute bleeding **A**
- Oral iron therapy for iron-deficiency anemia from chronic blood loss **A**
- Non-specific therapy: avoid aspirin, other antiplatelet drugs, and anticoagulation **A**
- Reverse severe coagulopathy if patient is actively bleeding (e.g., transfuse platelets for severe thrombocytopenia and transfuse fresh frozen plasma for elevated international normalized ratio [INR]) **A**
- Bevacizumab **B**
- Estrogen and progesterone hormonal therapy **B**

For epistaxis

- Non-specific (and very safe) general therapy: room humidification and nasal moisteners **A**
- Nasal packing **A**
- Septal dermoplasty **A**
- APC **A**

For GI bleeding

- Endoscopic APC **A**
- Endoscopic thermocoagulation or electrocoagulation **B**
- Angiographic embolization for bleeding refractory to endoscopic therapy **B**
- Segmental bowel resection – for bleeding refractory to endoscopic and angiographic therapy **A**

For cutaneous lesions

- Cosmetic therapy: laser or other focal ablation techniques for cutaneous lesions **A**

Treatment of bleeding gastrointestinal vascular malformations with oestrogen-progesterone. van Custen E, Rutgeerts P, Vantrappen G. *Lancet* 1990(8695); 335: 953–5.

In a double-blind, placebo-controlled crossover trial of 10 patients with frequent and severe GI bleeding from HHT, the number of transfusions decreased significantly from a mean of 10.9 units of packed erythrocytes in controls receiving placebo to a mean of 1.1 units in patients treated with estrogen-progesterone during a 6-month period.

Use of estrogen in treatment of familial hemorrhagic telangiectasia. Harrison DFN. *Laryngoscope* 1982; 92: 314–20.

Report of successful control of epistaxis with estrogen therapy in 67 patients with HHT, with few complications.

Treatment of hereditary hemorrhagic telangiectasia with submucosal and topical bevacizumab therapy. Karnezis TT, Davidson TM. *Laryngoscope* 2012; 122: 495–7.

In a prospective trial of 19 patients, 2 months after intranasal, submucosal injection of bevacizumab, the epistaxis severity score significantly decreased to 2.00, compared with the baseline, pre-treatment severity score of 8.12 ($p < 0.0001$). Bevacizumab therapy statistically, significantly protected against epistaxis for all 12 months of the clinical trial.

Bevacizumab in patients with hereditary hemorrhagic telangiectasia and severe hepatic vascular malformations and high cardiac output. Dupuis-Girod S, Ginon I, Saurin JC, et al. *JAMA* 2012; 307: 948–55.

In a prospective, open-labeled study, 25 adult patients with severe HHT received bevacizumab intravenously for 2.5 months. The mean duration of epistaxis decreased from 221 min/mo at baseline to 43 min/mo at 6 mo ($p = 0.008$), and the mean number of episodes decreased from 26 episodes/mo at baseline to 11 episodes/mo at 6 mo. This study suggests that IV bevacizumab may decrease the frequency and duration of epistaxis in patients with HHT.

Intravenous bevacizumab for refractory hereditary hemorrhagic telangiectasia-related epistaxis and gastrointestinal bleeding. Iyer VN, Apala DR, Pannu BS, et al. *Mayo Clin Proc* 2018 Feb; 93: 155–66.

Study of 34 patients treated with intravenous bevacizumab for severe GI bleeding and/or epistaxis in patients with HHT from 2013 to 2016 conducted at the Mayo Clinic, Rochester, Minnesota. Twenty-eight patients (82%) had received transfusions of packed erythrocytes, including 16 patients (47%) who depended on frequent transfusions of packed erythrocytes. Median baseline hemoglobin level was 9.1 g/dL. Anemia was primarily related to severe epistaxis (44%), severe GI bleeding (12%), or both (44%). Patients were followed up for a mean of 17.6 months after initiating bevacizumab therapy. The epistaxis severity score (a semiquantitative subjective assessment based on patient responses to six questions) significantly declined from a mean of 6.6 ± 2.2 to 3.0 ± 1.4 ($p < 0.001$) and packed erythrocyte transfusion requirements from a median of 75 to 12 units of packed erythrocytes ($p = 0.007$) comparing before treatment with after treatment. This study suggests that intravenous bevacizumab may be an effective therapy for severe, refractory bleeding from HHT.

Outcome of septal dermoplasty in patients with hereditary hemorrhagic telangiectasia. Fiorella ML, Ross D, et al. *Laryngoscope* 2005; 115: 301–5.

Retrospective study reporting outcome of 32 consecutive patients undergoing septal dermoplasty in whom accurate records of transfusion requirements were available. Mean blood

transfusion requirements declined significantly from a mean of 21 units of packed erythrocytes in the year before surgery to a mean of one unit in the year after surgery ($p < 0.001$). This study illustrates the fairly extensive literature supporting the efficacy of septal dermoplasty for treating recurrent, relatively severe epistaxis from HHT.

Diagnosis and management of gastrointestinal bleeding in patients with hereditary hemorrhagic telangiectasia. Longacre AV, Gross CP, Gallitelli M, et al. *Am J Gastroenterol* 2003; 98: 59–65.

In a non-randomized, long-term, observational study, the mean hemoglobin level increased and the chronic transfusion requirements decreased in about three-quarters of 17 patients after instituting chronic estrogen hormonal therapy, either alone or with other therapies, for GI bleeding from HHT.

Argon plasma coagulation is an effective treatment for hereditary hemorrhagic telangiectasia patients with severe nosebleeds. Pagella F, Matti E, et al. *Acta Otolaryngol* 2013; 133: 174–80.

In this retrospective study, 26 patients with HHT were followed by telephone calls one or more years after undergoing APC treatment of nasal mucosa for severe epistaxis requiring blood transfusions. The epistaxis severity score decreased significantly from 8.5 before APC therapy to 4.3 after therapy ($p < 0.005$), as did the number of patients requiring blood transfusions ($p < 0.02$). The frequency, intensity, and duration of epistaxis also decreased significantly after APC therapy compared to baseline ($p < 0.0001$). The beneficial effects of therapy lasted 22.9 months. This work demonstrates that APC is an effective therapy for severe epistaxis from HHT.

Long-term outcome of argon plasma ablation therapy for bleeding in 100 consecutive patients with colonic angiodysplasia. Olmos JA, Marcolongo M, Pogorelsky V, et al. *Dis Colon Rectum* 2006; 49: 1507–16.

In this prospective trial, 85 of 100 patients with moderate-to-severe bleeding from colonic angiodysplasia treated at colonoscopy with APC (mean 3.9 angiodysplasias treated per patient) had no further overt bleeding and had a stable hemoglobin level without further blood transfusions or iron therapy during a mean follow-up of 20 months. Only two minor procedure complications occurred. Although not specifically addressing APC for telangiectasias in HHT, this large, prospective study demonstrated high efficacy of this therapy for preventing rebleeding from the similar lesions of sporadic colonic angiodysplasia.

Second-Line or Temporizing Therapies

For epistaxis

- Arterial ligation B
- Topical vasoconstrictors B
- Cryosurgery/electrocautery B
- Unilateral or bilateral surgical closure of nostrils B
- Arterial embolization B
- Tamoxifen B
- Submucosal resection C
- Topical aminocaproic acid D

For GI bleeding

- Thalidomide B
- Oral aminocaproic acid therapy D
- α -Interferon D

Antiestrogen therapy for hereditary hemorrhagic telangiectasia: a double-blind placebo-controlled clinical trial. Yaniv E, Preis M, Hadar T, et al. *Laryngoscope* 2009; 119: 284–8.

In a randomized, placebo-controlled trial of 21 patients with HHT, nine of 10 patients (90%) treated with orally administered tamoxifen, an estrogen antagonist, had cessation of clinically significant epistaxis vs. three of 11 patients receiving placebo ($p = 0.01$). This small, placebo-controlled trial suggests that tamoxifen may be effective in preventing epistaxis in HHT.

Efficacy and safety of thalidomide for the treatment of severe recurrent epistaxis in hereditary haemorrhagic telangiectasia: results of a non-randomised, single-centre, phase 2 study. Invernizzi R, Quaglia F, Klersy C, et al. *Lancet Haematol* 2015; 2: e465–73.

In a non-randomized, open-label, single-center Italian study conducted from 2011 to 2014, 31 patients received low-dose oral thalidomide to reduce severe recurrent epistaxis associated with HHT refractory to minimally invasive surgical procedures. During a median follow-up of 15.9 months, all 31 patients responded to thalidomide therapy with a significant decrease in all three monitored parameters of epistaxis severity: frequency of epistaxis of $> \text{once/day}$ decreased from 61% at baseline to 3% at 12 weeks ($p < 0.0001$); intensity of epistaxis decreased from 84% requiring a bowl (rather than a handkerchief) to hold the bleeding to 16% ($p < 0.0001$); and duration of epistaxis of > 10 minutes from 83% to 19% ($p < 0.0001$). Also, from baseline to 24 weeks after initiating therapy, the hemoglobin increased from approximately 8.2 g/dL to 10.8 g/dL ($p < 0.0001$), and number of units of packed erythrocytes transfused per week decreased from approximately 1.5 to 0.5 units ($p < 0.0001$).

Herpes genitalis

Ritu Swali, Radhika Shah, Stephen K. Tying



Herpes genitalis (genital herpes) is a recurrent vesicular eruption of the skin and mucosa arising in the region between the navel, thighs, and buttocks. It is a common sexually transmitted disease, usually preceded by prodromal symptoms including itching, burning, and tingling, and caused predominantly by herpes simplex virus type 2 (HSV-2) and less frequently by HSV-1. First-episode genital herpes due to HSV-1 has become increasingly common in certain populations – namely, heterosexual women and men who have sex with men. Primary infection may have associated systemic, influenza-like signs and symptoms, including fever, headache, malaise, and myalgias, which occur 2–20 days following exposure. Lesions of the initial infection typically last 2–3 weeks, during which time they progress from grouped papules on an erythematous base, to vesicles, to ulcers with eventual crusting. Recurrences generally lack systemic symptoms and are less severe than the primary outbreak. Recurrent lesions, which typically last 5–10 days, occur in the same area but are fewer in number and heal quickly. Genital herpes infection due to HSV-1 results in fewer symptomatic recurrences than infection by HSV-2. Residual hypopigmentation, hyperpigmentation, and scarring may occur with healing.

MANAGEMENT STRATEGY

Because no cure exists for herpes genitalis, treatment is focused on reducing the number of recurrences through suppressive therapy and on promoting rapid healing when a recurrence is present. In addition, treatment aims to reduce infectivity by reducing viral shedding and to reduce complications, such as urinary retention and aseptic meningitis. In the past, topical and oral *acyclovir* were used as first-line treatments for recurrences. Due to its low bioavailability, it requires frequent dosing. The standard dosing of oral acyclovir for a recurrence is 200 mg five times daily for 5 days. Alternative regimens have also been shown to be effective, including 400 mg three times daily for 5 days, 800 mg three times daily

for 2 days, and 800 mg twice daily for 5 days. The frequent dosing of acyclovir led to the development of *valacyclovir* and *famciclovir* (the prodrugs of acyclovir and penciclovir, respectively) as alternative therapies with improved bioavailability. The use of topical acyclovir should be discouraged because it has lower efficacy in comparison to oral acyclovir. Valacyclovir has been shown to be effective when dosed 500 mg twice daily for 3 days or 1000 mg once daily for 5 days. A dosing regimen of oral valacyclovir, given 2000 mg twice daily for 1 day, has been studied and shown to be more convenient; however, further comparative studies are needed. Famciclovir is effective when prescribed as 1000 mg twice daily for 1 day. It may also be taken as 125 mg twice daily for 5 days. Acyclovir, valacyclovir, and famciclovir may all be used for suppressive therapy.

Immunocompromised individuals have more frequent recurrences and can develop more severe lesions, thus requiring longer treatment periods with higher doses than those used in the immunocompetent. Severe cases may require intravenous therapy. Suppressive dosage regimens have been used in this population. Long-term therapy may lead to the selection of resistant strains of the virus. In acyclovir-resistant cases, intravenous therapy with foscarnet may be required.

Addressing psychosocial issues is another important aspect of genital herpes management. The recurrent nature of genital HSV infection can have a negative emotional and psychological impact on patients. Counseling serves to help patients cope with the infection and to prevent sexual and perinatal transmission.

Specific Investigations

- Type-specific serologic testing
- Polymerase chain reaction (PCR)
- Viral culture
- Skin biopsy of atypical lesion

Type-specific laboratory testing should be performed to distinguish HSV-2 infections from HSV-1 infections, as this has implications for disease course and patient counseling. Patients with confirmed genital herpes should be offered testing for HIV and other sexually transmitted diseases. Severe or refractory cases may be due to underlying immunosuppression, which should be further investigated.

Clinical evaluation and cost analysis of a Trioplex real-time PCR assay for the detection and differentiation of herpes simplex virus 1 and 2 in cutaneous and mucocutaneous lesions. Navidad J, Pfothenhauer B, Leigh N, et al. *J Med Microbiol.* 2019; 68: 748–54.

Performance of ELISA and Western blot to detect antibodies against HSV-2 using dried blood spots. García-Cisneros S, Sánchez-Alemán MÁ, Conde-Glez CJ, et al. *J Infect Public Health* 2019; 12: 224–8.

Precision of the Kalon herpes simplex virus type 2 IgG ELISA: an international interlaboratory assessment. Patel EU, Manucci J, Kahle EM, et al. *BMC Infect Dis* 2015; 15: 398.

Performance of the Focus HerpeSelect-2 EIA for the detection of herpes simplex virus type 2 antibodies in seven African countries. Mujugira A, Morrow RA, Celum C, et al. *Sex Transm Infect* 2011; 87: 238–41.

Effect of sexually transmitted disease (STD) coinfections on performance of three commercially available immunosorbent assays used for detection of herpes simplex virus type 2-specific antibody in men attending Baltimore, Maryland, STD clinics. Summerton J, Riedesel M, Laeyendecker O, et al. *Clin Vaccine Immunol* 2007; 14: 1545–9.

Using the evidence base on genital herpes: optimizing the use of diagnostic tests and information provision. Scoular A. *Sex Transm Infect* 2002; 78: 160–5.

First-Line Therapies

• Valacyclovir (Valtrex)	A
• Acyclovir (Zovirax)	A
• Famciclovir (Famvir)	A

Primary Genital Infection

Antiviral treatment should be initiated promptly, ideally within 72 hours of the appearance of lesions, and should be continued for 7–10 days. Treatment duration may be extended if adequate healing has not occurred. The following regimens may be used: acyclovir 400 mg three times daily or 200 mg five times daily; valacyclovir 1000 mg twice daily; or famciclovir 250 mg three times daily. Because acyclovir, valacyclovir, and famciclovir demonstrate similar efficacy, the initial drug choice may be based on factors such as provider preference, cost, and availability. Valacyclovir may be preferable due to the convenience of twice-daily dosing.

Genital herpes. Gnann JW Jr, Whitley RJ. *N Engl J Med* 2016; 375: 666–74.

Neonatal herpes simplex virus infections. Pinninti SG, Kimberlin DW. *Semin Perinatol* 2018; 42(3): 168–75.

Acute Reactivation Episodes

Standard-dose and high-dose daily antiviral therapy for short episodes of genital HSV-2 reactivation: three randomised, open-label, crossover trials. Johnston C, Saracino M, Kuntz S, et al. *Lancet* 2012; 379: 641–7. Erratum in: *Lancet* 2012; 379: 616.

Three open-label crossover studies compared no medication with acyclovir 400 mg twice daily (standard dose), valacyclovir 500 mg daily (standard dose) with acyclovir 800 mg three times daily (high dose), and standard-dose valacyclovir with valacyclovir 1 g three times daily (high dose). High-dose acyclovir was associated with less viral shedding than standard-dose valacyclovir, but there was no significant difference in time to lesion healing between the groups. High-dose valacyclovir had less viral shedding and shorter lesion healing time compared with its standard dose. Viral shedding persisted even in high-dose regimens.

Single-day therapy for recurrent genital herpes. Tyring S, Berger T, Yen-Moore A, et al. *Am J Clin Dermatol* 2006; 7: 209–11.

A multicenter, randomized, double-blind, placebo-controlled clinical trial found that famciclovir 1000 mg twice daily for 1 day, taken within 6 hours of prodrome onset, resulted in a significant reduction in lesion healing time and reduced the time of all symptom resolution compared with placebo. A greater proportion of subjects who took famciclovir did not progress to a

full genital herpes outbreak compared with those taking placebo (23.3% vs. 12.7%, respectively).

Sexually transmitted diseases treatment guidelines 2015. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 2015; 64: 27–32.

Antiviral therapy should be initiated during the prodrome or within 24 hours of the appearance of lesions.

Single-day patient initiated famciclovir therapy for recurrent genital herpes: a randomized, double-blind, placebo-controlled trial. Aoki FY, Tyring S, Diaz-Mitoma F, et al. *Clin Infect Dis* 2006; 42: 8–13.

This study proved that in addition to being convenient, single-day therapy is safe and effective for the treatment of recurrent genital herpes. Subjects receiving 1000 mg famciclovir orally twice daily for 1 day healed approximately 2 days faster than those on placebo.

A randomized, placebo-controlled comparison of oral valacyclovir and acyclovir in immunocompetent patients with recurrent genital herpes infections. Tyring SK, Douglas JM, Corey LC, et al. *Arch Dermatol* 1998; 134: 185–91.

This multicenter, double-blind, placebo-controlled, randomized, parallel-design study showed that oral valacyclovir 1000 mg twice daily for 5 days was as effective and well tolerated as acyclovir five times daily for 5 days for the treatment of recurrent genital herpes.

Prophylactic Treatment

Prophylactic treatment for frequent reactivation, recurrent severe attacks, or before delivery.

Effect of valacyclovir on viral shedding in immunocompetent patients with recurrent herpes simplex virus 2 genital herpes: a US-based randomized, double-blind, placebo-controlled clinical trial. Fife KH, Warren TJ, Ferrera RD, et al. *Mayo Clin Proc* 2006; 81: 1321–7.

Over a 60-day period 1 g of valacyclovir daily was well tolerated and effectively reduced clinical and subclinical HSV-2 shedding compared with placebo.

Once-daily valacyclovir to reduce the risk of transmission of genital herpes. Corey L, Wald A, Patel R, et al. *N Engl J Med* 2004; 350: 11–20.

Among heterosexual HSV-2 discordant couples, once-daily valacyclovir (500 mg) significantly reduced the risk of transmission of genital herpes. Clinically symptomatic HSV-2 infection was reduced by 75%, and acquisition of HSV-2 was reduced by 48% in the valacyclovir group versus placebo.

Prevention and management of genital herpes simplex infection during pregnancy and delivery: Guidelines from the French College of Gynaecologists and Obstetricians. Sénat MV, Anselem O, Picone O, et al. *Eur J Obstet Gynecol Reprod Biol* 2018; 224: 93–101.

During pregnancy, the first episode of genital herpes should be treated with acyclovir (200 mg five times daily) or valacyclovir (1000 mg twice daily) for 5–10 days, and recurrent herpes should be treated with acyclovir (200 mg five times daily) or valacyclovir (500 mg twice daily) for symptom relief. There is no evidence suggesting that the risk of neonatal herpes can be reduced during pregnancy.

Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. Brown ZA, Wald A, Morrow RA, et al. JAMA 2003; 289: 203–9.

Among women with HSV in genital secretions at the time of labor, the risk of neonatal HSV was significantly reduced in those who had a cesarean delivery.

Sexually transmitted diseases treatment guidelines 2015. Centers for Disease Control and Prevention. MMWR Recomm Rep 2015; 64: 27–32.

Severe HSV infection, or complications requiring hospitalization, such as disseminated infection, requires intravenous antiviral therapy. A regimen of acyclovir 5–10 mg/kg intravenously every 8 hours for a minimum of 2 days until clinical improvement occurs is recommended. Transition to oral antiviral therapy is recommended to complete a 10-day course.

Frequent reactivation of herpes simplex virus among HIV-1-infected patients treated with highly active antiretroviral therapy. Posavad CM, Wald A, Kuntz S, et al. J Infect Dis 2004; 190: 693–6.

In HIV-infected individuals, antiretroviral therapy reduced the frequency and severity of symptomatic genital herpes. However, frequent asymptomatic viral shedding occurred.

The anti-human immunodeficiency virus drug tenofovir, a reverse transcriptase inhibitor, also targets the herpes simplex virus DNA polymerase. Andrei G, Gillemot S, Topalis D, et al. J Infect Dis 2018; 217: 790–801.

Through selection of tenofovir (TFV)-resistant HSV mutants, this study demonstrated that TFV and PMEO-DAPy (6-phosphorylmethoxyethoxy-2,4-diaminopyrimidine, an acyclic nucleoside phosphonate with dual anti-HSV and anti-HIV activity) can be used for prophylaxis in HIV patients.

Sexually transmitted diseases treatment guidelines 2015. Centers for Disease Control and Prevention. MMWR Recomm Rep 2015; 64: 27–32.

Acyclovir, valacyclovir, and famciclovir are safe to use in immunocompromised patients. Treatment duration is generally for 5–10 days of the following: acyclovir 400 mg three times daily, famciclovir 500 mg twice daily, or valacyclovir 1 g twice daily. Intravenous therapy may be required in severe cases.

Second-Line Therapies

- Foscarnet **B**
- Cidofovir **A**

A multicenter phase I/II dose escalation study of single-dose cidofovir gel for treatment of recurrent genital herpes. Sacks SL, Shafran SD, Diaz-Mitoma F, et al. Antimicrob Agents Chemother 1998; 42: 2996–9.

A randomized, double-blind, clinic-initiated, sequential dose-escalation pilot study compared the safety and efficacy of single applications of 1%, 3%, and 5% cidofovir gel with placebo in the treatment of early lesional recurrent genital herpes. At all strengths, cidofovir significantly reduced the median time to negative virus culture in a dose-dependent fashion. Single-dose application of cidofovir gel confers a significant antiviral effect on lesions of recurrent genital herpes.

Clinical potential of the acyclic nucleoside phosphonates cidofovir, adefovir, and tenofovir in treatment of DNA virus and retrovirus infections. De Clercq E. Clin Microbiol Rev 2003; 16: 569–96.

The acyclic nucleoside phosphonate HPMPC (cidofovir) proved effective in vitro and in vivo against a wide variety of DNA viruses and retroviruses, including HSV-1 and 2.

Foscarnet treatment of acyclovir-resistant herpes simplex virus infection in patients with acquired immunodeficiency syndrome: preliminary results of a controlled, randomized, regimen-controlled trial. Hardy WD. Am J Med 1992; 92: 30s–5s.

Twenty-five patients with AIDS and acyclovir-resistant HSV infection were treated with foscarnet infusions for 2 weeks, followed by 8 more weeks either with 4 mg/kg daily or without further treatment. Lesions healed most quickly in those treated for a total of 10 weeks.

Third-Line Therapies

- Aspirin **B**
- Resiquimod **A**
- Topical imiquimod **E**

Aspirin in the management of recurrent herpes simplex virus infection. Karadi I, Karpatis S, Romics L. Ann Intern Med 1998; 128: 696–7.

This study showed that patients treated with aspirin 125 mg daily had significantly fewer days of active HSV infection than controls who took no antiviral or antiinflammatory drugs. Of the 21 subjects, only two had recurrent genital HSV; the remainder had recurrent oral HSV.

Topical resiquimod 0.01% gel decreases herpes simplex virus type 2 genital shedding: a randomized, controlled trial. Mark KE, Corey L, Meng TC, et al. J Infect Dis 2007; 195: 1324–31.

A randomized, double-blind, vehicle-controlled trial assessed the efficacy of resiquimod 0.01% gel for reducing human anogenital HSV-2 mucosal reactivation. Adults with genital HSV-2 applied topical resiquimod or vehicle to anogenital lesions twice weekly for 3 weeks. The median lesion and shedding rates were lower for the treatment group than in the vehicle group for both sampling periods. The length of recurrence was not influenced by resiquimod treatment.

Treatment of recalcitrant herpes simplex virus with topical imiquimod. Hirokawa D, Woldow A, Lee SN, et al. Cutis 2011; 88: 276–7.

In this case report, an HIV-positive man with valacyclovir-resistant genital HSV-2 was successfully treated with topical imiquimod 5% cream three times weekly for 8 weeks.

NOVEL AND OTHER THERAPIES

- Helicase-primase inhibitors
- Psychosocial counseling
- Hygiene techniques

Effect of pritelivir compared with valacyclovir on genital HSV-2 shedding in patients with frequent recurrence: a randomized clinical trial. Wald A, Timmler B, Magaret A, et al. JAMA 2016; 316: 2495–503.

This phase II, randomized, double-blind, crossover trial compared oral pritelivir, a novel HSV helicase-primase inhibitor, dosed at 100 mg once daily, to oral valacyclovir 500 mg once daily. The study demonstrated a significantly lower rate of genital HSV shedding and lesions in the pritelivir arm versus the valacyclovir arm. Pritelivir appears to be significantly more effective than valacyclovir, though further investigation into long-term safety and efficacy is needed.

Sexually transmitted diseases treatment guidelines 2015. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 2015; 64: 27–32.

Counseling of infected individuals serves to prevent sexual and perinatal infection and to help individuals cope with infection. Education for infected individuals seems to be of benefit both at the time of diagnosis and after resolution of the acute infection to further their understanding of the chronic nature of the disease.

Genital herpes: a review. Beaman JG, Maj MC. *Am Fam Phys* 2005; 72: 1527–34, 1541–2.

Prevention of secondary infection and spread of the infection can be achieved by keeping the affected area clean and dry, wearing loose-fitting clothing and cotton underwear, avoiding contact with the lesions, and washing hands immediately should contact with any sores occur.

PREVENTION

- Condoms
- Vaccine
- Disclosure to sexual partners

Serologic screening for genital herpes infection: US Preventive Services Task Recommendation Statement. US Preventive Services Task Force. *JAMA* 2016; 316(23): 2525–30.

An evidence review on the accuracy, benefits, and harms of serologic screening for HSV-2 infections was performed by the US Preventive Services Task Force. Routine serologic screening for genital HSV infection in asymptomatic adolescents, adults, and pregnant patients is not recommended.

A pooled analysis of the effect of condoms in preventing HSV-2 acquisition. Martin ET, Krantz E, Gottlieb SL, et al. *Arch Intern Med* 2009; 169: 1233–40.

This pooled analysis of over 5000 HSV-2-negative individuals at baseline showed that consistent use of condoms was associated with a 30% reduction in risk of acquiring HSV-2 compared with those with no condom use (HR of 0.70, 95% confidence interval (CI), 0.40–0.94, $p = 0.01$).

Knowledge of partners' genital herpes protects against herpes simplex virus type 2 acquisition. Wald A, Krantz E, Selke S, et al. *J Infect Dis* 2006; 194: 42–52.

This study utilized a time-to-event design to demonstrate that disclosure of genital herpes to an individual's partner increased the mean time to HSV-2 acquisition (270 days vs. 60 days, $p = 0.03$) compared with those who did not disclose their condition. Disclosure of infection to sexual partners has the potential to serve as a protective factor against HSV-2 transmission.

Effects of different doses of GEN-003, a therapeutic vaccine for genital herpes simplex virus-2, on viral shedding and lesions: results of a randomized placebo-controlled trial. Van Wagoner N, Fife K, Leone PA, et al. *J Infect Dis*. 2018; 218: 1890–9.

This phase II, randomized, placebo-controlled trial of a 3-dose series, GEN-003 (20 mcg of glycoprotein D from HSV-2 with alum and 3-O-deacylated monophosphoryl lipid A as an adjuvant) decreased viral shedding for up to 12 months, with the 60/50 and 60/75 doses representing the most promising combinations for further evaluation.

Therapeutic HSV-2 vaccine decreases recurrent virus shedding and recurrent genital herpes disease. Bernstein DI, Flechtner JB, McNeil LK, et al. *Vaccine* 2019; 37(26): 3443–50.

HSV-2 seropositive persons with genital herpes were randomized into cohorts. Three doses of GEN-003 or placebo were administered 21 days apart. This study found that the 60/50 dose demonstrated the maximal effect, warranting further evaluation.

Herpes labialis

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Herpes labialis (also known as 'cold sores') is characterized by recurrent vesicular eruptions primarily on the lips and perioral skin. The condition is contagious, can cause significant discomfort/pain, and can have an adverse effect on quality of life. Herpes labialis is caused by reactivation of herpes simplex virus type 1 (HSV-1). After a primary infection, HSV-1 establishes chronic latency within the trigeminal ganglion. When an appropriate trigger occurs, the virus reactivates, replicates in the trigeminal ganglion, descends along the sensory nerve axon to the perioral epithelium, and results in herpes labialis. A prodrome including irritation, pruritus, tingling, numbness, burning, and pain may occur at the site of future lesion development.

MANAGEMENT STRATEGY

Antiviral therapy shortens the duration of discomfort/pain, hastens healing, and reduces viral shedding, thereby reducing dissemination of HSV. Treatment should be initiated ideally in the prodromal stage and no later than 48 hours from the onset of lesions to obtain maximal clinical effect. Oral antiviral agents for herpes labialis include aciclovir, famciclovir, and valaciclovir and they are superior to topical antiviral agents. The metabolites of these nucleoside derivatives interfere with the synthesis of viral DNA. For episodic treatment, the recommended oral dose of aciclovir for children is 15 mg/kg (maximum 200 mg) and that for adults 400 mg five times a day for 5 days. Oral famciclovir and valaciclovir are alternate options for individuals ≥ 18 years and ≥ 12 years, respectively. Famciclovir and valaciclovir have greater oral bioavailability and are better absorbed than aciclovir and require less frequent dosing, but are more expensive. The recommended oral dose of famciclovir is 750 mg twice a day or a single dose of 1500 mg for 1 day and that of valaciclovir is 2000 mg twice a day for 1 day.

Topical antiviral agents such as 5% aciclovir cream/ointment alone or in combination with 1% hydrocortisone and 1% penciclovir cream are also available for the episodic treatment of herpes labialis. Topical aciclovir requires applications five times a day

whereas penciclovir requires applications nine times a day. The duration of treatment depends on the response to therapy. Topical aciclovir mucoadhesive buccal tablet once a day has also been shown to be effective.

Topical application of docosanol 10% cream five times daily has also been shown to be effective.

The use of intravenous aciclovir should be considered in immunocompromised patients and those with severe infections. The recommended dose of aciclovir is 5 mg/kg infused over an hour, delivered every 8 hours. The duration of treatment depends on the severity of symptoms and response to treatment.

Avoidance of known triggers such as emotional stress and ultraviolet radiation may diminish the number of recurrences. In patients with a history of solar-induced reactivation of herpes labialis, avoidance of sun exposure especially during hours of peak ultraviolet intensity (11 am–4 pm), regular use of broad-spectrum sunscreens, and wearing of protective wide-brimmed hats should be considered.

Chronic suppressive therapy with aciclovir or valaciclovir should be considered for patients with severe or frequent (six or more episodes per year) recurrences. The recommended oral dose of aciclovir is 400 mg 2–4 times a day and that of valaciclovir is 500 mg daily or twice a day. There is no data on the use of famciclovir for this purpose.

Other treatment modalities for the management and prevention of recurrent herpes labialis include laser therapy and photodynamic therapy.

Specific Investigations

- Real-time HSV polymerase chain reaction of specimen from mucocutaneous site
- Viral culture
- Direct fluorescent antibody testing
- Tzanck smear
- HSV serology

The diagnosis is mainly clinical. Laboratory investigations should be considered if the diagnosis is in doubt.

First-Line Therapies

• Oral aciclovir	A
• Oral famciclovir	A
• Oral valaciclovir	A

Efficacy and safety of nucleoside antiviral drugs for treatment of recurrent herpes labialis: a systematic review and meta-analysis. Chen F, Xu H, Liu J, et al. J Oral Pathol Med 2017; 46: 561–8.

A meta-analysis of 25 randomized controlled trials (RCTs) ($n = 8453$ patients) showed that both topical and systemic nucleoside antiviral agents decreased time to healing of all herpes labialis lesions and increased the percentage of aborted lesions. Oral antiviral agents were superior to topical antiviral agents and required less frequent applications. Oral valaciclovir was more effective than aciclovir in reducing the time of healing of all lesions and the time of resolution of pain.

Single-dose, patient-initiated famciclovir: a randomized, double-blind, placebo-controlled trial for episodic treatment of herpes labialis. Spruance SL, Bodsworth N, Resnick H, et al. J Am Acad Dermatol 2006; 55: 47–53.

An RCT for episodic treatment of herpes labialis ($n=701$) showed that single-dose famciclovir was as efficacious as single-day, twice-daily dosing in time to healing of herpes labialis lesions and was superior compared with placebo.

Oral acyclovir and herpes labialis: a randomized, double-blind, placebo-controlled study. Raborn GW, McGaw WT, Grace M, et al. *J Am Dent Assoc* 1987; 115: 38–42.

An RCT ($n=149$) showed oral acyclovir, 200 mg five times per day for 5 days, showed a significant antiviral effect in the treatment of herpes labialis, but that higher doses or a loading dose could improve its efficacy.

Treatment of recurrent herpes simplex labialis with oral acyclovir. Spruance SL, Stewart JC, Rowe NH, et al. *J Infect Dis* 1990; 161: 185–90.

In an RCT ($n=174$), patients treated with aciclovir 400 mg five times a day for 5 days had a decreased frequency of HSV culture-positive lesions, decreased duration of pain, and decreased duration of lesions compared with placebo.

High-dose, short-duration, early valacyclovir therapy for episodic treatment of cold sores: results of two randomized, placebo-controlled, multicenter studies. Spruance SL, Jones TM, Blatter MM, et al. *Antimicrob Agents Chemother* 2003; 47: 1072–80.

Two RCTs ($n=1247$) comparing the efficacy of valacyclovir administered upon the first prodromal symptoms of herpes labialis showed that the time to lesion healing and time to cessation of pain/discomfort were significantly reduced with valacyclovir compared with placebo, and that treatment for 1 day was as effective as treatment for 2 days.

Second-Line Therapies

• Topical aciclovir	A
• Topical aciclovir with hydrocortisone	A
• Topical penciclovir	A
• Topical aciclovir mucoadhesive buccal tablet	A

Acyclovir cream for treatment of herpes simplex labialis: results of two randomized, double-blind, vehicle-controlled, multicenter clinical trials. Spruance SL, Nett R, Marbury T, et al. *Antimicrob Agents Chemother* 2002; 46: 2238–43.

Two RCTs ($n=1385$) showed that topical application of 5% aciclovir cream five times daily for 4 days beginning within 1 hour of the onset of herpes labialis significantly reduced the duration of herpes labialis episodes and the duration of lesional pain.

Efficacy of topical 5% acyclovir-1% hydrocortisone cream (ME-609) for treatment of herpes labialis: a systematic review. Rosa MI, Souza SL, Farias BE, et al. *An Acad Bras Cienc* 2015; 87(2 Suppl): 1415–20.

A meta-analysis of two RCTs ($n=1213$) showed that treatment with a combination of 5% aciclovir and 1% hydrocortisone had a significant positive effect on developed ulcerative lesions in patients with herpes labialis (relative risk: 0.77; 95% confidence interval: 0.7–0.86; $p<0.001$).

Penciclovir cream for the treatment of herpes simplex labialis. A randomized, multicenter, double-blind, placebo-controlled trial. Topical Penciclovir Collaborative Study

Group. Spruance SL, Rea TL, Thoming C, et al. *JAMA* 1997; 277: 1374–9.

An RCT ($n=2209$) showed that topical application of 1% penciclovir cream decreased time to lesion healing, lesional pain, and viral shedding compared with patients treated with vehicle control cream.

Efficacy and safety of aciclovir mucoadhesive buccal tablet in immunocompetent patients with labial herpes (LIP Trial): a double-blind, placebo-controlled, self-initiated trial. Bieber T, Chosidow O, Bodsworth N, et al. *J Drugs Dermatol* 2014; 13: 791–8.

A multicenter RCT ($n=775$) showed that a single application of an aciclovir mucoadhesive buccal tablet (50 mg) significantly reduced the time to healing and the duration of herpes labialis episodes.

Third-Line Therapies

• Topical docosanol	A
• Intravenous aciclovir	A

Clinical efficacy of topical docosanol 10% cream for herpes simplex labialis: a multicenter, randomized, placebo-controlled trial. Sacks SL, Thisted RA, Jones TM, et al. *J Am Acad Dermatol* 2001; 45: 222–30.

A multicenter RCT ($n=370$) showed that topical application of docosanol 10% cream five times daily significantly reduced times from initiation of treatment to cessation of lesional symptoms and complete healing of lesions of herpes labialis.

Multicenter collaborative trial of intravenous acyclovir for treatment of mucocutaneous herpes simplex virus infection in the immunocompromised host. Meyers JD, Wade JC, Mitchell CD, et al. *Am J Med* 1982; 73: 229–35.

An RCT ($n=97$) of intravenous aciclovir in the treatment of immunocompromised patients with mucocutaneous herpes simplex infection showed that intravenous aciclovir significantly reduced periods of viral shedding, lesional pain, and healing of lesions.

Prophylactic Treatment

• Sunscreen	A
• Oral aciclovir	A
• Oral valacyclovir	A

Do sunscreen prevent recurrent herpes labialis in summer? Mazzaello V, Ferrari M, Piu G, et al. *J Dermatolog Treat* 2019; 30(2): 179–82.

A randomized crossover study performed on 20 adults who served as their own controls showed that in individuals with sun-block stick (SPF 30) protection, the number of herpes labialis attacks was significantly reduced.

Interventions for prevention of herpes simplex labialis (cold sores on the lips). Chi CC, Wang SH, Delamere FM, et al. *Cochrane Database Syst Rev* 2015; (8): CD010095.

A Cochrane meta-analysis of 32 RCTs ($n=2640$) showed that long-term use of oral aciclovir and valacyclovir had a modest beneficial effect in the prevention of recurrent herpes labialis.

OTHER THERAPIES

Efficacy of low-level laser therapy in management of recurrent herpes labialis: a systematic review. Al-Maweri SA, Kalakonda B, AlAizari NA, et al. *Lasers Med Sci* 2018; 33: 1423–30.

A systematic review of six clinical trials using low-level laser therapy found laser therapy was effective in the management and prevention of herpes labialis, without any adverse events. The wavelengths, power output, and energy density ranged between 632.5 and 870 nm, 5 and 80 W, and 2.04 and 48 J/cm², respectively. Because of the inconsistency in laser parameters and high variability in study designs, large-scale, well-designed RCTs with standardized laser parameters are warranted.

Efficacy of photodynamic therapy on the treatment of herpes labialis: a systematic review. Lotufo MA, Tempestini Horliana ACR, Santana T, et al. *Photodiagnosis Photodyn Ther* 2020; 29: 101536.

A systemic review of case reports and five studies showed that photodynamic therapy could be effective treatment for herpes labialis. The number of treated patients varied from two to six per article. Most studies used methylene blue as a photosensitizer, while one used 5-aminolevulinic acid. For light irradiation, most studies used laser while one used a red light from a halogen lamp. It is hoped that future, well-designed, large-scale RCTs will provide more information on the efficacy of photodynamic therapy in the treatment of herpes labialis.

Herpes zoster

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Reactivation of latent varicella zoster virus (VZV) produces the clinical syndrome herpes zoster (shingles), which manifests as a unilateral eruption along a single dermatome and is usually preceded by prodromal pain and paresthesia. The eruption lasts around 7–10 days and progresses from erythematous macules and papules to vesicles, then pustules, and finally crusts over. One of the most common complications of herpes zoster is postherpetic neuralgia (PHN), which is dermatomal pain persisting longer than 3 months.

MANAGEMENT STRATEGY

Early treatment – within the first 72 hours of vesicle formation – is important for antiviral efficacy, time to lesion healing, and minimizing zoster-associated pain (although initiating treatment after 72 hours may still be effective). *Aciclovir*, *valaciclovir*, and *famciclovir* are guanosine analogs that are phosphorylated by thymidine kinase to a triphosphate form that inhibits viral deoxyribonucleic acid (DNA) polymerase. The oral bioavailability of the antivirals determines the number of daily administrations. Patient compliance tends to decrease as the number of daily administrations increases. The most common side effects seen are headache and gastrointestinal upset, but these drugs are otherwise safe and well tolerated. Patients with renal insufficiency will need an adjusted dose, as these medications are excreted by the kidneys.

Aciclovir-resistant VZV infections have been reported in immunocompromised patients (i.e., acquired immune deficiency syndrome [AIDS], transplant patients), and in these cases *foscarnet*

(given intravenously 40 mg/kg three times daily) can be used as an alternative.

Acutely, *corticosteroids* may reduce zoster-associated pain, but they are associated with a risk of serious adverse events and have shown no benefit in reducing time to complete cessation of pain or prevention of PHN.

Pain management is especially difficult with conventional analgesics in zoster patients who develop PHN. Calcium channel $\alpha_2\text{-}\delta$ ligands (gabapentin and pregabalin), tricyclic antidepressants, opioids, topical lidocaine (Table 105.1), selective serotonin and norepinephrine reuptake inhibitors (duloxetine and venlafaxine), and topical capsaicin have been shown to reduce the pain associated with PHN. Of these medications, only gabapentin, pregabalin, 5% lidocaine patch, and 8% capsaicin patch have been approved by the Food and Drug Administration (FDA) specifically for the treatment of PHN. Adding gabapentin to an antiviral in patients with acute herpes zoster appears to significantly reduce the incidence of PHN. In January 2011, the FDA approved Gralise as a once-daily medication for the treatment of postherpetic neuralgia. Gralise is an extended-release form of gabapentin that not only has been shown to significantly decrease PHN pain scores but may also be associated with fewer side effects than its immediate-release counterpart. In 2012 the FDA approved Horizant, gabapentin enacarbil, for the once-daily therapy of PHN.

Vaccination of patients aged 50 years and over is the most promising option for preventing herpes zoster and, therefore, PHN. As of February 2020, there are two types of FDA-approved zoster vaccines. The first is Zostavax, a live attenuated varicella vaccine approved in 2006. The second is Shingrix, a recombinant zoster vaccine approved in 2017, which is the current recommended vaccine. Studies in adults aged 50 and older showed that five randomized controlled trials compared the live attenuated vaccine with the adjuvant recombinant subunit vaccine and placebo. Shingrix demonstrated a vaccine efficacy superior to both Zostavax and placebo (85% and 94%, respectively). In a clinical trial involving over 15,000 adults aged 50 or older, Shingrix reduced the risk of herpes zoster by 97.2%. However, there is an increased risk of injection site reactions with Shingrix compared with Zostavax. The Advisory Committee on Immunization Practices recommends two doses of Shingrix administered within 2–6 months for immunocompetent adults aged 50 years or older.

Specific Investigations

No investigation is usually required

- Tzanck smear
- Virology (culture, serology [acute plus chronic], electron microscopy, polymerase chain reaction)

First-Line Therapies

• Aciclovir 800 mg five times daily for 7 days	A
• Famciclovir 500 mg three times daily for 7 days	A
• Valaciclovir 1 g three times daily for 7 days	A

Valaciclovir compared with aciclovir for improved therapy for herpes zoster in immunocompetent adults. Beutner KR, Friedman DJ, Forszpaniak C, et al. *Antimicrob Agents Chemother* 1995; 39: 1546–53.

Table 105.1 Treatment options for postherpetic neuralgia

Drug class	Examples	Initial daily dose (mg)	Titration to maximum dose
Calcium channel $\alpha 2$ - δ ligands	Gabapentin	100–300	Start once at night and increase to three times daily dosing; increase by 100–300 mg every 3 days to total dose of 1800–2400 mg/day
	Gabapentin enacarbil		600 mg once daily in the morning for 3 days, then increase to 600 mg twice daily
Opioids	Pregabalin	150	Titrate up to 300 or 600 mg/day
	Hydrocodone	5–10	No titration
	Oxycodone (extended release)	20	Titrate up to 60 mg daily
Tricyclic antidepressants	Nortriptyline	10–25	Increase by 10–25 mg weekly, with a target dose of 75–150 mg daily; single dose or two divided doses
	Amitriptyline	10–25	Titrate up to 100 mg daily; single dose
	Desipramine	10–25	Increase every 3 days as needed up to 150 mg daily; single dose

Valaciclovir is comparable to aciclovir in the resolution of zoster eruption, but it accelerates the resolution of pain compared with aciclovir and is more convenient.

Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia. A randomized, double-blind, placebo-controlled trial. Tying S, Barbarash RA, Nahlik JE, et al. *Ann Intern Med* 1995; 123: 89–96.

Famciclovir recipients had faster resolution of pain after an acute episode than those receiving placebo.

Double-blind, randomized, aciclovir-controlled, parallel-group trial comparing the safety and efficacy of famciclovir and acyclovir in patients with uncomplicated herpes zoster. Shen MC, Lin HH, Lee SS, et al. *J Microbiol Immunol Infect* 2004; 37: 75–81.

Famciclovir is comparable to aciclovir in the resolution of zoster cutaneous eruption but is more convenient and had a more favorable adverse event profile.

A comparative study to evaluate the efficacy and safety of aciclovir and famciclovir in the management of herpes zoster. Gopal MG, Shannoma, Kumar S, et al. *Clin Diagn Res* 2013; 7: 2904–7.

Oral famciclovir given at 250 mg three times daily for 7 days is as effective as aciclovir 800 mg five times daily.

Second-Line Therapies

Agents to reduce postherpetic neuralgia

• Calcium channel $\alpha 2$ - δ ligands (gabapentin, pregabalin)	A
• Tricyclic antidepressants	A
• Lidocaine patch	A
• Oxycodone	A

Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Dworkin RH, Corbin AE, Young JP, et al. *Neurology* 2003; 60: 1274–83.

Pregabalin is effective in the treatment of pain and sleep interference associated with PHN.

Efficacy and safety of gabapentin 1800 mg treatment for postherpetic neuralgia: a meta-analysis of randomized controlled trials. Fan H, Yu W, Zhang Q, et al. *J Clin Pharm Ther* 2014; 39: 334–42.

A meta-analysis of randomized controlled trials found gabapentin 1800 mg significantly reduced postherpetic neuralgia up to 14 weeks. Treatment at this dose was safe up to 24 weeks. Comparison between once-daily and divided-dose gabapentin showed no significant difference in efficacy.

Incidence of postherpetic neuralgia after combination treatment with gabapentin and valaciclovir in patients with acute herpes zoster: open-label study. Lapolla W, Digiorio C, Haitz K, et al. *Arch Dermatol* 2011; 147: 901–7.

The addition of gabapentin to valaciclovir produced a significant reduction in PHN. Therefore, it is recommended that gabapentin be initiated in addition to antivirals for the treatment of acute zoster with moderate-to-severe pain at presentation.

Gabapentin versus nortriptyline in postherpetic neuralgia patients: a randomized, double blind clinical trial: the GONIP Trial. Chandra K, Shafiq N, Pandhi P, et al. *Int J Clin Pharmacol Ther* 2006; 44: 358–63.

Gabapentin and nortriptyline are equally efficacious, but gabapentin is better tolerated.

Topical lidocaine for the treatment of postherpetic neuralgia. Khaliq W, Alam S, Puri N. *Cochrane Database Syst Rev* 2007; 2: CD004846.

A meta-analysis combining two studies found that lidocaine is more effective than placebo, but there is insufficient evidence to recommend it as a first-line therapy. The studies cited in the review used 5% lidocaine gel applied for 8–24 hours or 5% lidocaine patch applied up to three times daily.

Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. Watson CPN, Babul N. *Neurology* 1998; 50: 1837–41.

Patients on slow-release oxycodone had significantly greater pain relief and reduction in allodynia and disability.

Third-Line Therapies

• Vaccination of adults	A
• Contact with varicella or with children	C
• Topical capsaicin	A
• Topical non-steroidal antiinflammatory cream	C
• Tramadol	A
• Sympathetic nerve block	B
• Transcutaneous electrical stimulation	B
• Methylcobalamin injection	B

A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. Oxman MN, Levin MJ, Johnson GR, et al. *N Engl J Med* 2005; 352: 2271.

A randomized, double-blind, placebo-controlled trial live attenuated Oka/Merck VZV vaccine enrolled 38,546 immunocompetent adults aged 60 years or over. The vaccine significantly reduced morbidity from herpes zoster and PHN.

Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. Lal H, Cunningham AL, Godeaux O, et al. *N Engl J Med* 2015; 372: 2087–96.

A clinical trial involving over 15,000 adults aged 50 or older showed that Shingrix reduced the risk of developing herpes zoster by 97.2%.

Efficacy, effectiveness, and safety of herpes zoster vaccines in adults aged 50 and older: systematic review and network meta-analysis. Tricco AC, Zarin W, Cardoso R, et al. *BMJ* 2018; 363: k4029.

A meta-analysis found Shingrix to have a vaccine efficacy of 94%, superior to both Zostavax and placebo. Shingrix also demonstrated a greater risk of adverse injection site reactions compared to Zostavax and placebo.

Family history and herpes zoster risk in the era of shingles vaccination. Hernandez PO, Javed S, Mendoza N, et al. *J Clin Virol* 2011; 52: 344–8.

The most important risk factor for development of zoster, after age and immune status, is a family history of shingles. Therefore, patients over age 50 with a family history of shingles should be particularly encouraged to receive the zoster vaccine.

Shingrix, a new recombinant zoster vaccine approved in 2017, is the current recommended vaccine for shingles in the US for healthy adults aged 50 and over.

Shingrix for herpes zoster: a review. Shah RA, Limmer AL, Nwannunu CE, et al. *Skin Therapy Lett* 2019; 24: 5–7.

Shingrix was approved by the US FDA in October 2017 as a herpes zoster prophylaxis.

Contacts with varicella or with children and protection against herpes zoster in adults: a case-controlled study. Thomas SL, Wheeler JG, Hall AJ. *Lancet* 2002; 360: 678–82.

Social contact with many children outside the household, or occupational contacts with children ill with chickenpox, results in a graded protection against zoster.

A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. Watson CP, Tyler KL, Bickers DR, et al. *Clin Ther* 1993; 15: 510–26.

Capsaicin 0.075% cream applied three to four times per day was effective. The only side effect was burning or stinging at sites of application.

Benzydamine cream for the treatment of postherpetic neuralgia: minimum duration of treatment periods in a cross-over trial. McQuay HJ, Carroll D, Moxon A, et al. *Pain* 1990; 40: 131–5.

Some patients benefit from 3% benzydamine hydrochloride cream applied six times daily.

Tramadol in postherpetic neuralgia: a randomized, double-blind, placebo-controlled trial. Boureau F, Legallier P, Kabir-Ahmadi M. *Pain* 2003; 104: 323–31.

A double-blind study with 127 patients found tramadol to be effective in reducing pain intensity and increasing the percentage of pain relief compared with placebo. All patients were treated for 6 weeks with doses ranging from 100 to 400 mg based on therapeutic response. Patients over 75 years of age received divided doses (morning and night); others received a single-dose regimen.

Neuraxial and sympathetic blocks in herpes zoster and postherpetic neuralgia: an appraisal of current evidence. Kumar V, Krone K, Mathieu A. *Regional Anesth Pain Med* 2004; 29: 454–61.

Sympathetic blocks for herpes zoster and PHN appear to be useful but require randomized, controlled trials for validation.

Modified Jaipur block for the treatment of post-herpetic neuralgia. Puri N. *Int J Dermatol* 2011; 50: 1417–20.

Subcutaneous injections of 2% Xylocaine and 0.5% bupivacaine in 4 mg/mL methylprednisolone can provide significant pain relief in persistent PHN. Approximately 90% of patients in a recent study experienced complete pain relief after three rounds of subcutaneous injections administered at 6-week intervals.

Transcutaneous electrical nerve stimulation for chronic postherpetic neuralgia. Ing MR, Hellreich PD, Johnson DW, et al. *Int J Dermatol*. 2015; 54: 476–80.

A randomized study of patients with PHN refractory to other medical treatments found that transcutaneous electrical nerve stimulation produced significantly reduced pain scores.

Comparison of the efficacy of continuous epidural block with epidural electrical stimulation and conventional continuous epidural block for management of zoster-associated pain beyond the acute phase: a retrospective study. Lee CH, Choi SS, Lee MK, et al. *Medicine (Baltimore)* 2019; 98: e17026.

A retrospective study demonstrated reduced subacute PHN using epidural block via electrical stimulation catheters.

Cryoanalgesia for postherpetic neuralgia: a new treatment. Calandria L. *Int J Dermatol* 2011; 50: 746–50.

Liquid nitrogen applied in a non-freezing manner can safely reduce PHN pain. In a recent study, 75% of patients reported a >70% reduction in pain after a total of five weekly sessions.

A single-center randomized controlled trial of local methylcobalamin injection for subacute herpetic neuralgia. Xu G, Lv ZW, Feng Y, et al. *Pain Med* 2013; 14: 884–94.

Local methylcobalamin injection was effective in relieving pain and discomfort caused by subacute herpetic neuralgia and was well tolerated.

Corticosteroids for preventing postherpetic neuralgia. Han Y, Zhang J, Chen N, et al. Cochrane Database Syst Rev 2013; 3: CD005582.

A systematic review and meta-analysis of randomized controlled trials found moderate-quality evidence that corticosteroids given acutely during herpes zoster infection are ineffective in preventing postherpetic neuralgia.

Hidradenitis suppurativa

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Hidradenitis suppurativa (HS) is a chronic relapsing skin disease, characterized by recurring flares of inflamed painful nodules, abscesses, tunnels, and scarring involving apocrine-bearing skin. Pain and suppuration cause considerable morbidity. The disease is associated with comorbidities and an increased all-cause mortality and risk of suicide. Associated with HS are anxiety, depression, obesity, smoking, polycystic ovarian disease, inflammatory bowel disease, pyoderma gangrenosum, spondyloarthropathy, arthritis, metabolic syndrome, dyslipidemia, psychiatric disorders, drug dependence, hypertension, diabetes, thyroid disease, alcohol dependence, and lymphoma.

MANAGEMENT STRATEGY

HS is a clinical diagnosis, based on the identification of morphology, location, and the chronic/recurrent nature of lesions. The morphology may include non-inflamed or inflamed nodules, abscesses, non-draining or draining tunnels (sinus tracts), and scars. The locations are bilateral and must involve one or more of these areas: axillae, inframammary area, groin (including genitals). No pathognomonic test exists. Preclinical follicular changes can be identified with ultrasound. Age of onset is usually in the third decade of life and is rare before puberty. An underlying endocrine disorder must be considered in prepubertal cases.

Outcome assessment includes pain, e.g., a numerical rating scale, such as 0–10; health-related quality of life, e.g., Dermatology Life Quality Index (DLQI) or Hidradenitis Suppurativa Quality of Life (HISQOL); symptoms, physical signs, e.g., the

International Hidradenitis Suppurativa Severity Score System (IHS4); and global assessment and progression.

Early lesions are mainly painful 'blind' boils, i.e., deep and rounded nodules. These may be transient and flare to become abscesses that either subside or transform into draining or non-draining tunnels. Gradually, postinflammatory scarring and tunnel formation occur in separate areas of the affected regions, and ultimately coalesce to form stage III lesions. Early lesions can remit without treatment. Tunnels and scars are not generally amenable to medical treatment and thus indicate the need for surgical intervention.

Clinically, HS can be distinguished from furunculosis (randomly occurring boils, and not limited to inverse areas) or epidermal cysts, solitary clinically stable lesions, pyogenic granulomas, and scarring folliculitis. Microbiology is most useful when presentations are atypical and in later stages of disease when superinfection may occur. If there is suspicion that a mimic of HS is present, for example, mycobacterial infection, squamous cell carcinoma, or Crohn disease, skin biopsies and/or additional relevant tests should be performed.

Current medical practice is mainly empirical. Several guidelines have been suggested for the management of HS. They all share the use of multimodal management, i.e., simultaneously using a three-pronged approach:

1. Adjuvant therapy, which includes pain management, treatment of established superinfections, weight loss, and tobacco cessation. Treatment of superinfections is directed by bacterial culture sensitivities. Appropriate bandaging of suppurating lesions and patient support groups are helpful.
2. Medical therapy, which may be topical in mild cases. *Topical clindamycin* has been shown to have an effect on early lesions. *Resorcinol 15% BD* can also be used as first-line treatment. Systemic tetracycline (500 mg BD) or doxycycline (100 mg BD) may be used as an alternative for severe/refractory disease. Cohort studies support coadministering *oral clindamycin 300 mg BD* and *rifampicin 300 mg BD* for limited HS. Smaller studies indicate that long-term intensive antibiotic treatment, e.g., the oral combination of *rifampin* (10 mg/kg once daily), *moxifloxacin* (400 mg once daily), and *metronidazole* (250–500 mg TD) (RMoM) for 6 weeks, followed by 4 weeks of RMo alone, then by *cotrimoxazole* after remission may provide long-term disease control in mild cases. Antibiotic resistance is frequent in the microbiota of HS patients and calls for more stringent antibiotic stewardship. For localized flares, *intralesional corticosteroids* (3–5 mg single dose) may provide significant pain relief within 24 hours. *Adalimumab* has been shown to be effective in moderate-to-severe HS when administered weekly (week 0: 160 mg; week 2: 80 mg; and from week 4: 40 mg weekly). Onset of effect has been shown to be at week 2 of treatment. A post hoc analysis of a smaller trial indicated that *infliximab* 5 mg/kg may also be effective. *Anakinra* (100 mg daily) and *apremilast* (30 mg BD) may also be effective. An open-label study of *ustekinumab* (45 mg or 90 mg based on patient weight) also indicated utility. Palliative medication includes systemic antiinflammatory drugs such as *oral corticosteroid*, *dapsone*, and *ciclosporin*. Patients may also benefit from *acitretin* 25 mg BD/TID, although this treatment is often limited by side effects and teratogenicity. HS shows little sign of improvement with isotretinoin. Hormonal therapy with *cyproterone acetate* may be helpful in some females but requires high and continued use, which raises safety concerns. A study found that *spironolactone* at doses ranging from 25 mg BD to 100 mg BD might be useful.
3. Surgery, from local to extensive, can be helpful. Milder cases can benefit from localized excisions or de-roofing (exteriorization)

of single tunnels. Only fluctuant soft abscesses should undergo lancing. Lancing of inflamed nodules is painful to the patient, is ineffective, and causes additional scarring. Non-fluctuant symptomatic lesions are better treated using intralesional corticosteroids. A CO₂ laser can be used to evaporate lesions. More advanced cases require major surgery, which should involve excision of the affected tissue or careful de-roofing of all tunnels. The recurrence rate is inversely proportional to the extent of surgery, and wide excisions generally offer a better chance of remission. Similarly, it is suggested that secondary intention healing is superior to primary closure of postexcisional wounds. Secondary healing requires longer periods of wound management, but generally does not preclude resumption of work 3–4 weeks after treatment.

Specific Investigations

Diagnosis is based on morphology, location, and chronicity/recurrence. Specific investigations may be necessary to rule out other diagnoses depending on clinical findings.

- GI workup if Crohn disease suspected
- Biopsy if squamous cell carcinoma suspected
- Culture and sensitivity

First-Line Therapies

- Antibiotics – topical clindamycin or oral tetracycline **B**
- Oral clindamycin and rifampin for 10 weeks **B**
- Surgery **B**
- Intralesional triamcinolone **D**

Topical treatment of hidradenitis suppurativa with clindamycin. Clemmensen OJ. *Int J Dermatol* 1983; 22: 325–8.

Topical clindamycin 0.1% BD topical clindamycin for 3 months was significantly more effective than placebo in early lesions.

A randomised trial of topical clindamycin vs. systemic tetracycline in hidradenitis suppurativa with special reference to disease assessment. Jemec GBE, Wendelboe P. *J Am Acad Dermatol* 1998; 39: 971–4.

No difference of efficacy between topical clindamycin 0.1% BD and oral tetracycline 250 mg (two tablets twice daily) for 3 months in 46 patients.

Combination therapy with clindamycin and rifampicin for hidradenitis suppurativa: a series of 116 consecutive patients. Gener G, Canoui-Poitaine F, Revuz JE, et al. *Dermatology* 2009; 219: 148–54.

Disease severity assessed by Sartorius score reduced by 50% after 10 weeks.

De-roofing: a tissue-saving surgical technique for the treatment of mild to moderate hidradenitis suppurativa lesions. van der Zee HH, Prens EP, Boer J. *J Am Acad Dermatol* 2010; 63(3): 475–80.

De-roofing appears to be a useful form of limited surgery for tunnels.

Recurrence of HS after surgical management: a systematic review and meta-analysis. Mehdizadeh A, Hazen PG, Bechara FG, et al. *J Am Acad Dermatol* 2015; 73(5 Suppl 1): S70–7.

Drainage alone carries a recurrence rate of up to 100%; radical excision has a recurrence rate of 25% at a median interval of 20 months. Success of surgery is affected by such variables as location, extent, and duration of disease.

Intralesional corticosteroid injections as a treatment option for acute lesions in patients diagnosed with hidradenitis suppurativa. Maini P, Posso-De Los Rios C, Gooderham M. *J Amer Acad Derm* 2015; 72 (Suppl 1): AB51.

A total of 33 (29%) patients received intralesional triamcinolone acetone injections at concentrations of 2.5 mg/mL (14.3%), 3.33 mg/mL (34.7%), 5.0 mg/mL (38.8%), or 10 mg/mL (12.2%) as treatment to control acute lesions. Only 6/25 (25%) female subjects treated with intralesional injections required concomitant systemic antibiotics during flare-ups. The mean follow-up duration was 10.1 months for females and 23.2 months for males. An 8-year experience involving intralesional triamcinolone injections effectively treated inflammatory HS and reduced the use of systemic antibiotics.

Second-Line Therapies

- 1064 nm (for prevention rather than treatment of lesions) surgery **B**
- CO₂ laser **B**
- Metformin **C**
- Acitretin **C**
- Quinolone with rifampin and metronidazole **C**
- Spironolactone **C**
- Topical resorcinol **C**

Prospective controlled clinical and histopathologic study of hidradenitis suppurativa treated with the long-pulsed neodymium:yttrium-aluminum-garnet laser. Mahmoud BH, Tierney E, Hessel CL, et al. *J Am Acad Dermatol* 2010; 62: 637–45.

In patients with milder disease, treated with topical benzoyl peroxide and clindamycin, weekly treatment with long-pulsed neodymium:yttrium-aluminum-garnet laser for months was significantly more effective than topical treatment alone.

Surgical treatment of chronic hidradenitis suppurativa: CO₂ laser stripping-secondary intention technique. Lapins J, Marcussan JA, Emtestam L. *Br J Dermatol* 1994; 131(4): 551–6.

CO₂ evaporation of diseased tissue under visual control, followed by secondary healing.

Metformin for the treatment of hidradenitis suppurativa: a little help along the way. Verdolini R, Clayton N, Smith A, et al. *J Eur Acad Dermatol Venereol* 2013; 27: 1101–8.

Open case series describing benefits of monotherapy using metformin, gradually increasing dosing up to 500 mg TID, and dosing for 24 weeks.

Acitretin treatment for hidradenitis suppurativa: a prospective series of 17 patients. Matusiak L, Bieniek A, Szepietowski JC. *Br J Dermatol* 2014; 171(1): 170–4.

Eight of 17 patients (47%) experienced benefit of 50 mg once daily for 9 months; relapses occurred 2–8 months after stopping therapy.

A study on the management of hidradenitis suppurativa with retinoids and surgical excision. Puri N, Talwar A. *Indian J Dermatol* 2011; 56(6): 650–1.

The relapse rate following surgery was reduced from 40% to 20% by subsequent treatment with acitretin.

Efficacy of rifampin–moxifloxacin–metronidazole combination therapy in hidradenitis suppurativa. Join-Lambert O, et al. *Dermatology* 2011; 222: 49–58.

In this retrospective study, 28 consecutive HS patients, including 6, 10, and 12 Hurley stage I, II, and III patients, respectively, were treated with a combination of rifampin (10 mg/kg once daily), moxifloxacin (400 mg once daily), and metronidazole (250–500 mg TID) (RMoM) for 6 weeks, followed by 4 weeks of RMo alone, then by cotrimoxazole after remission. Complete remission, defined as a clearance of all inflammatory lesions including hypertrophic scars, was obtained in 16 patients, including 6/6, 8/10, and 2/12 patients with Hurley stage I, II, and III after up to 12 months of treatment.

Antiandrogen therapy with spironolactone for the treatment of hidradenitis suppurativa. Golbari NM, Porter ML, Kimball AB. *J Am Acad Dermatol* 2019; 80: 114–9.

Retrospective case series of 46 women treated with spironolactone (average 75 mg spironolactone for 7 months) describing reduced lesion count, HS-PGA score, and pain.

Topical 15% resorcinol for hidradenitis suppurativa: an uncontrolled prospective trial with clinical and ultrasonographic follow-up. Pascual JC, Encabo B, Ruiz de Apodaca RE, et al. *J Am Acad Dermatol* 2017; 77: 1175–8.

Open prospective case series of 32 patients applying resorcinol BD to individual lesions for 30 days. Clinical and ultrasonographic (US) resolution was achieved in 21/32 (65.6%) lesions at day 30; however, six showed only clinical but not US resolution, and five lesions persisted both clinically and on ultrasound. The mean pain score was significantly reduced at day 7 and at day 30.

Third-Line Therapies

• TNF- α monoclonal antibodies	A
• IL-1 blockade	B
• Apremilast	B
• Ustekinumab	C
• Immunosuppressants	D
• IV antibiotics	D

Adalimumab for the treatment of moderate to severe hidradenitis suppurativa: a parallel randomized trial. Kimball AB, Kerdell F, Adams D, et al. *Ann Intern Med* 2012; 157(12): 846–55.

Significant effect of adalimumab 40 mg every week.

Two phase 3 trials of adalimumab for hidradenitis suppurativa. Kimball AB, Okun MM, Williams DA, et al. *N Engl J Med* 2016; 375: 422–44.

Two similar randomized controlled studies with a total of 633 patients enrolled comparing adalimumab week 0: 160 mg, week 2: 80 mg, and from week 4: 40 mg weekly with matched controls.

Response rates at week 12 were significantly higher for the groups receiving adalimumab weekly.

Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. Zouboulis CC, Okun MM, Prens EP, et al. *J Am Acad Dermatol* 2019; 80: 60–9.

Pooled results of the PIONEER phase 3 trials and an open-label extension study.

Responders and partial responders were evaluated. Response was maintained through week 168 in 52.3%–57.1%. Sustained improvement in lesion counts, skin pain, and DLQI score were also observed.

Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. Grant A, Gonzalez T, Montgomery MO, et al. *J Am Acad Dermatol* 2010; 62: 205–17.

A randomized controlled trial indicating effect of infliximab in post hoc analysis. With an initial placebo-controlled treatment phase of 8 weeks, patients were randomized to treatment with IFX (5 mg/kg) or placebo on weeks 0, 2, and 6. After week 8 and every 8th week until week 22, the patients crossed into a 30-week observational phase.

Safety and efficacy of anakinra in severe hidradenitis suppurativa: a randomized clinical trial. Tzanetakou V, Kanni T, Giatrakou S, et al. *JAMA Dermatol* 2016; 152(1): 52–9.

In this trial, 7/9 (78%) achieved clinical response in the actively treated group (100 mg daily) after 12 weeks.

Apremilast for moderate hidradenitis suppurativa: results of a randomized controlled trial. Vossen ARJV, van Doorn MBA, van der Zee HH, et al. *J Am Acad Dermatol* 2019; 80: 80–8.

Results showed that 8/15 (53%) achieved clinical response in the actively treated group (30 mg BD) after 16 weeks.

Ustekinumab in hidradenitis suppurativa: clinical results and a search for potential biomarkers in serum. Blok JL, Li K, Brodmerkel C, et al. *Br J Dermatol* 2016; 174: 839–46.

In this open-label study, 8/17 (47%) achieved clinical response at week 40 at dose 45/90 mg at weeks 0 and 12 and every 3 months.

Dapsone therapy for hidradenitis suppurativa: a series of 24 patients. Yazdanyar S, Boer J, Ingvarsson G, et al. *Dermatology* 2011; 222: 342–6.

Nine of 24 patients (38%) experienced benefits from therapy with dapsone.

Cyclosporine treatment of severe hidradenitis suppurativa – a case series. Anderson MD, Zauli S, Bettoli V, et al. *J Dermatol Treat* 2016; 27(3): 247–50.

Nine of 18 previously extensively treated patients (50%) experienced benefits from therapy with cyclosporin.

Histoplasmosis

Mahreen Ameen, Wanda Sonia Robles



Histoplasmosis is an endemic mycosis caused by a dimorphic fungus, *H. capsulatum*, of which there are two varieties that are pathogenic to humans. The most common variety worldwide is *H. capsulatum* var. *capsulatum*, which is highly endemic in the United States, particularly in the Mississippi and the Ohio valleys. *H. capsulatum* var. *duboisii* is endemic only in Central and West Africa (where it coexists with *H. capsulatum* var. *capsulatum*), and it is therefore sometimes referred to as African histoplasmosis. The infection is usually contracted through inhalation of spores in dry soil or bird or bat droppings. Disease progression and severity depend on the intensity of exposure to *H. capsulatum* and host immunity. There is a wide clinical spectrum of disease. Acute pulmonary disease is the most common presentation, and most cases are either asymptomatic or mild and self-limiting. Chronic pulmonary histoplasmosis, usually occurring in patients with underlying lung disease, produces cavities and later progression to pulmonary fibrosis. Haematogenous dissemination occurs within the first few weeks but resolves with the development of cell-mediated immunity to *H. capsulatum*. Progressive disseminated histoplasmosis occurs in the immunocompromised. Patient groups at risk include those with acquired immunodeficiency syndrome (AIDS), hematological malignancies, those on immunosuppressive therapy (including corticosteroids and tumor necrosis factor [TNF] antagonists), transplant recipients, and infants. Disseminated histoplasmosis is an AIDS-defining illness. It is usually a reactivation of prior infection and a sign of advanced immunosuppression, generally occurring in those with CD4 counts <150 cells/mm³.

Disseminated histoplasmosis can involve every organ system, most commonly presenting with hepatosplenomegaly and mucocutaneous lesions. Molluscum-like papules, nodules, or ulcerative lesions affect the skin, and are usually localized to the face, upper chest, and arms. Oropharyngeal ulcers affect the buccal mucosa, tongue, gingiva, lips, pharynx, and larynx. Histoplasmosis may also present to the dermatologist as a cause of erythema multiforme or erythema nodosum, which are thought to be a

hypersensitivity response to the *H. capsulatum* antigen. Rarely, primary cutaneous lesions may arise from direct inoculation.

MANAGEMENT STRATEGY

Pulmonary forms of histoplasmosis in the acute phase usually resolve spontaneously and only require treatment if symptoms persist for more than 1 month. Oral *itraconazole* is the treatment of choice for mild-to-moderate histoplasmosis. Severe pulmonary infection, disseminated histoplasmosis, and infection in the immunocompromised, particularly in association with AIDS, should be treated with *amphotericin B* (AmB) formulations (AmB deoxycholate, liposomal AmB, or AmB lipid complex). The lipid formulations carry a lower risk of nephrotoxicity but are more expensive. Treatment is commenced with AmB until there is clinical improvement, and then stepped down to oral itraconazole. *Fluconazole* and *ketoconazole* are second-line alternatives to itraconazole. Ketoconazole carries higher risks of adverse effects than the other azoles. The new triazoles, voriconazole and posaconazole, demonstrate *in vitro* activity against *H. capsulatum*, and have been successfully used in individual cases for different forms of histoplasmosis infection.

Patients with AIDS-related histoplasmosis who undergo antiretroviral treatment have better outcomes than those who are not treated with antiretrovirals. Some clinicians defer commencement of antiretroviral therapy until there is a reduction in fungal burden to avoid precipitating immune reconstitution inflammatory syndrome (IRIS). However, IRIS is a rare complication of histoplasmosis and is not usually severe. Therefore, others advocate early antiretroviral therapy to improve cellular immunity, a key defense against *H. capsulatum*.

Specific Investigations

- Culture
- Histology
- Serology
- Serology for human immunodeficiency virus (HIV) (where relevant)
- Imaging studies to detect disseminated disease (chest X-ray [CXR]/computed tomography [CT]/magnetic resonance imaging [MRI])

The gold standard method for diagnosing histoplasmosis is the isolation of *H. capsulatum* from culture. The use of several specimens (sputum, bronchoalveolar lavage, skin lesions, blood, bone marrow, or liver) for culture will increase the yield. Culture is highly specific but is limited by slow growth, and plates must be kept for as long as 12 weeks. Blood culture using the lysis-centrifugation system is more rapid and increases sensitivity. Histopathology is also more rapid, but its sensitivity is $<50\%$ in patients with disseminated disease, and even lower in pulmonary histoplasmosis. Biopsy specimens may demonstrate the distinctive 2–4-micrometer oval, narrow-based budding yeasts of *H. capsulatum*. Serological tests are rapid but may be falsely negative in immunosuppressed patients, and during the first 2 months following exposure while antibodies are still developing. In addition, elevated antibody titres persist for several years following initial infection. Antigen detection is a rapid means of diagnosis and can be useful in individuals who are immunocompromised when antibody production may be impaired. Sensitivity is greater with urine and plasma compared with other body fluids. Antigen quantitation enables treatment response to be monitored.

In disseminated disease, general laboratory tests will reveal a pancytopenia, hyperbilirubinemia, elevated liver enzyme and serum lactate dehydrogenase levels.

Histoplasmosis: up-to-date evidence-based approach to diagnosis and management. Hage CA, Azar MM, Bahr N, et al. *Semin Respir Crit Care Med* 2015; 36(5): 729–45.

This is a comprehensive and up-to-date review. Liposomal AmB is recommended for more severe cases and itraconazole for milder cases and ‘step-down’ therapy following response to AmB.

Histoplasmosis complicating tumor necrosis factor- α blocker therapy: a retrospective analysis of 98 cases. Vergidis P, Avery RK, Wheat LJ, et al. *Clin Infect Dis* 2015; 61(3): 409–17.

Disseminated histoplasmosis is a potential complication of anti-TNF- α therapy. This is a multicenter retrospective review of 98 patients diagnosed with histoplasmosis between 2000 and 2011. The most commonly used biologic agent was infliximab (67.3%). Based on these data the authors recommend that antifungal therapy is administered for at least 12 months. Thereafter resumption of TNF- α blocker therapy appears safe. They also conclude that disease outcomes were generally favorable.

HIV-associated histoplasmosis: current perspectives. Myint T, Leedy N, Cari EV, et al. *HIV AIDS* 2020; 12: 113–25.

This review outlines the impact of HIV on the prevalence and clinical manifestations of histoplasmosis. It assesses the clinical trial data of drug therapies for histoplasmosis in HIV-infected individuals. It recommends that liposomal AmB is given for 1–2 weeks followed by itraconazole for at least 1 year until CD4 counts are above 150 cells/mm³, HIV viral load is below 400 copies/mL, and *Histoplasma* urine antigen is negative. Serum itraconazole level should be monitored to avoid drug toxicity. Antigen should be measured periodically to establish that treatment is effective and to assist in identifying relapse. IRIS should be considered in patients failing antifungal treatment.

Treating progressive disseminated histoplasmosis in people living with HIV. Murray M, Hine P. *Cochrane Database Syst Rev* 2020; 4(4): CD013594.

This review concluded that liposomal AmB was a better choice compared with deoxycholate AmB for treating disseminated histoplasmosis in people with HIV. They concluded that fluconazole performed poorly compared with other azoles.

First-Line Therapies

• Amphotericin B	B
• Itraconazole	B

Disseminated histoplasmosis in patients with AIDS in Panama: a review of 104 cases. Gutierrez ME, Canton A, Sosa N, et al. *Clin Infect Dis* 2005; 40(8): 1199–1202.

In this study from Panama, the authors report that prior to the spread of AIDS, disseminated histoplasmosis was rarely seen. Now it is often the first manifestation of AIDS in this region, and must be suspected in anyone with fever, respiratory symptoms, weight loss, diarrhea, and a CD4 cell count <100 cells/microliter. Of 104 patients with AIDS-related disseminated histoplasmosis, 100 (96%) received AmB deoxycholate induction therapy, most receiving 1 g in total before being switched over to oral itraconazole. Forty patients had therapy-related adverse effects with hypokalemia reported in 50% and an increased creatinine level in 43%.

Itraconazole therapy for blastomycosis and histoplasmosis.

NIAID Mycoses Study Group; Dismukes WE, Bradsher RW Jr, Cloud GC, et al. *Am J Med* 1992; 93(5): 489–97.

This was a prospective, non-randomized, multicenter open trial where 37 patients with histoplasmosis received itraconazole 200–400 mg daily. After a median treatment period of 9 months, 81% ($n=30$) were cured. Treatment failure occurred only in those patients with chronic cavitary pulmonary disease. Minor adverse effects were experienced in 29% ($n=25$), requiring therapy withdrawal in only one patient.

Itraconazole treatment of disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trial Group; Wheat J, Hafner R, Korzun AH, et al. *Am J Med* 1995; 98: 336–42.

A multicenter, non-randomized prospective trial. Itraconazole 300 mg twice daily for 3 days followed by 200 mg twice daily was given for 12 weeks. Evaluation of 59 patients showed that 50 (85%) responded well to therapy. Five withdrew from the study because of progressive infection. One died within the first week of therapy, and two withdrew because of itraconazole-related adverse effects. Resolution of systemic symptoms occurred after a median of 3 weeks in the less severely affected, and 6 weeks in the moderately severe cases. Fungemia cleared after a median period of 1 week.

Itraconazole demonstrates efficacy in the treatment of mild disseminated histoplasmosis in patients with AIDS. For patients with moderately severe or severe histoplasmosis, AmB is the drug of first choice, which can be switched to itraconazole after clinical improvement.

Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. Johnson PC, Wheat LJ, Cloud GA, et al; US National Institute of Allergy and Infectious Diseases Mycoses Study Group. *Ann Intern Med* 2002; 137: 105–9.

A multicenter, randomized, controlled trial compared AmB deoxycholate with liposomal AmB for induction therapy of moderate-to-severe disseminated histoplasmosis in patients with AIDS. The trial demonstrated a higher response rate (88% vs. 64%) and lower mortality rate (2% vs. 13%) in patients who were treated with liposomal amphotericin ($n=51$) than with AmB deoxycholate ($n=22$). Infusion-related side effects were greater with AmB deoxycholate (63%) than with liposomal AmB (25%) ($p=0.002$). Nephrotoxicity was also higher with AmB deoxycholate (37%) than with liposomal AmB (9%) ($p=0.003$).

This study demonstrated that liposomal amphotericin is associated with higher efficacy, lower mortality, and better tolerance during induction treatment of disseminated histoplasmosis.

Safety of discontinuation of maintenance therapy for disseminated histoplasmosis after immunologic response to antiretroviral therapy. Goldman M, Zackin R, Fichtenbaum CJ, et al; AIDS Clinical Trials Group A5038 Study Group. *Clin Infect Dis* 2004; 38: 1485–9.

Traditionally, lifelong maintenance therapy with itraconazole had been the standard of care to reduce the risk of relapse of histoplasmosis infection. This was a prospective observational study to assess the safety of stopping maintenance therapy for disseminated histoplasmosis in patients with HIV infection after treatment with antiretroviral therapy. The study concluded that discontinuation of antifungal therapy after 12 months appears to be safe in patients with previously treated disseminated histoplasmosis that have sustained immunological improvement with antiretroviral therapy.

Disseminated histoplasmosis: a comparative study between patients with acquired immunodeficiency syndrome and non-human immunodeficiency virus-infected individuals. Tobón AM, Agudelo CA, Rosero DS, et al. *Am J Trop Med Hyg* 2005; 73(3): 576–82.

In this study of 52 patients with disseminated histoplasmosis, 30 patients had AIDS. Skin lesions were significantly higher in patients with AIDS, occurring in 53% of them ($p=0.001$). *H. capsulatum* was isolated more often in AIDS patients ($p<0.05$), but antibodies to *H. capsulatum* were detected more frequently in non-HIV patients ($p<0.05$). Itraconazole treatment was less effective in AIDS patients ($p=0.012$), but in this group, too, HAART improved the response to antifungals when compared with individuals who were not given HAART ($p=0.003$), who exhibited higher mortality rates ($p=0.025$). These results indicate the need to promote restoration of the immune system in patients with AIDS and histoplasmosis.

The authors highlight that the skin constitutes a more important target organ for *H. capsulatum* in HIV-infected Latin American patients than in HIV-infected North American patients.

Literature review and case histories of *Histoplasma capsulatum* var. *duboisii* infections in HIV-infected patients. Loulergue P, Bastides F, Baudouin V, et al. *Emerg Infect Dis* 2007; 13(11): 1647–52.

African histoplasmosis caused by *Histoplasma capsulatum* var. *duboisii* is much rarer than histoplasmosis caused by variety *capsulatum*, and its association with HIV infection is rarely reported. This article reports three such cases and reviews the literature on similar cases. All cases were successfully treated, initially with AmB, which was subsequently switched to itraconazole. Conventional amphotericin was given at a dose of 1 mg/kg daily (total dose of 1200 mg) and liposomal amphotericin at 3 mg/kg daily (for 1 month). Itraconazole was commenced at a dose of 400 mg daily (for 1–2 years) and switched to a maintenance dose of 200 mg daily after clinical cure. No clinical trials or efficacy studies have been performed for African histoplasmosis, and therefore its treatment is usually extrapolated from the guidelines of the Infectious Diseases Society of America established for histoplasmosis due to variety *capsulatum*.

Disseminated primary cutaneous histoplasmosis successfully treated with itraconazole. Singhi MK, Gupta L, Kachawa D, et al. *Indian J Dermatol Venereol Leprol* 2003; 69(6): 405–7.

Primary cutaneous histoplasmosis is rare. This is a report of a case of disseminated primary cutaneous histoplasmosis caused by *H. capsulatum* in an immunocompetent patient. The patient presented with a 2-year history of progressive erythematous nodules and plaques distributed mainly over the trunk. There was no evidence of systemic involvement. There was an excellent response to itraconazole 100 mg BD. Lesions began improving within 4 weeks and cleared within 16 weeks, and the total treatment period was 24 weeks. There was no recurrence 6 months after cessation of treatment.

Second-Line Therapies

• Ketoconazole	B
• Fluconazole	B
• Posaconazole	D
• Voriconazole	D
• Isavuconazole	E

Treatment of blastomycosis and histoplasmosis with ketoconazole. Results of a prospective randomized clinical trial. Dismukes WE, Cloud G, Bowles C and the National Institute of Allergy and Infectious Diseases Mycoses Study Group. *Ann Intern Med* 1985; 103(6 Pt 1): 861–72.

This was a multicenter, prospective, randomized trial evaluating the efficacy and toxicity of low-dose (400 mg/day) and high-dose (800 mg/day) oral ketoconazole in the treatment of histoplasmosis. Among 19 patients with chronic cavitary histoplasmosis treated for 6 months or more, both regimens were equally effective (overall success rate, 84%). In 20 patients with localized or disseminated histoplasmosis treated for 6 months or more, low-dose treatment was more effective (100% vs. 57% success rate, $p=0.03$). The success rate for all patients with histoplasmosis treated for 6 months or more was 85%. Adverse effects occurred in 60% of patients, and were commoner with the high-dose regimen. Ketoconazole is effective for non-life-threatening histoplasmosis in immunocompetent patients. Because of the higher frequency of side effects associated with the high dose, the authors suggested that ketoconazole therapy should be initiated at the lower dose.

With the availability of better-tolerated and new generation azoles, there are no recent studies evaluating ketoconazole therapy for histoplasmosis. However, it is still a drug that is commonly used in endemic settings, because of its availability and low cost.

Fluconazole therapy for histoplasmosis. The National Institute of Allergy and Infectious Diseases Mycoses Study Group. McKinsey DS, Kauffman CA, Pappas PG, et al. *Clin Infect Dis* 1996; 23(5): 996–1001.

Of the 27 patients enrolled in this trial, two had acute pulmonary histoplasmosis, 11 had chronic pulmonary histoplasmosis, and 14 had disseminated histoplasmosis. Twenty patients received fluconazole 400–800 mg/day, and seven patients received fluconazole 200 mg daily. Successful treatment was reported in 17 patients (63%). There were no significant adverse effects. The authors concluded that fluconazole was only moderately effective and should be reserved for patients intolerant to itraconazole.

Treatment of histoplasmosis with fluconazole in patients with acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases, Acquired Immunodeficiency Syndrome Clinical Trials Group and Mycoses Study Group. Wheat J, MaWhinney S, Hafner R, et al. *Am J Med* 1997; 103: 223–32.

This was a multicenter, open-label, non-randomized prospective trial. The aim of the study was to assess the efficacy and safety of fluconazole in patients with AIDS and mild-to-moderate disseminated histoplasmosis. The initial protocol of fluconazole 1200 mg on day one followed by 600 mg daily for 8 weeks demonstrated a high failure rate of 50%. The therapy schedule was revised to 1600 mg on day 1 followed by 800 mg daily for 12 weeks, and then maintenance therapy with 400 mg daily for at least 1 year. Seven patients failed to respond to induction therapy with progression of histoplasmosis leading to death in one patient. Two withdrew due to liver toxicity. Seventy-three percent (36/49 patients) responded but 30.5% (11/36) subsequently relapsed and one died. On the basis of historical comparison, maintenance therapy to prevent relapse with fluconazole 400 mg daily was less effective than itraconazole 200–400 mg daily or AmB 50 mg weekly.

Fluconazole may have a role in the treatment of non-AIDS-related histoplasmosis. However, this study of AIDS-related infection demonstrated a comparatively poor efficacy rate with even high-dose

fluconazole induction therapy, and an unacceptably high relapse rate with maintenance therapy.

Salvage treatment of histoplasmosis with posaconazole. Restrepo A, Tobón A, Clark B, et al. *J Infect* 2007; 54(4): 319–27.

Six patients with severe histoplasmosis infection were successfully treated with oral posaconazole (800 mg/day in divided doses) having previously failed on AmB, itraconazole, fluconazole, or voriconazole. One patient had pulmonary disease and the rest had disseminated infection. Treatment duration ranged from 6 to 34 weeks. Significant clinical improvement was noted within the first month of treatment.

Although the patient numbers are small, this study suggests that posaconazole may be a useful treatment option for disseminated histoplasmosis refractory to other drug therapies

Voriconazole use for endemic fungal infections. Freifeld A, Proia L, Andes D, et al. *Antimicrob Agents Chemother* 2009; 53(4): 1648–51.

Nine patients with mostly disseminated histoplasmosis who had either failed or were intolerant of AmB and itraconazole were treated with voriconazole 200–400 mg daily. All of them improved or remained clinically stable after treatment and responses were apparent within the first 2 months of voriconazole initiation. However, two of the patients whose response was 'stable' had to discontinue treatment because of high costs of treatment. The others received treatment from 31 to 640 days.

HIV-associated disseminated histoplasmosis successfully treated with isavuconazole consolidation therapy. Mazzella A, Stone NRH, Pool ERM, et al. *Med Mycol Case Rep* 2019; 27: 42–3.

A 30-year-old man with advanced HIV and disseminated histoplasmosis deteriorated after stepping down from intravenous liposomal AmB to itraconazole. Liposomal AmB was reintroduced and step-down treatment was successfully switched to oral isavuconazole 200 mg daily given as long-term maintenance treatment.

Isavuconazole, one of the new antifungal azoles, has a broader pathogen spectrum and is increasingly being used in fungal infections refractory to other antifungals.

Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Wheat LJ, Freifeld AG, Kleiman MB, et al.; Infectious Diseases Society of America. *Clin Infect Dis* 2007; 45(7): 807–25.

Evidence-based guidelines for the management of patients with histoplasmosis.

Mild Acute Pulmonary Histoplasmosis

Treatment is usually unnecessary unless symptoms persist for more than 1 month, when itraconazole is given at a loading dose

(200 mg three times daily for 3 days) followed by 200 mg once or twice daily for 6–12 weeks.

Severe Acute Pulmonary Histoplasmosis

Parenteral AmB (deoxycholate formulation, 0.7–1.0 mg/kg daily, or lipid formulation, 3.0–5.0 mg/kg daily) for 1–2 weeks followed by 'step-down' itraconazole therapy, with an initial loading dose and then 200 mg twice daily for a total of 12 weeks.

Chronic Cavitary Pulmonary Histoplasmosis

Itraconazole, initial loading dose and then 200 mg once or twice daily for at least 12 months.

Mild Disseminated Histoplasmosis

Itraconazole, initial loading dose and then 200 mg twice daily for at least 12 months.

Severe Disseminated Histoplasmosis

AmB (doses as above for severe pulmonary infection) for 1–2 weeks followed by oral itraconazole, initial loading dose and then 200 mg twice daily for at least 12 months.

Central Nervous System Histoplasmosis

Liposomal AmB (5.0 mg/kg daily for a total of 175 mg/kg given over 4–6 weeks) followed by itraconazole 200 mg two or three times daily for at least 1 year and until resolution of cerebrospinal fluid (CSF) abnormalities, including *Histoplasma* antigen levels.

Treatment of Histoplasmosis in Pregnancy

Azoles are teratogenic and therefore AmB is recommended.

Immunosuppressed patients may require lifelong suppressive therapy with itraconazole (200 mg daily) if immunosuppression cannot be reversed. For those on long-term itraconazole therapy, blood itraconazole levels need to be measured 2 weeks after initiation of treatment. Women of childbearing age who are being treated with azoles need to use effective contraception during treatment and for 2 months after the drug is stopped.

An official American Thoracic Society statement: treatment of fungal infections in adult pulmonary and critical care patients. Limper AH, Knox KS, Sarosi GA, et al.; American Thoracic Society Fungal Working Group. *Am J Respir Crit Care Med* 2011; 183(1): 96–128.

The American Thoracic Society convened a working group of experts in fungal infections to develop a concise clinical statement of current therapeutic options. The document discusses drug therapy for the different manifestations of histoplasmosis including asymptomatic as well as symptomatic lung disease in immunocompetent hosts and disease in immunocompromised hosts.

Hydroa vacciniforme

Hiva Fassihi, Robert P.E. Sarkany



Hydroa vacciniforme (HV) is a photosensitive dermatosis mainly found in children. It is rare in Europe and the United States, and more common in Asia and South America. It is one of the group of diseases caused by chronic active Epstein-Barr virus (EBV) infection. It is now grouped within the spectrum of diseases known as 'HV EBV-associated lymphoproliferative disorder' (HV EBV-associated LPD).

MANAGEMENT STRATEGY

Onset is generally in childhood between the ages of 5 and 8 years. It is characterized by sun exposure-induced eruptions of vesicular, bullous, and pustular lesions that leave scarring. Lesions develop a few hours after sun exposure, with itchy erythema, progressing over a few days to painful papules and then umbilicated vesicles that crust, and heal with scarring. The cheeks, ears, nose, and dorsum of the hands are the most commonly affected sites. Eye involvement is rare.

Differential diagnosis includes vesicular polymorphic light eruption, actinic prurigo, bullous photosensitive lupus erythematosus, and erythropoietic protoporphyria. However, HV differs from all these conditions, and the clinical diagnosis is usually clear cut.

The photosensitivity and scarring may be severe with a major impact on quality of life.

The rarity of HV explains the lack of large or randomized trials. Recommendations for treatment are based on evidence from case series and single case reports.

Photoprotection is crucial in this disease, which is resistant to specific treatments in most patients. Key measures include restriction of sun exposure, wearing ultraviolet (UV)-protective clothing, regular application of a broad-spectrum sunscreen containing an effective UVA filter, and covering windows in the car and home with films that filter out UV wavelengths below 380 nm.

In patients with the most severe photosensitivity, courses of narrowband UVB (NB-UVB) phototherapy or psoralen with UVA (PUVA) (usually twice weekly for 4–6 weeks as administered for polymorphic light eruption) may help. Phototherapy must be given cautiously to avoid provoking a flare.

More recently *antivirals* have been considered in view of the causative role of EB virus. A small case series has suggested that this may reduce photosensitivity, but the experience of the authors (HF and RS) is less positive.

Antimicrobial therapy has been tried, as have *antimalarials*. Systemic immunosuppressants (intermittent oral corticosteroids, azathioprine, and ciclosporin) have been tried in HV; however, none are reliably effective, and we do not recommend their use since they may be hazardous in chronic active EB virus infection. *β-Carotene*, used in several studies, has mostly been ineffective.

Dietary fish oil rich in omega-3 polyunsaturated fatty acids was associated with clinical improvement in a small number of patients in four older reports.

All HV is caused by chronic active EBV infection of NK or $\gamma\delta$ -T cells. HV is now grouped within the spectrum of diseases known as "HV EBV-associated lymphoproliferative disorders" (HV-LPD).

The higher incidence of HV-LPD in Asia and South America reflects the higher incidence of chronic active EBV infection (CAEBV) of T- and NK-cell types in these populations.

CAEBV infection of NK or $\gamma\delta$ -T cells causes a spectrum of severe lymphoproliferative diseases. The only diseases involving the skin are the 'hypersensitivity to mosquito bites' syndrome and 'classic' and 'severe' HV.

'Severe' HV has a similar eruption to 'classic' HV, but involvement of non-exposed skin, facial edema, and deep ulceration are common, and some patients develop 'hypersensitivity to mosquito bites' (necrotic and systemic reactions to insect bites). 'Severe' HV is a systemic illness with a bad prognosis, usually requiring treatment with allogeneic bone marrow transplantation.

The major determinant of prognosis is ethnicity. White children from the United States and Europe are unlikely to progress from 'classic' HV to 'severe' HV. Asian and Hispanic patients are likely to develop the severe disease with systemic involvement.

All patients with HV should be reviewed at least every 6 months for systemic involvement.

HV patients should be managed jointly with an infectious disease or haemato-oncology specialist. If that is not possible, they must be referred to such a specialist if any features are identified, suggesting possible transformation from 'classic HV' to a less benign EBV-associated disorder.

Specific Investigations at Presentation

- Monochromator phototesting and photoprovocation testing with UVA (*increased sensitivity to UVA in half the patients*)
 - Serological testing for antinuclear antibody and antibodies to extractable nuclear antigens (*to exclude bullous lupus erythematosus*)
 - Red cell porphyrin measurement (*to exclude erythropoietic protoporphyria*)
 - EBV viral load measurement from whole blood
- Skin biopsy is not usually required

Table 108.1 Prognostic assessment

Clinical variant's name	Cause	Incidence	Clinical features	Key predisposing factor	Prognosis	Treatment
Classic HV	Chronic active EBV infection of NK or $\gamma\delta$ -T cells	Rare: United States and Europe	Childhood presentation: photosensitive eruption (no systemic involvement)	Ethnicity: White children from United States and Europe	Good: general health unaffected. Often resolves by early adulthood	Treatment of photosensitivity
Severe HV	Chronic active EBV infection of NK or $\gamma\delta$ -T cells	Common: mainly Asia and Latin America	Childhood presentation: photosensitive eruption + • non-exposed skin affected • facial edema • deep ulceration • 'hypersensitivity to mosquito bites' (necrotic and systemic reactions to insect bites) • systemic features: • persistent fever • weight loss • lymphadenopathy • hepatosplenomegaly • hepatitis • leukopenia	Ethnicity: Asian and Hispanic patients	Poor: life-threatening systemic illness	Allogeneic bone marrow transplantation

Table 108.2 HV: 6-monthly review for systemic involvement**Ask about:**

- Severe cutaneous or systemic reactions to insect bites
- Persistent unexplained fever
- Unexplained weight loss
- Other unexplained health problems

Examine for:

- Facial swelling
- Skin ulcers
- Involvement of non-exposed skin
- Pyrexia
- Lymphadenopathy
- Hepatosplenomegaly

Investigations:

- EB viral load in blood (looking for significant upward trend)
- Full blood count: for leukopenia or other abnormality
- Abdominal ultrasound scan: once every 3 years (looking for hepatosplenomegaly)

Epstein-Barr virus-associated T- and NK-cell lymphoproliferative diseases: an update and diagnostic approach. Hue SS, Oon ML, Wang S, et al. *Pathology* 2020; 52: 111–27.

A review discussing the range of EBV-associated T- and NK-cell lymphoproliferative disorders. 'Hypersensitivity to mosquito bites' is classified with HV-LPD in the 'indolent/variable outcome group'.

Chronic EBV infection of T and NK cells also causes 'EBV-associated hemophagocytic lymphohistiocytosis' (with life-threatening immunological hyperactivation), leukemias, and lymphomas.

EBV involvement in the pathogenesis of hydroa vacciniforme: an assessment of seven adult patients with long-term follow-up. Verneuil L, Gouarin S, Comoz E, et al. *Br J Dermatol* 2010; 163: 174–82.

Chronic active EBV infection was present in and persisted long term in adult HV patients.

Hydroa vacciniforme is associated with increased numbers of EBV-infected $\gamma\delta$ T cells. Hirai Y, Yamamoto T, Kimura H, et al. *J Invest Dermatol* 2012; 132: 1401–8.

All 29 HV patients had raised levels of EBV DNA in peripheral blood mononuclear cells. Of 33 biopsied skin lesions, 31 contained EBER+ T cells.

Hydroa vacciniforme: a review of ten cases. Sonnex TS, Hawk JL. *Br J Dermatol* 1988; 118: 101–8.

A study of 10 White children in England. The disease resolved in two patients (mean disease duration 12 years) and slowly improved in another two. None developed systemic ill health.

Hydroa vacciniforme: a clinical and follow-up study of 17 cases. Gupta G, Man I, Kemmett D. *J Am Acad Dermatol* 2000; 42: 208–13.

A study of 17 White children with HV in Scotland. Spontaneous remission occurred in nine of the 17 patients after a mean period of 9 years. Disease prevalence in the Scottish population was estimated at 0.34/100,000.

Hydroa vacciniforme-like lymphoproliferative disorder: an EBV disease with a low risk of systemic illness in whites. Cohen JL, Manoli I, Dowdell K, et al. *Blood* 2019; 133: 2753–64.

Accompanying commentary: deciphering hydroa vacciniforme. Quintanilla-Martinez L, Fend F. *Blood* 2019; 133: 2735–37.

A study of 16 patients, 10 with 'classic' HV and six with 'severe' HV. All 16 had very high blood levels of EBV DNA in blood. Ethnicity correlated with disease severity. All 10 White patients were in good health at the end of follow-up, whereas four of the six non-White patients (Asian or Hispanic) had been treated with hematopoietic stem cell transplantation for severe systemic disease and persistent fever (accompanied by lymphoma in two patients).

This study explains the difference between cases of HV reported in Europe and in Asia/South America. Ethnic differences among patients determine whether chronic active EBV infection of T and NK cells causes the benign photodermatosis 'classic HV' or the severe systemic illness 'severe HV'. The features associated with the poor prognosis and systemic involvement of severe HV are reinforced.

Hydroa vacciniforme: a review of ten cases. Sonnex TS, Hawk JLM. *Br J Dermatol* 1988; 118: 101–8.

Monochromator phototesting responses were abnormal in three of the 10 patients with increased photosensitivity to UVA.

Hydroa vacciniforme: a clinical and follow-up study of 17 cases. Gupta G, Man I, Kemmett D. *J Am Acad Dermatol* 2000; 42: 208–13.

Nine of the 17 patients showed increased sensitivity to UVA on monochromator phototesting.

Action spectrum for UV erythema and reproduction of the skin lesions in hydroa vacciniforme. Sunohara A, et al. *Photodermatol* 1988; 5: 139–45.

Vesicles were successfully reproduced by repeated daily monochromatic irradiations of 330, 340, 350, and 360 nm for 5, 6, or 7 days in four HV patients.

First-Line Therapy for Photosensitivity

- High-factor, broad-spectrum sunscreens and behavioral sunlight avoidance

C

Hydroa vacciniforme: a clinical and follow-up study of 17 cases. Gupta G, Man I, Kemmett D. *J Am Acad Dermatol* 2000; 42: 208–13.

In 9 of 15 patients the disease was controlled satisfactorily with high-factor, broad-spectrum sunscreens and sunlight avoidance.

Hydroa vacciniforme: a review of ten cases. Sonnex TS, Hawk JLM. *Br J Dermatol* 1988; 118: 101–8.

Disease severity was reduced in 8 of 10 patients using either Coppertone Supershade 15 or RoC factor 10.

The sunscreens described do not meet current standards. Modern sunscreens now offer broad-spectrum protection against UVB and UVA.

Borrowing from museums and industry: two photo-protective devices. Dawe R, Russell S, Ferguson J. *Br J Dermatol* 1996; 135: 1016–7.

The Museum 200 Film (manufactured by Sun Guard, Florida, United States) prevents transmission of all wavelengths less than 380 nm. This clear, lightweight film can be stuck on any glass surface without being visible. It may be useful in HV but will be less helpful in patients sensitive in the 380–400 nm waveband.

Second-Line Therapies for Photosensitivity

- NB-UVB phototherapy (TL-01)
- PUVA
- Aciclovir/valaciclovir

C

D

D

Hydroa vacciniforme: a clinical and follow-up study of 17 cases. Gupta G, Man I, Kemmett D. *J Am Acad Dermatol* 2000; 42: 208–13.

Five patients who had not responded to photoprotective measures were treated with NB-UVB phototherapy: three had good or moderate disease control, and two had no response.

Hydroa vacciniforme: a review of ten cases. Sonnex TS, Hawk JLM. *Br J Dermatol* 1988; 118: 101–8.

Two of the 10 patients were treated with UVB and had improvement of their disease. There was a flare in the one patient treated with PUVA.

Broadband UVB was probably used in this report, though the methodology is unclear.

Narrow-band UVB (TL-01) phototherapy: an effective preventative treatment for the photodermatoses. Collins P, Ferguson J. *Br J Dermatol* 1995; 132: 956–63.

An open clinical trial of a standard regimen of narrowband UVB desensitization. Two of four HV patients reported an increase in tolerance to sunshine from 1 hour to 3–6 hours.

Antiviral therapy in children with hydroa vacciniforme. Lysell J, Wiegleb Edström D, Linde A, et al. *Acta Derm Venereol* 2009; 89: 393–7.

Four children with HV were treated with aciclovir and one also treated with valaciclovir therapy. All four reported improvement in photosensitivity, although one developed EBV-related lymphoma during treatment.

Antiviral treatment of a boy with EBV-associated hydroa vacciniforme. Pahlow Mose A, Fisker N, Clemmensen O, et al. *BMJ Case Rep* 2014. doi: 10.1136/bcr-2014-206488.

Marked improvement of EBV-associated HV photosensitivity reported in a 6-year-old boy treated initially with aciclovir, followed by valaciclovir.

The personal (unpublished) experience of the authors (HF and RS) of antiviral therapy in four patients with HV is less favorable.

Third-Line Therapies for Photosensitivity

- Antimalarials
- β -Carotene
- Dietary fish oil
- Antiinflammatory agents

D

E

E

E

Hydroa vacciniforme: diagnosis and therapy. Goldgeier MH, Nordlund JJ, Lucky AW, et al. *Arch Dermatol* 1982; 118: 588–91.

Treatment with hydroxychloroquine sulfate, but not indomethacin, reduced photosensitivity to sunlight and to artificial UV-A irradiation in one patient.

Hydroa vacciniforme: an unusual clinical manifestation. Leenutaphong V. *J Am Acad Dermatol* 1991; 25: 892–5.

One patient treated with chloroquine phosphate 500 mg daily did not find it helpful.

Hydroa vacciniforme. Ketterer R, Morier P, Frenk E. *Dermatology* 1994; 189: 428–9.

One patient treated with chloroquine 100 mg daily and broad-spectrum sunscreen showed good disease control.

It is unclear whether the response was due to chloroquine or the sunscreen.

Hydroa vacciniforme. Bickers DR, Demar LK, DeLeo V, et al. *Arch Dermatol* 1978; 114: 1193–6.

Two patients reported an improvement of the skin disease with β -carotene 180 mg daily.

Hydroa vacciniforme: induction of lesions with ultraviolet A. Halasz CLG, Leach EE, Walther RR, et al. *J Am Acad Dermatol* 1983; 8: 171–6.

One patient treated with β -carotene 180 mg daily reported subjective improvement of skin disease.

Hydroa vacciniforme: diagnosis and therapy. Goldgeier MH, Nordlund JJ, Lucky AW, et al. *Arch Dermatol* 1982; 118: 588–91.

β -Carotene 120 mg daily for 2 months in one patient was ineffective.

Hydroa vacciniforme treated by a combination of beta-carotene and canthaxanthin. Bruderer P, Shahabpour M, Christoffersen S, et al. *Dermatology* 1995; 190: 343–5.

One patient reported improvement with carotenoids (10 mg of β -carotene and 15 mg of canthaxanthin).

Efficacy of ω -3 polyunsaturated fatty acids for the treatment of refractory HV. Durbec F, Reguiai Z, Léonard F, et al. *Pediatr Dermatol* 2012; 29: 118–9.

One patient was successfully treated with dietary fish oil after unsuccessful treatment with other measures.

Dietary fish oil as a photoprotective agent in hydroa vacciniforme. Rhodes LE, White SI. *Br J Dermatol* 1998; 138: 173–8.

Three patients were treated with dietary fish oil, five capsules daily, for 3 months. A mild-to-good improvement was reported in two patients, but no improvement in the third.

Hydroa vacciniforme: dietary fish oil. Modeste AB, Cordel N, Balguerie X, et al. *Ann Dermatol Venereol* 2001; 128: 247–9.

A 15-year-old girl unresponsive to antimalarial drugs and photoprotection was treated with Maxepa and her skin lesions regressed within a few weeks. The treatment was stopped at the patient's request due to fetid breath.

Fish oil rich in omega-3 polyunsaturated fatty acids are thought to reduce inflammation by increasing the level of omega-3 polyunsaturated fatty acids in the epidermis and reducing the level of prostaglandins in the skin.

Two cases of hydroa vacciniforme-like lymphoproliferative disease controlled by anti-inflammatory agents. Kim YJ, Choi SY, Lee WJ, et al. *Photodermatol Photoimmunol Photomed* 2017; 33: 287–90.

One patient treated with sunscreen and minocycline 50 mg twice daily for 6 months reported improvement in skin lesions. A second patient treated with topical pimecrolimus cream 1% twice daily and sunscreen reported improvement after 3 months.

Hyperhidrosis

Michael E. Farrugia, Gina M. Kavanagh



Hyperhidrosis is a condition characterized by abnormally increased perspiration, beyond that required for thermoregulation. It may indicate an underlying medical disorder, but more commonly it is idiopathic and results in significant deterioration in quality of life, psychologically and socially. Sufferers typically describe the condition as highly embarrassing and frustrating.

Primary hyperhidrosis is idiopathic and is the more common form, affecting 90% of sufferers. It is typically localized to specific body areas, bilateral and symmetrical. One patient may have multiple focal areas affected. It tends to worsen with stress and heat (including local occlusion). Onset typically occurs in puberty and a family history of the condition is present in some 60% of cases. Hyperhidrosis does not usually occur during sleep, and further investigation is usually not necessary. The most commonly affected site is the axilla, followed by the palms and soles (the latter often complicated by bromhidrosis). Craniofacial involvement is seen more commonly in postmenopausal women. Other sites include the groin, buttocks, and inter- and inframammary folds. Stump amputee focal hyperhidrosis is largely due to inability of sweat to evaporate through the prosthesis silicone lining and can make wearing of prosthetic limbs very difficult.

Secondary hyperhidrosis may be generalized or localized and is less common, affecting 10% of sufferers. See [Table 109.1](#) for some causes of secondary hyperhidrosis.

MANAGEMENT STRATEGY

The treatments discussed here apply to primary idiopathic hyperhidrosis. Therapy for secondary hyperhidrosis should be directed

toward the underlying condition. Simple conservative measures can be advocated as an adjunct to treatment:

- Acknowledging what a difficult condition this can be is often validating
- Inform the patient about support groups such as *Hyperhidrosisuk.org* or *SweatHelp.org*
- Provide advice regarding practical measures such as:
 - wear absorbent underlayers such as loose-fitting cotton T-shirts
 - use adhesive underarm pads or absorbent insoles
 - wear cotton socks with leather shoes and, if necessary, change socks and shoes throughout the day

The evidence on all of the following treatments is of limited quality and predominantly comprises small, non-randomized, retrospective, observational studies and case series with a high risk of bias. Nevertheless, many patients respond well to available treatments and current recommendations are based on expert consensus. Plantar hyperhidrosis, as well as inframammary, groin, and buttock hyperhidrosis, may be complicated by secondary bacterial and fungal overgrowth and may require additional topical treatment.

Topical aluminum chlorohydrate ($Al_2Cl(OH)_6$) *antiperspirants* are the first-line treatment. Aluminum-based complexes react with the electrolytes in sweat to form a gel plug causing a functional inability of the gland to produce sweat. Correct application technique is crucial: in the axillae, the solution should be applied at night to unshaven skin and washed off the next morning before daytime sweating is established. The skin must be dry during application as the presence of moisture results in hydrochloric acid formation and skin irritation. To prevent this, the skin should be gently dabbed dry or blow-dried. Mild-potency topical corticosteroids may be used to reduce the common problem of skin irritation, which is the usual reason for treatment failure. Application of yellow soft paraffin to axillary margins can also minimize irritation. Hyperhidrosis may take 2–3 weeks to be controlled with aluminum chlorohydrate, at which time application can be reduced to once or twice a week, or any interval that maintains control. Formulas with concentrations of 15%–20% are commercially available and used for most areas of the body, although concentrations of 20%–40% are typically used for the soles of the feet.

Iontophoresis is a process of transdermal delivery of an ionized substance (typically sodium) through intact skin using a voltage gradient. It is predominantly reserved for palmoplantar hyperhidrosis. Several iontophoretic devices are commercially available and patients typically need to purchase them. Plug-in variants are superior to battery-operated ones. It is cost-effective in the long term. Cheap homemade variants are increasingly becoming popular, but their efficacy is not validated.

The precise mechanism through which sweating is reduced is unknown given that the current densities employed are below the threshold known to cause damage to the acrosyngium, as well as the fact that mechanical obstruction does not occur. Iontophoresis is contraindicated in patients with cardiac pacemakers or defibrillators and metal implants, as well as in pregnancy.

A direct current is transmitted to electrodes in two trays filled with hard tap water (or soft water with an added teaspoon of sodium bicarbonate/baking soda per tray), and the hands or feet are placed flat in the bottom of the trays. The current is increased until the patient experiences slight discomfort (typically 15 mA for the palms and 20 mA for the soles). Three sessions a week of 20–30 min each are continued for approximately 6 weeks until sweating is sufficiently reduced; thereafter, the frequency can be dropped to once weekly as maintenance. Treatments need to be

Table 109.1 Causes of secondary hyperhidrosis

Endocrine	Diabetes mellitus, hyperthyroidism, hyperpituitarism, hypoglycemia, pheochromocytoma, pregnancy, menopause
Febrile infections	Tuberculosis, malaria, subacute bacterial endocarditis
Malignancy	Lymphoma (night sweats), carcinoid syndrome, pheochromocytoma
Autonomic	Diabetic neuropathy, paraplegia, syringomyelia, stroke, shock
Neurological	Parkinson disease
Drugs	SSRIs, e.g., fluoxetine, opioid withdrawal
Gustatory	Frey syndrome
Hereditary	Chediak–Higashi syndrome, phenylketonuria, blue rubber bleb nevus syndrome
Localized	Amputation stump–related, cold injury, extensive segmental anhidrosis with compensatory hyperhidrosis (Ross syndrome), erythrocyanosis, functional nevus, arteriovenous malformation

conducted regularly and before sweating begins to return in order to maintain dryness.

The anticholinergic drug glycopyrrolate can be added (2 mg per tray) to increase efficacy. Alternatively, 2% glycopyrrolate cream can be applied the night before tap water iontophoresis. Unfortunately, glycopyrrolate can be expensive as it may need to be imported. A special electrode for axillary use is available for some iontophoretic devices, but appears to be less effective due to poor contact.

Botulinum toxin injected intradermally produces sustained anhidrosis by irreversibly blocking the release of acetylcholine from cholinergic junctions. New cholinergic junctions are produced through the natural process of tissue turnover and repair, so the effect is temporary. Anhidrosis occurs within 24 to 72 hours and lasts on average 6 months.

It has shown high efficacy in the treatment of axillary, palmar, craniofacial, postamputation stump hyperhidrosis, compensatory sweating, and Frey syndrome. The commercially available botulinum toxin A products (Botox, Dysport, Xeomin, and Jeuveau) differ in their potency and are not equivalent unit for unit.

Botulinum toxin injected into the axilla is simple and well tolerated with a 90% reduction in sweating expected. Multiple injections, 1–2 cm apart in a grid pattern, are performed in the axillary vault corresponding to the area of maximum sweating (an area of approximately 200 cm²). Typically, 50 units of Botox are injected into each axilla, but larger males ideally should be treated with 100 units per axilla. Several reports describe the increase in duration of efficacy of repeated treatments over time.

Palmar skin is responsive to botulinum toxin with good outcomes, but use is precluded by the need for regional anesthesia due to pain. Local anesthetic nerve blocks, cryoanesthesia, or nitrous oxide (Entonox) inhalation have been employed. The latter is a safe and simple method that provides adequate anesthesia for the duration required. Twice the number of injections as the axilla is required. Avoiding injection into the thenar eminence minimizes the risk of weakening small muscles of the hand. Administration of botulinum toxin to the palms by iontophoresis or by needle-free injectors is still largely experimental.

Botulinum toxin injections work well for craniofacial hyperhidrosis, injecting along the hairline. It is rarely used for plantar hyperhidrosis as it is less effective and more painful at this site.

Oral anticholinergic drugs produce a dose-related inhibition of sweating and are best suited for patients with generalized hyperhidrosis and craniofacial hyperhidrosis, and those with focal forms of hyperhidrosis that do not respond to more localized approaches. The main limitations of treatment are anticholinergic side effects. Medications in this class include glycopyrrolate, oxybutynin,

benztropine, and propantheline. In the UK, only propantheline is licensed for this indication; the other agents are used off-label.

Side effects include dry mouth and impaired taste, pupillary dilatation and blurred vision, glaucoma, urinary retention, constipation, and tachycardia. Overheating can occur due to too effective a block on sweating. There is some evidence that they may increase the risk of dementia in the elderly. Typical prescribed doses include glycopyrrolate 2 mg three times daily; slow release oxybutynin, starting at 5 mg daily, increasing to a maximum of 20 mg daily; and propantheline 15 mg three times daily (this should be taken on an empty stomach and has a half-life of 6 hours). Glycopyrrolate and oxybutynin have liquid formulations that can be prescribed to children and are also significantly cheaper.

Topical glycopyrrolate tosylate (Qbrexza) has been approved by the US Food and Drug Administration (FDA) in 2018 and comes in individually packaged cloths (or wipes) that are to be used at home once per day – with one wipe used for two axillae.

Other systemic drugs that have been used in hyperhidrosis include β -blockers and benzodiazepines, which inhibit the physical manifestations of anxiety and are best suited for patients with episodic or event-driven hyperhidrosis such as during oral presentations, examinations, or job interviews. Agents such as clonidine, indomethacin, gabapentin, and diltiazem all have a few anecdotal reports of their use. Clonidine at a dose of 0.1 mg twice daily is recommended for women beyond the menopause who suffer from troubling hyperhidrosis if anticholinergic agents are ineffective; however, drowsiness is the main limiting side effect.

Surgical and physical techniques are generally used as third-line options.

Microwave-based devices such as miraDry, approved by the FDA in 2011, are believed to work by causing thermolytic injury to localized sweat glands. Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser used with an interstitial fiber; photodynamic therapy using an eosin photosensitizer; and fractional microneedle radiofrequency devices may also work by causing tissue destruction using electromagnetic energy.

Sympathectomy involves the selective ablation of the sympathetic innervation and reduces sweating effectively and with satisfactory long-term results, improved quality of life, and low recurrence rates. It is performed endoscopically through a trans-thoracic route using electrocautery or laser. It has been shown to be successful in children and adolescents. Unfortunately, it may result in a number of severe complications including compensatory hyperhidrosis (which for many patients is even more debilitating), Horner syndrome, pneumothorax, and intraoperative cardiac arrest. It is best reserved for severe palmar hyperhidrosis with an upper thoracic sympathectomy performed at the T2–T3

ganglion. Lumbar sympathectomy for plantar hyperhidrosis is not recommended due to the significant risks of ejaculatory failure, impotence, and anorgasmia.

Underarm surgery techniques include excision, subcutaneous curettage, and liposuction – all performed under local anesthesia. Combinations of these approaches can be employed, and the results are typically permanent due to the destruction of sweat glands. Several skin incisions and reconstructive flaps are described to gain access to the subcutaneous axillary tissues in order to trim away the deep dermis and subcutaneous tissue. The Shelley procedure is a minimally invasive procedure that involves the removal of dermal eccrine sweat glands and denervation of other sweat glands through a central axillary incision with reinnervation being disrupted by subsequent scar formation. This method is noted to have a higher rate of postoperative infection with both systemic and topical antimicrobial prophylaxis recommended.

Specific Investigations

- Starch iodine testing – defines area of sweating
- Gravimetric testing – quantifies sweating

Tests are not necessary for a diagnosis of most cases of focal hyperhidrosis; however, investigation appropriate to the clinical history and physical examination is necessary when hyperhidrosis is generalized.

First-Line Therapies

- Topical ACH solution in ethanol **B**
- Topical ACH in salicylic acid gel **C**

Generalised hyperhidrosis and its treatment. Boni R. *Curr Prob Dermatol* 2002; 30: 44–7.

A review on the more common as well as the rarer causes of secondary generalized hyperhidrosis and how these are treated.

Interventions for hyperhidrosis in secondary care: a systematic review and value-of-information analysis. Wade R, Rice S, Llewellyn A, et al. *Health Technol Assess* 2017; 21(80): 1–280.

A systematic review and economic model designed to establish the expected value of undertaking additional research to determine the most effective interventions for the management of refractory primary hyperhidrosis in secondary care. There was insufficient evidence to draw conclusions for most interventions assessed and the cost-effectiveness analysis was restricted to hyperhidrosis of the axilla.

Aluminium chloride hexahydrate versus palmar hyperhidrosis. Evaporimeter study. Goh CL. *Int J Dermatol* 1990; 29: 368–70.

A single-blind study of unilateral palmar treatment with 20% ACH daily for 4 weeks in 12 patients. Efficacy was reported for all patients; however, four experienced skin irritancy, three patients clearing after 1 week of stopping treatment, and one patient withdrew from the study.

Axillary hyperhidrosis. Local treatment with aluminium-chloride hexahydrate 25% in absolute ethanol with and without supplementary treatment with triethanolamine. Glent-Madsen L, Dahl JC. *Acta Derm Venereol* 1988; 68: 87–9.

A randomized, double-blind, half-sided experiment in 30 volunteers. Triethanolamine in 50% ethanol was applied after treatment to one axilla to neutralize the pH and reduce skin irritation. The combined treatment was found to be less irritating, but also less effective in reducing sweating, although the reduction in efficacy was not noted by the volunteers.

Aluminum chloride hexahydrate in a salicylic acid gel: a novel topical agent for hyperhidrosis with decreased irritation. Woolery-Lloyd H, Valins W. *J Clin Aesthet Dermatol* 2009; 2(6): 28–31.

A small case series of seven patients with a history of severe irritation from aluminum chloride who maintained excellent results with a switch to a 2% salicylic acid base without any significant irritation.

Second-Line Therapies

- Iontophoresis **B**
- Botulinum toxin A **A**
- Botulinum toxin A delivered by needleless injectors **C**
- Botulinum toxin A delivered by iontophoresis **D**
- Botulinum toxin B **C**
- Oral anticholinergics **B**

Iontophoresis for palmar and plantar hyperhidrosis. Pariser DM, Ballard A. *Dermatol Clin* 2014; 32(4): 491–4.

Review article indicating that iontophoresis is a safe, efficacious, and cost-effective primary treatment of palmar and plantar hyperhidrosis.

Iontophoresis with alternating current and direct current offset (AC/DC iontophoresis): a new approach for the treatment of hyperhidrosis. Reinauer S, Neusser A, Schauf G, et al. *Br J Dermatol* 1993; 129: 166–9.

Palmar hyperhidrosis was controlled after an average of 11 treatments, with both the conventional DC and the AC/DC iontophoresis units studied. The AC/DC method, however, eliminated skin irritation and discomfort.

Iontophoresis with glycopyrrolate for the treatment of palmo-plantar hyperhidrosis. Dolianitis C, Scarff CE, Kelly J, et al. *Australas J Dermatol* 2004; 45: 208–12.

A single-blinded, right–left comparison study of 20 patients with palmo-plantar hyperhidrosis to determine the comparative efficacy of tap water iontophoresis to iontophoresis with the anticholinergic glycopyrrolate. The results suggest glycopyrrolate iontophoresis is more effective due to both local and systemic effects on perspiration.

The effectiveness of tap water iontophoresis for palmo-plantar hyperhidrosis using a Monday, Wednesday, Friday treatment regime. Siah TW, Hampton PJ. *Dermatol Online J* 2013; 19: 14.

A retrospective study of 23 patients reported effective treatment with this regimen.

Botox™ delivery by iontophoresis. Kavanagh GM, Oh C, Shams K. *Br J Dermatol* 2004; 151: 1093–5.

Two patients with palmar hyperhidrosis had treatment with BTX-A (Botox) delivered by iontophoresis. Control of approximately 70% was achieved for 3 months, without side effects.

Treatment of primary hyperhidrosis with oral anticholinergic medications: a systematic review. Cruddas L, Baker DM. *J Eur Acad Dermatol Venereol* 2017; 31(6): 952–63.

This review of 23 articles assesses clinical evidence of efficacy, impact on quality of life, and adverse events associated with oral anticholinergic therapy for primary hyperhidrosis, specifically with oxybutynin, glycopyrrolate, and methantheline.

Oxybutynin as a treatment for generalized hyperhidrosis: a randomized, placebo-controlled trial. Schollhammer M, Brenaut E, Menard-Andivot N, et al. *Br J Dermatol* 2015; 173: 1163–8.

A prospective, randomized, placebo-controlled trial in 62 patients, most with generalized hyperhidrosis, using oxybutynin at an initial dose of 2.5 mg/day and increased gradually to 7.5 mg/day. The mean improvement in Hyperhidrosis Disease Severity Scale and Dermatology Life Quality Index (DLQI) were significantly better in the oxybutynin arm, with side effects infrequent and minor.

Use of oral glycopyrronium bromide in hyperhidrosis. Baja V, Langtry JAA. *Br J Dermatol* 2007; 157: 118–21.

In this retrospective analysis of 19 patients with idiopathic hyperhidrosis of varying distribution, 79% reported response to treatment at a dose of 2 mg twice daily, increasing to 2 mg three times daily. In one-third of patients, treatment was limited by side effects.

Systemic therapy for primary hyperhidrosis: a retrospective study of 59 patients treated with glycopyrrolate or clonidine. Walling HW. *J Am Acad Dermatol* 2012; 66: 387–92.

Results of systemic anticholinergic treatment in 71 patients of whom 59 (mean age 29 years, 37 females, mean follow-up 19.5 months) had at least 2 months' follow-up data. Forty-two had palmo-plantar or axillary, nine had generalized, and eight had craniofacial hyperhidrosis. Thirty out of 45 responded to glycopyrrolate at 1–2 mg twice daily. In the 15 treatment failures, six were non-responders and nine had adverse effects. Six out of 13 responded to clonidine 0.1 mg twice a day. In the seven treatment failures, three were non-responders and four had adverse effects relating to hypotension. One patient responded to treatment with oxybutynin 5 mg twice a day.

A randomized placebo-controlled trial of oxybutynin for the initial treatment of palmar and axillary hyperhidrosis. Wolosker N, de Campos JRM, Kauffamn P, et al. *J Vasc Surg* 2012; 55: 1696–700.

A study on 50 patients with palmar or axillary hyperhidrosis treated with either placebo or oxybutynin 5 mg twice a day for 6 weeks and assessed by clinical questionnaire and for quality of life. Improvement was noted in the oxybutynin-treated group in 70% with palmar and axillary hyperhidrosis, and in 90% with plantar hyperhidrosis; 65% showed improvement in quality of life, although 48% experienced dry mouth.

Individualized dosing of oral oxybutynin for the treatment of primary focal hyperhidrosis in children and teenagers. Del Boz J, Millán-Cayetano JF, Blázquez-Sánchez N, et al. *Pediatr Dermatol* 2016; 33(3): 327–31.

A prospective study to assess the effectiveness and safety of individualized dosing regimens of oral oxybutynin for treating primary focal hyperhidrosis in 16 children and teenagers. The study showed high response to treatment as well as persistent

efficacy with longer term use. Dry mouth was the most common side effect.

Oral glycopyrrolate as second-line treatment for primary pediatric hyperhidrosis. Paller AS, Shah PR, Silverio AM, et al. *J Am Acad Dermatol* 2012; 67(5): 918–23.

A retrospective study of 31 children performed to assess the response to oral glycopyrrolate in pediatric patients. In total, 90% of patients experienced improvement and 29% experienced adverse effects.

Botulinum toxin A for axillary hyperhidrosis (excessive sweating). Heckmann M, Ceballos-Baumann AO, Plewig G. *N Engl J Med* 2001; 344: 488–93.

A multicenter trial in 145 patients with axillary hyperhidrosis comparing 200 U and 100 U of BTX-A (Dysport) per axilla. Changes in the rates of sweat production were measured gravimetrically. Two weeks after injection, sweat production was slightly less in the axilla injected with 200 U, and sweat reduction in both was significantly more than with placebo. After 24 weeks, sweat rates after 100 and 200 U were almost identical and less than half the baseline rate. At questionnaire, 98% of the patients said they would recommend this therapy to others.

Botulinum toxin for axillary hyperhidrosis. Trindade de Almeida AR, Montagner S. *Dermatol Clin* 2014; 32(4): 494–504.

Review article on the use of botulinum toxin A in axillary hyperhidrosis and how this is performed.

Onabotulinum toxin A for sacral and intergluteal cleft hyperhidrosis. Totonchy MD. *JAMA Dermatol* 2020; 156: 470–1.

Hyperhidrosis of the groin, including the inguinal folds, perineum, gluteal cleft, anal fold, and buttocks, is an important cause of psychosocial distress that is not widely acknowledged. Botulinum toxin may be very effective in these locales.

Treatment of palmar hyperhidrosis with needle injection versus low-pressure needle-free jet injection of onabotulinum toxin A: an open label study. Vadeboncoeur S, Richer V, Nantel-Battista M, et al. *Dermatol Surg* 2017; 43: 264–9.

A prospective open-label study showing efficacy of onabotulinum toxin A treatment with needle-free injector.

A comparative trial of ice application versus EMLA cream in alleviation of pain during botulinum toxin injections for palmar hyperhidrosis. Alsantali A. *Clin Cosmet Investig Dermatol* 2018; 11: 137–40.

An unblinded comparative trial of 23 patients between ice and topical anesthetic showing statistically significant lower pain scores in the group receiving botulinum toxin after prior ice application.

Botulinum toxin therapy for hyperhidrosis: reduction of injection site pain by nitrous oxide/oxygen mixtures. Paracka L, Kollewe K, Dengler R, et al. *J Neural Transm (Vienna)* 2015; 122(9): 1279–82.

A case series of 13 patients showing the efficacy, safety, and ease of use of nitrous oxide as a non-sedative inhaled analgesic.

Botulinum toxin type B: a new therapy for axillary hyperhidrosis. Nelson L, Bachoo P, Holmes J. *Br J Plast Surg* 2005; 58: 228–32.

The efficacy of BTX-B (NeuroBloc) was demonstrated in the treatment of 13 patients with axillary hyperhidrosis.

Third-Line Therapies

• Topical anticholinergics	B
• Microwave-based devices	B
• Thoracoscopic sympathectomy	B
• Surgical excision inc. Shelley procedure (axillae only)	C
• Fractional microneedle radiofrequency devices	C
• Lasers and photodynamic therapy	D
• Biofeedback and behavioral modification	D
• Diltiazem, clonazepam, clonidine	E

Topical glycopyrronium tosylate for the treatment of primary axillary hyperhidrosis: results from the ATMOS-1 and ATMOS-2 phase 3 randomized controlled trials. Glaser DA, Hebert AA, Nast A, et al. *J Am Acad Dermatol* 2019; 80(1): 128–38.

Two replicate randomized, double-blind, 4-week phase 3 trials comparing glycopyrronium tosylate as a topical anticholinergic once-daily for primary axillary hyperhidrosis with a vehicle control. The treatment reduced sweat production as measured gravimetrically and was generally well tolerated in patients.

Clinical evaluation of a microwave-based device for treating axillary hyperhidrosis. Hong HC, Lupin M, O'Shaughnessy KF. *Dermatol Surg* 2012; 38: 728–35.

Thirty-one patients with primary axillary hyperhidrosis had one to three microwave-based device treatments to both axillae over 6 months and by 12 months 90% had a 50% reduction in axillary sweating from baseline and 85% had a reduction of at least 5 points on the DLQI. The case series was funded by Miramar labs who produce miraDry.

Efficacy of fractional microneedle radiofrequency device in the treatment of primary axillary hyperhidrosis: a pilot study. Kim M, Shin JY, Lee J, et al. *Dermatology* 2013; 227(3): 243–9.

Uncontrolled prospective study using a fractional microneedle radiofrequency device receiving two sessions at 4-week intervals

with significant improvement in disease severity scores and starch iodine tests.

New treatment techniques for axillary hyperhidrosis. Mordon SR, Trelles MA, Leclerc FM, et al. *J Cosmet Laser Ther* 2014; 16: 230–5.

Review article looking at the recent evidence as well as outlining the specific techniques for using Nd:YAG laser, microwave devices, and photodynamic therapy as potential new treatments for axillary hyperhidrosis.

Shelley procedure in axillary hyperhidrosis. Hussain AB, Holme SA, Kavanagh GM. *Clin Exp Dermatol* 2016; 41(2): 229–31.

Case series involving 31 patients (mostly female) with axillary hyperhidrosis treated at a single center using this minimally invasive procedure. Of the 31 patients, 29 experienced a clinically significant reduction in sweating and an improvement in DLQI scores. The paper outlines the procedure itself and provides recommendations for perioperative care.

A prospective cohort study on quality of life after endoscopic thoracic sympathectomy for primary hyperhidrosis. Dhar-maraj B, Kosai NR, Gendeh H, et al. *Clin Ter* 2016; 167(3): 67–71.

Questionnaire on quality of life and self-esteem filled in by 50 patients undergoing the procedure, the results showing that it can significantly improve the quality of life and self-esteem of patients, but the rate of compensatory hyperhidrosis is high (78%).

Transthoracic endoscopic sympathectomy for palmar hyperhidrosis in children and adolescents: analysis of 350 cases. Lin TS. *J Laparoendosc Adv Surg Tech A* 1999; 9: 331–4.

A total of 699 sympathectomies were performed in 350 patients with highly satisfactory results reported in 95% of patients, although compensatory hyperhidrosis (86%) affected the axillae (12%), back (86%), abdomen (48%), or lower limbs (78%). The recurrence rates of palmar hyperhidrosis were 0.6% in the first year, 1.1% in the second, and 1.7% in the third.

Hypertrichosis and hirsutism

Katherine Glaser, Wilma F. Bergfeld



INTRODUCTION

Hirsutism is the excessive growth of terminal hair in women in male androgen-dependent areas (face, breasts, thighs, abdomen, back). Approximately 5–10% of women are affected worldwide with significant impacts on quality of life. The Ferriman–Gallwey (F-G) scoring system is the gold standard for diagnosis in which nine androgen-sensitive body areas are evaluated and rated on a scale of 0–4 (no hair to frankly virile). A cumulative score ≥ 8 is diagnostic but must be modified for certain races and ethnicities.

Hirsutism results from endogenous androgens (ovarian or adrenal), exogenous androgens, or from increased hair follicle sensitivity to androgens. Most hirsute women have raised circulating androgen levels; however, in idiopathic hirsutism circulating androgen levels can be normal. Polycystic ovarian syndrome (PCOS) and idiopathic hirsutism are the most common causes. Rarer etiologies must also be considered including endocrinopathies, non-classical congenital adrenal hyperplasia, and androgen-secreting tumors.

Hypertrichosis, by contrast, results from increased vellus hair growth in a generalized androgen-independent distribution and usually is familial or drug-induced (e.g., phenytoin, ciclosporin).

Main Causes of Hirsutism

Ovarian

- **Polycystic ovarian syndrome (PCOS)** – menstrual irregularities, metabolic syndrome,* polycystic ovaries on ultrasound

- **HAIR-AN syndrome** – hyperandrogenism, acanthosis nigricans, metabolic syndrome*
- **Ovarian hyperthecosis** – gradual hirsutism, adult-onset virilization, metabolic syndrome*
- **Ovarian tumors** – rapidly progressive hirsutism and virilization

Adrenal

- **Classical congenital adrenal hyperplasia** – ambiguous genitalia, menstrual irregularities, prepubertal virilization
- **Non-classical congenital adrenal hyperplasia** – menstrual irregularities, family history of hirsutism, certain ethnic groups (Mediterranean, Hispanic, Ashkenazi Jew)
- **Cushing syndrome** – Cushingoid (striae, central obesity, easy bruising, acanthosis nigricans, proximal muscle wasting, mood disturbances, insulin resistance)
- **Adrenal tumors** – rapidly progressive hirsutism and virilization, Cushingoid

Pituitary†

- **Cushing disease** – skin hyperpigmentation, Cushingoid
- **Acromegaly** – coarse facies, large hands, doughy skin
- **Hyperprolactinemia** – galactorrhea

Idiopathic

- Abnormal peripheral 5 α -reductase activity or androgen receptor – hirsutism, normal menses

Exogenous

- **Medications** – testosterone, anabolic steroids, androgenic progestins, adrenocorticotrophic hormone (ACTH), valproic acid

*Metabolic syndrome: obesity, insulin resistance/diabetes mellitus type 2, lipid abnormalities, cardiovascular disease

†Pituitary tumors can also present with visual field defects and cranial nerve palsies

MANAGEMENT STRATEGY

A thorough history and complete physical examination is critical to identify the etiology of hypertrichosis and hirsutism. Offending drugs, if implicated, should be promptly discontinued. Laboratory screening for elevated androgen levels should be performed in women with a positive F-G score or clinical signs of hyperandrogenism (e.g., menstrual irregularities, infertility, galactorrhea, acanthosis nigricans, central obesity). Ultimately, treatments are tailored based on the underlying cause.

For women with localized hair growth or a normal F-G score, treatments are typically limited to *physical hair removal methods*. Women with true hirsutism require additional systemic pharmacologic therapy, often indefinitely. *Combined estrogen–progestin oral contraceptive pills (OCP)* and *antiandrogens* are preferred first-line therapies. Less common and less efficacious therapies include *gonadotropin-releasing hormone agonists (GnRH)*, *insulin-lowering drugs*, and *topical antiandrogens*.

Signs of metabolic syndrome may be seen in PCOS, HAIR-AN syndrome, and ovarian hyperthecosis. In obese women with these conditions, weight loss improves markers of metabolic syndrome and reduces cardiovascular risk.

Hirsutism that is acute, rapidly progressive, or accompanied by signs of virilization (clitoromegaly, deep voice, or increased muscularity) indicates potential androgen-secreting tumors or congenital adrenal hyperplasia (CAH). Additional laboratory and/or radiographic screening is required in these cases. *Glucocorticoid therapy* is utilized in CAH to suppress adrenal androgen production and induce ovulation, but OCPs and/or systemic antiandrogens are often required for the hirsutism.

Specific Investigations

Detailed medication history

Screening test

- Testosterone level (free and total)*

If testosterone level elevated or signs of hyperandrogenism/virilization†

- 17-hydroxyprogesterone*
- Sex hormone-binding globulin
- β -hCG level
- Dehydroepiandrosterone sulfate (DHEAS)
- Androstenedione
- Thyroid-stimulating hormone (TSH)
- Follicular-stimulating hormone (FSH)
- Luteinizing hormone (LH)
- Prolactin
- Dexamethasone suppression test
- 24-hour urinary free cortisol
- Somatomedin C (IGF-1)

Imaging if PCOS or tumor suspected‡

- Transvaginal ultrasound
- Computed tomography/magnetic resonance imaging (CT/MRI) of abdomen/pelvis
- MRI brain

*Ideally obtained in the morning in the follicular phase of the menstrual cycle

†Additional screening should be tailored based on the suspected underlying etiology

Physical Hair Removal Methods

Hair removal therapies offer significant cosmetic benefits and can be used first-line or adjunctively. *Bleaching* with hydrogen peroxide preparations disguises dark hair. *Depilation* removes the hair shaft at the skin surface such as with *shaving* or with *chemical depilatory creams* to dissolve the hair. Importantly, depilation does not affect the diameter or rate of hair growth. Skin irritation, discomfort, and dyspigmentation are known side effects.

Epilation removes the entire hair shaft, including the root. Temporary epilation therapies include *tweezing*, *threading*, or *waxing*. *Electrolysis* is a form of permanent epilation that can be used on any skin or hair color but is time consuming, requires multiple treatments, and is operator dependent. A fine needle is inserted into the hair follicle to deliver direct current (galvanic electrolysis), high-frequency alternating current (thermolysis), or a blend of the two to damage the hair follicle. In addition to the aforementioned side effects, folliculitis, pseudofolliculitis, infection, and scarring are possible.

Photoepilation is a popular form of permanent epilation using pulses of light absorbed by melanin in the hair shaft to cause selective photothermolysis. Devices include ruby (694 nm),

alexandrite (755 nm), diode (800–810 nm), or Nd:YAG (1064 nm) lasers and IPL (intense pulsed light) non-coherent light (590–1200 nm). While significant pigmented hair reduction can be achieved with photoepilation, no device can guarantee complete or persistent hair removal. Efficacy improves greatly with repeat treatments. Caution should be taken in darker skin types and around the eye due to high melanin concentrations. Side effects include erythema, pain, blistering, dyspigmentation, burns, scarring, and, rarely, paradoxical hypertrichosis.

Pharmacologic Therapies for Hirsutism

Although several meta-analyses and treatment guidelines are published, evidence is limited by small sample sizes and inconsistent methodology. Systemic therapy is not recommended for women planning pregnancy due to teratogenic potentials.

Combined OCPs are first-line, which work by suppressing ovarian androgen synthesis, increasing sex hormone-binding globulin levels, and suppressing free plasma testosterone levels. OCPs with low androgenic progestins (desogestrel, gestodene, norgestimate) and progestins with antiandrogenic properties (cyproterone acetate, drospirenone) are preferred. Importantly, progestin-only contraception is ineffective for hirsutism. The risks of venous thromboembolism should be considered in higher risk patients (e.g., older, obese, smoker), which can be mitigated using lower ethinyl estradiol (EE) doses and lower risk progestins (levonorgestrel). Clinical response requires 6 months of treatment. Combination treatment with another antiandrogen (spironolactone, finasteride) is recommended if response to monotherapy is inadequate.

Spironolactone inhibits 5- α -reductase activity and blocks androgen receptors. Common dosing is 100–200 mg daily. Side effects include hyperkalemia, hypotension, and irregular menses. Tumorigenicity has been shown in animals, but relevance in humans is questionable. Spironolactone is pregnancy category C; however, all antiandrogens have feminizing teratogenic potential and should be used with a reliable form of contraception. For this reason, OCPs are preferred first-line over antiandrogens except in women who have undergone permanent sterilization, are not sexually active, or are using long-acting reversible contraception.

Finasteride inhibits type II 5- α -reductase activity and is typically dosed as 2.5–5 mg daily. It is considered pregnancy category X, limiting its use in certain populations, as previously mentioned. No reports exist for dutasteride, a type I and II 5- α -reductase inhibitor, in the treatment of hirsutism.

Cyproterone acetate (CPA) is another antiandrogen, though currently unavailable in the US, with various mechanisms of action including androgen receptor blockade, weak 5- α -reductase inhibition, and gonadotrophin reduction. It can be prescribed as a combination OCP (2 mg CPA and 35 mcg EE) or used cyclically (50–100 mg CPA daily on menstrual cycle days 1–10 and 35 mcg EE on days 1–21). Side effects are similar to other OCPs.

Flutamide is an antiandrogen, which inhibits androgen receptors in a dose-dependent fashion. Lower doses (62.5–250 mg daily) may be equally as efficacious as higher doses (500 mg daily). However, serious reports of hepatotoxicity and even death reduced its use in clinical practice.

GnRH agonists, such as leuprolide, reduce luteinizing hormone and downstream ovarian androgens. Side effects include hot flashes and osteoporosis, for which supplementary low-dose estrogen is often required. These medications are expensive, injectable, and show no advantages over first-line therapies; thus, they are not recommended except in severe forms of hirsutism that have already failed OCPs and antiandrogens.

Eflornithine hydrochloride 13.9% cream is approved by the Food and Drug Administration (FDA) for facial hirsutism. It slows the rate of hair growth by irreversibly inhibiting ornithine decarboxylase. Results require 6–8 weeks of twice-daily application; however, benefits reverse approximately 8 weeks after discontinuation. Side effects include acne, pseudofolliculitis, and contact dermatitis. Adjuvant use with photoepilation improves efficacy.

Several therapies are no longer recommended as more recent studies show little to no efficacy in the treatment of hirsutism. *Insulin-lowering drugs* such as metformin and thiazolidinediones, *topical finasteride*, and *topical canrenone* (the active metabolite of spironolactone) demonstrate inconsistent results but generally offer minimal to no benefits.

Evaluation and treatment of hirsutism in premenopausal women: an Endocrine Society Clinical Practice Guideline. Martin KA, Anderson RR, Chang RJ, et al. *J Clin Endocrinol Metab* 2018; 103: 1233–57.

The most up-to-date practice guideline that reviews etiology, diagnostic approach, and evidence-based treatment algorithms for hirsutism. Recommendations have been incorporated throughout this chapter.

American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society disease state clinical review: guide to the best practices in the evaluation and treatment of Polycystic Ovary Syndrome—Part 1. Goodman NF, Cobin RH, Futterweit W, et al. *Endocr Pract* 2015; 21: 1291–300.

Current PCOS diagnostic guidelines require two of the following criteria: chronic oligoovulation, hyperandrogenism, and polycystic ovaries on transvaginal ultrasound. Metabolic screening is important but not incorporated into the diagnostic criteria.

First-Line Therapies

Screening and treatment of underlying pathology

• Weight loss if obese	B
• Combined OCPs	B
• Spironolactone	A
• Finasteride	A
• Cyproterone acetate	B
• Eflornithine cream	B
• Mechanical hair removal, bleaching, or camouflage	B
• Electrolysis	B
• Photoepilation	A

Lifestyle changes in women with polycystic ovary syndrome. Moran LJ, Hutchison SK, Norman RJ, et al. *Cochrane Database Syst Rev* 2011; 7: CD007506.

Meta-analysis of four PCOS studies ($n = 132$) showed lifestyle changes alone improve hirsutism and markers of metabolic syndrome (weight and fasting insulin concentrations). Serum testosterone levels and F-G scores improved slightly (mean difference -1.19 , with 95% confidence interval -2.35 to -0.03).

Anti-androgenic therapy in young patients and its impact on intensity of hirsutism, acne, menstrual pain intensity and sexuality – a preliminary study. Fuchs A, Matonóg A, Sieradzka P, et al. *Ginek Pol* 2019; 90: 520–6.

Combined OCPs with antiandrogen properties improved acne severity, menstrual pains, and F-G scores in premenopausal women ($n = 570$) after 3 months. Women with excessive hairiness ($n = 192$) noted greater improvements with CPA, chlormadinone, and drospirenone (though not with dienogest) than those taking OCPs without antiandrogen properties. Head-to-head studies are lacking, and guidelines generally do not suggest one OCP over another. However, OCPs containing low androgenic or antiandrogen progestins are preferred.

Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. Moghetti P, Tosi E, Tosti A, et al. *J Clin Endocrinol Metab* 2000; 85: 89–94.

Spironolactone 100 mg daily, flutamide 250 mg daily, and finasteride 5 mg daily were compared in a small 6-month double-blind, placebo-controlled randomized controlled trial (RCT). Measured outcomes included patient questionnaires, endocrine labs, F-G scores, and hair shaft diameter. Despite variable mechanisms of action, each antiandrogen demonstrated similar positive efficacy. Tolerability was overall good; only mild polymenorrhea was reported with spironolactone (50%).

Cyproterone acetate for hirsutism. Van der Spuy ZM, Le Roux PA. *Cochrane Database Syst Rev* 2003; 4: CD001125.

No studies to date compare CPA with placebo; however, a small placebo-controlled trial demonstrates efficacy of CPA 2 mg with EE. Another small trial shows when combined with EE, there is no significant difference in F-G score or endocrine labs when comparing CPA 2 mg with CPA 25–100 mg.

Evidence based review of hair removal using lasers and light sources. Haedersdal M, Wulf HC. *J Eur Acad Dermatol Venerol* 2006; 20: 9–20.

Meta-analysis of nine RCTs and 21 controlled trials suggests photoepilation is superior and preferred by patients to conventional hair removal treatments (shaving, waxing, electrolysis). Short-term partial hair reduction up to 6 months postprocedure can be expected with improved efficacy with repetitive treatments.

Meta-analysis of hair removal laser trials. Sadoghha A, Mohaghegh Zahed G. *Lasers Med Sci* 2009; 24: 21–5.

A systematic review of laser hair removal clinical trials showed hair reductions of 57.5%, 42.3%, 54.7%, and 52.8% at 6 months posttreatment after three sessions with diode, Nd:YAG, alexandrite, and ruby lasers, respectively.

Laser-assisted hair removal for facial hirsutism in women: a review of evidence. Lee CM. *J Cosmet Laser Ther* 2018; 20: 140–4.

Lasers are highly effective for unwanted hair removal; however, the mean hair reduction following multiple laser sessions is, on average, one-third less in individuals with hyperandrogenism. Long-term follow-up data is lacking but most women with androgen excess require maintenance sessions. Patients with darker skin types require lower fluences and have less adverse events using long-pulsed Nd:YAG.

Photoepilation with a diode laser vs. intense pulsed light: a randomized, inpatient left-to-right trial. Klein A, Steinert S, Baeumler W, et al. *Br J Dermatol* 2013; 168: 1287–93.

Diode laser more effectively decreased axillary hair counts compared with IPL ($n = 30$). Mean hair reductions 12 months after six treatment sessions were 69.2% for diode and 52.7% for IPL ($p < 0.01$). Diode treatment was more painful than IPL.

Randomized, double blind clinical evaluation of the efficacy and safety of topical eflornithine HCl 13.9% cream in the treatment of women with facial hair. Wolf JE, Shander D, Huber F, et al. *Int J Dermatol* 2007; 46: 94–8.

Using a physician's global assessment and evaluating facial hair length and mass, 58% of eflornithine-treated patients ($n = 393$) were improved compared to 34% with vehicle ($n = 201$) after 24 weeks of twice-daily application. Cutaneous adverse events were generally mild, self-resolving, and comparable between treatment groups.

Combination of intense pulse light and topical eflornithine therapy versus intense pulse light therapy alone in the treatment of idiopathic facial hirsutism: a randomized controlled trial. Zahoor H, Noor SM, Paracha MM. *J Pak Med Assoc* 2019; 69: 930–3.

Topical eflornithine is substantially more effective when used in combination with a light-based treatment such as IPL. In this RCT, 78 women were treated with monthly IPL sessions or twice-daily eflornithine application with IPL. After 6 months, a statistically significant mean hair reduction was noted in the combination group (90.44%) compared with IPL only (59.23%).

Second-Line Therapy

- Combination of OCPs with antiandrogen

B

Antiandrogens for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials. Swiglo BA, Cosma M, Flynn DN, et al. *J Clin Endocrinol Metab* 2008; 93: 1153–60.

Meta-analysis identified five small RCTs comparing OCPs with a combination OCP and antiandrogen: 1) OCP containing 2 mg CPA versus with 100 mg CPA for 10 days per month; 2) OCP containing desogestrel versus with 50 mg spironolactone, and 3–5) OCP containing 2 mg CPA versus with 5 mg finasteride. Overall methodological quality was low and not standardized but combination treatment showed mild advantages over monotherapy. Subgroup analyses by antiandrogen type suggest benefit with additional spironolactone or finasteride but no added benefit of higher dose CPA when taken with an OCP containing CPA.

Long-term response of hirsutism and other hyperandrogenic symptoms to combination therapy in polycystic ovary syndrome. Ezeh U, Huang A, Landay M, et al. *J Womens Health (Larchmt)* 2018; 27: 892–902.

Menstrual irregularities, acne, and F-G scores improved more in PCOS patients treated with combination spironolactone 100–200 mg/day and OCP ($n = 138$) when compared to OCP monotherapy or other therapies ($n = 62$). While the second treatment group received variable therapies making interpretation complex, the study offers long follow-up over an average 34 months and statistically significant measured outcomes.

Third-Line Therapies

• Flutamide	A
• GnRH agonists	B
• Glucocorticoids	B
• Insulin-lowering drugs	A
• Topical finasteride	B
• Topical canrenone	C

Very low dose of flutamide in the treatment of hyperandrogenism. Fulghesu AM, Melis F, Murru G, et al. *Gynecol Endocrinol* 2018; 34: 394–8.

Adolescent females ($n = 145$) with severe hirsutism noted statistically significant reductions in F-G scores (–39.99%) after 18 months of treatment with flutamide 62.5 mg daily and a contraceptive (EE and gestodene) compared to controls ($n = 30$) on OCP monotherapy (EE and drospirenone). One case of self-resolving mild transaminitis was reported. Other studies in adults have reported more severe liver toxicities and, thus, flutamide should be used with caution.

Interventions for hirsutism (excluding laser and photoepilation therapy alone): review. Van Zuuren EJ, Fedorowicz Z, Carter B, et al. *Cochrane Database Syst Rev* 2015; 4(4): CD010334.

GnRH analogs show inconsistent results in several studies and have significant side effects.

Management of the female with non-classical congenital adrenal hyperplasia (NCCAH): a patient-oriented approach. Livadas S, Bothou C. *Front Endocrinol (Lausanne)* 2019; 10: 366.

CAH treatment should be individualized and implemented for symptomatic females with adjustments based on age-group. Hydrocortisone 10–15 mg/m² divided in three doses is more commonly prescribed in childhood, and prednisone 5 mg daily or dexamethasone 0.25 mg daily in adolescence.

Insulin sensitizers for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials. Cosma M, Swiglo BA, Flynn DN, et al. *J Clin Endocrinol Metab* 2008; 93: 1135–42.

Meta-analysis suggests metformin and thiazolidinediones provide little benefit compared with placebo and no significant benefit when compared or added to OCPs or antiandrogens. Usage for insulin sensitivity is appropriate but generally not recommended solely for hirsutism.

Topical finasteride in hirsutism: a double blind randomized clinical trial on adult women. Iraj F, Karbasioun S, Aminoroaya A. *Int J Res Med Sci* 2005; 10: 337–42.

A double-blind, split-face, placebo-controlled trial ($n = 35$) showed no difference in mean hair thickness or count after 6 months of twice-daily application of finasteride (0.5%) cream in the treatment of facial hirsutism.

Lack of effect of a spironolactone-containing cream on hair growth in hirsute women. Gomez F, Ramelet AA, Rüedi B, et al. *Dermatologica* 1987; 174: 102–3.

A small ($n = 12$), double-blind, placebo-controlled trial of spironolactone (5%) cream applied twice daily for 3 months to the face, thighs, and legs showed no improvements in hirsutism. Newer studies are unavailable.

Hypopigmented disorders

Ramiro Rodriguez Jr., Amit G. Pandya



Progressive macular hypomelanosis

Hypopigmented disorders present as areas of skin that are lighter than normal due to reduced melanin. In contrast, depigmented lesions, such as those caused by vitiligo, present as milky-white patches due to complete absence of melanocytes. Classification of these disorders may be based on lesion pattern and distribution, underlying cause, or time of lesion onset. In general, hypopigmentation occurs due to alterations in the melanin synthesis pathway, a decrease in melanocytes, or impairment in the melanocyte-melanin transfer system. This chapter briefly discusses common hypopigmented disorders with an overview of treatment options.

Nevus Depigmentosus

This disorder is a non-progressive, congenital form of cutaneous mosaicism affecting melanin synthesis and transfer from melanocyte to keratinocyte. Clinically, lesions present in early childhood as well-defined hypopigmented patches with serrated borders. Three variants have been described (localized, segmental, and linear or whorled) with the localized type being the most common. A negative diascopy test is helpful to rule out nevus anemicus.

Postinflammatory Hypopigmentation

Inflammatory reactions in various dermatoses may lead to hypopigmentation after resolution of the inflammatory phase.

Cutaneous injuries, burns, and cosmetic procedures (dermabrasion, chemical peels, cryosurgery) can also lead to pigment loss through postinflammatory changes. Severity of pigment loss and distribution coincides with the distribution of original lesions and the degree of previous inflammation. This disorder is seen most frequently in darker-skinned individuals, due to contrast of the lesions with surrounding skin. The lesional course may vary from spontaneous resolution to permanent hypopigmentation.

Pityriasis Alba

A form of postinflammatory hypopigmentation, this self-limiting, benign disorder is associated with eczema and is especially common among children with a personal or family history of atopy. Lesions present as hypopigmented macules with or without associated scaling, erythema, and/or pruritus. Involvement of the face, neck, shoulders, and upper extremities is common. In contrast with pityriasis versicolor, lesions tend to have more facial involvement, are less numerous, and show no yeast elements on KOH (potassium hydroxide) preparations of overlying scale.

Idiopathic Guttate Hypomelanosis

Idiopathic guttate hypomelanosis (IGH), also called *senile depigmented spots*, is an acquired leukoderma common among older persons. Lesions present as 1–6 mm hypopigmented to porcelain-white, oval-to-round guttate macules on sun-exposed areas, especially the legs. Although asymptomatic, lesions tend to increase with age and may be of cosmetic concern. Etiology of this disorder is unknown; however, the *HLA-DQ3* gene, autoimmunity, trauma, and chronic sun exposure are among suspected culprits. Light microscopy of lesions reveals a hyperkeratotic stratum corneum, an atrophic epidermis, and flattened rete ridges with senescent melanocytes and decreased melanin content.

Chemical Leukoderma

Lesions of chemical leukoderma present as hypo- or depigmented macules at sites of contact with chemicals, especially phenols, catechols, or hydroquinone. A history of onset of lesions after chemical exposure and distribution involving only the exposed sites or similar cases in individuals in the same workplace are needed to establish a diagnosis and distinguish it from vitiligo or other causes of hypo- and depigmentation.

Pityriasis Versicolor

Also known as *tinea versicolor*, this is an infectious disorder affecting the epidermal keratin layer. The responsible agent is a lipophilic budding yeast, *Pityrosporum orbiculare*, found in normal skin flora. The disease is active when the yeast changes to its hyphal form. Skin involvement is seen on sites with a high density of sebaceous glands, especially the shoulders, chest, and upper back. Lesions present as well-defined hypopigmented macules or small patches with overlying scale. The pigment loss is attributed to the inhibition of the enzyme tyrosinase by azelaic acid, a dicarboxylic acid formed by the organism. Less commonly, the lesions may be hyperpigmented to erythematous in color. Diagnosis is confirmed with a KOH preparation of scale obtained from a lesion demonstrating the 'spaghetti and meatball' appearance of the organism. Wood lamp examination helps with diagnosis, as *tinea versicolor* often has a yellow-white or coppery-orange fluorescence.

Progressive Macular Hypomelanosis

This is an acquired hypomelanosis presenting as round, pale, poorly circumscribed and coalescent macules over the trunk, with a tendency toward confluence at the midline. Lesions are non-scaly and are not preceded by inflammation, differentiating it from pityriasis versicolor and postinflammatory hypopigmentation, respectively. Although the pathogenic factors are not known, hormonal interactions and colonization of *Propionibacterium* spp. around the pilosebaceous units are thought to be contributors. Wood lamp examination may reveal a characteristic punctate red fluorescence at the center of lesions suggestive of *Propionibacterium* colonization. Microscopic analysis reveals a disruption in melanosome maturation and distribution. The course of the disorder is unpredictable, as spontaneous cure has been reported over time in some patients.

Leprosy (Hansen Disease)

This is an infectious disorder caused by *Mycobacterium leprae*, a bacterium that affects skin and peripheral nerves. Lesions may present as hypopigmented or erythematous macules with varying degrees of scale and induration; hypoesthesia and peripheral nerve enlargement are characteristic findings.

Hypopigmented Variants of Common Dermatoses

Mycosis fungoides, morphea, scleroderma, and sarcoidosis are dermatoses that may present as hypopigmented variants.

In patients with mycosis fungoides, lesions present as ill-defined, light-colored macules and patches, which characteristically occur in sun-protected areas. Histopathologic examination of a skin biopsy helps confirm the diagnosis by revealing atypical lymphocytes within the epidermis, also known as epidermotropism.

In lichen sclerosis, a chronic inflammatory disorder, lesions present with hypo- and depigmented porcelain-white macules and thin plaques, which may be associated with associated pruritus and/or pain. The distribution commonly involves anogenital areas and affects women after the fourth decade of life.

Morphea and systemic sclerosis may also present with patches of hypopigmentation, with characteristic perifollicular hyperpigmentation and associated induration, giving a 'salt and pepper' appearance.

Less commonly, sarcoidosis may present as a hypopigmented variant that predominantly affects dark-skinned individuals. These lesions are often indurated, favor the extremities, and have a yellow tinge on diascopy.

Specific Investigations

- Diascopy
- Wood lamp exam
- Scraping for yeast and fungus
- Skin biopsy

MANAGEMENT STRATEGY

A thorough history and clinical exam are essential for diagnosis of hypopigmented dermatoses. Details of lesion duration, age of onset, preceding history, associated symptoms, exposure to chemicals, and family history aids to narrow the differential. On exam, one must assess the nature of pigment loss (hypo/depigmentation), the site and distribution of lesions, and the

presence of associated findings (induration, scaling, erythema, pruritus, or sensory loss). A Wood lamp exam helps differentiate hyperpigmentation from depigmentation. Confocal microscopy helps assess the melanin content and distribution of lesions and histopathologic analysis of a skin biopsy helps identify specific diseases.

The most important aspect of management is to *treat the underlying inflammatory disorder*. Once the inflammation has resolved, various strategies can be used to bring back normal pigmentation. Sun exposure aids with repigmentation of lesions through residual functional melanocytes. *Ultraviolet light therapy* may help stimulate melanin synthesis; however, overexposure may risk increased contrast from tanning of surrounding normal skin.

First-Line Therapies

• Phototherapy	D
• Topical corticosteroids	D
• Topical calcineurin inhibitors	D

Laser resurfacing induced hypopigmentation: histologic alterations and repigmentation with topical photochemotherapy. Grimes PE, Bhawan J, Kim J, et al. *Dermatol Surg* 2001; 27: 515–20.

In this study, 10 patients with postlaser resurfacing hypopigmentation underwent treatment with topical 0.001% 8-methoxypsoralen ointment applied to the lesions twice weekly for 30 min followed by ultraviolet A exposure at an initial dose of 0.2–0.5 J/cm² and increased by 0.2–0.5 J/cm² weekly. Moderate-to-excellent repigmentation was seen in 71% of patients. Adverse effects were minimal.

Benzoyl peroxide/clindamycin/UVA is more effective than fluticasone/UVA in progressive macular hypomelanosis: a randomized study. Relyveld GN, Kingswijk MM, Reitsma JB, et al. *J Am Acad Dermatol* 2006; 55: 836–43.

A total of 45 patients participated in this left–right randomized trial. Patients applied benzoyl peroxide 5% hydrogel on one side of the body affected by lesions of progressive macular hypomelanosis and fluticasone 0.05% on the contralateral side nightly. Clindamycin 1% lotion was applied in the morning on the benzoyl peroxide site. UVA therapy was provided three times a week for 20 min at 233 J/cm². Pigment was measured by colorimeter at baseline, 2, 6, 10, and 14 weeks of treatment. After 14 weeks, patients stopped treatment and underwent a 12-week period without treatment for final measurement. While the benzoyl peroxide/clindamycin/UVA side showed superior results, both groups showed improvement by colorimeter and visual evaluation.

Pilot trial of 1% pimecrolimus cream in the treatment of seborrheic dermatitis in African American adults with associated hypopigmentation. High WA, Pandya AG. *J Am Acad Dermatol* 2006; 54: 1083–8.

Five African American patients with seborrheic dermatitis-induced hypopigmentation were treated with pimecrolimus applied to the affected areas twice daily for 16 weeks. Hypopigmentation was assessed using a Mexameter. Marked improvement was noted starting at 2 weeks in all patients, which continued until the end of treatment.

Topical tacrolimus significantly promotes repigmentation in idiopathic guttate hypomelanosis: a double blind, randomized, placebo-controlled study. Rerknimitr P, Disphanurat W, Achariyakul M. *J Eur Acad Dermatol Venereol* 2013; 27: 460–4.

In this within-patient, left–right comparison study, 26 patients with IGH were randomized. One side was randomly assigned to be treated with 0.1% tacrolimus while the other side received placebo. Both topicals were applied twice daily for 6 months, with measurements at 2, 4, and 6 months. Colorimeter measurements and patient self-evaluation at 6 months showed that tacrolimus treated lesions improved more than placebo.

Second-Line Therapies

• Laser	D
• Cosmetic camouflage	B
• Melanocyte grafting	C

The safety and efficacy of the 308-nm excimer laser for pigment correction of hypopigmented scars and striae alba. Alexiades-Armenakas MR, Bernstein LJ, Friedman PM, et al. *Arch Dermatol* 2004; 140: 955–60.

A group of 31 adults with hypopigmented scars (22) and striae alba (9) were enrolled. Lesions were treated with xenon chloride excimer laser (308 nm, 3.2 cm², 30 ns) starting at 50 mJ/cm² minus the minimal erythema dose of the patient. Treatment was performed biweekly until a maximum of 10 treatment

sessions, 75% improvement with colorimetry, and 100% visual pigment correction. If no improvement was noted, the dose was increased by 50 mJ/cm² per treatment; otherwise, the same dose was maintained throughout treatment. Posttreatment evaluation was performed at 1, 2, and 4 months. Statistically significant improvement was noted using colorimetric analysis after the first treatment; 60%–70% visual improvement was noted compared with control sites.

Melanocyte autologous grafting for treatment of leukoderma. Suvanprakorn P, Dee-Ananlap S, Pongsomboon C, et al. *J Am Acad Dermatol* 1985; 13: 968–74.

Patients with vitiligo, IGH, and postinflammatory hypomelanosis were included in the study. Blisters were created by suction/liquid nitrogen at the affected and healthy site. The roof of the bullae from the donor site was transferred to the affected area. Repigmentation was noted 7–14 days later.

Cosmetic camouflage. Antoniou C, Stefanaki C. *J Cosmet Dermatol* 2006; 5: 297–301.

Cosmetic camouflage may be helpful for patients not relieved by conventional treatment, especially when lesions are located over a cosmetically important area such as the face. The products may be oil or water based, depending on patient skin type.

Ichthyoses

Qisi Sun, Keith Choate



Mutations in over 50 genes cause ichthyosis, resulting in abnormal barrier function with increased transepidermal water loss (TEWL) and compensatory epidermal hyperproliferation. Most are inherited and classified as either non-syndromic (findings limited to the skin) or syndromic (involving other organs). Acquired ichthyosis can arise from malignancy, autoimmune or inflammatory disease, nutritional deficiency, and medications.

MANAGEMENT STRATEGY

Newborns (0–2 Months)

Newborns with ichthyosis can present with a range of phenotypes including collodion membrane, widespread erosions, armor-like scale, red/scaly skin, or normal skin that subsequently develops scaling and erythema. In recessive ichthyosis, collodion membrane presentations are common and are characterized by a taut, translucent layer of skin, which sheds within a month of birth to reveal scaly and/or red skin. A minority of collodion babies heal spontaneously, leaving mild scaling. In severe cases, morbidity is possible due to increased TEWL, difficulties in thermoregulation, and increased infection risk, especially with *Staphylococcus aureus* and dermatophytes. It is also important to recognize that other disorders such as Omenn syndrome and neonatal Gaucher disease can also cause collodion membrane. Therefore, genetic testing is the cornerstone of diagnostic workup.

It is common practice to place collodion babies in a 40–60% humidified incubator to minimize dehydration and prevent fissures. Since eclabium can interfere with oral feeding, newborns may require modified bottle nipples or nasogastric feeding.

Newborn care also includes pain control, ophthalmologic attention to prevent conjunctivitis and keratitis secondary to ectropion, and close monitoring for infection and fluid and electrolyte imbalances, especially hyponatremia. Prophylactic antibiotics are discouraged given a lack of evidence supporting their efficacy. Medicated ointments, such as salicylic acid, lactic acid, and sulfadiazine cream, should be avoided, given the risk of percutaneous absorption. *Bland emollients* including white petrolatum and Aquaphor are preferred.

Newborns with epidermolysis bullosa (EB) can present with widespread blistering, so epidermolysis bullosa and staphylococcal scalded skin infection are in the differential. A biopsy can distinguish among these diagnoses because suprabasal vacuolar degeneration, coarse keratohyalin granules, and hyperkeratosis are pathognomonic for EB. Treatment includes use of a humidified incubator, pain control, infection surveillance, and nutritional intervention to compensate for increased metabolic demands.

Harlequin ichthyosis (HI) has a severe neonatal presentation and while formerly often lethal, advances in intensive care have enabled survival in a large fraction of infants who are born encased in a thick stratum corneum separated by deep, red fissures that form geometric plates of skin. Surviving infants ultimately shed the hyperkeratosis to evolve to an ichthyosiform erythroderma phenotype. Upon birth, coordinated care with attention to fluid and electrolyte balance, signs of infection, and respiratory compromise is appropriate. Treatment recommendations include pain control, nutritional supplementation, and daily bathing with hypochlorite baths followed by application of bland emollients every 4–6 hours. Those surviving the neonatal period should be monitored for achievement of developmental milestones since many are at risk for growth and developmental delay.

Oral *retinoids* are employed in HI if there is evidence that the thick scale is causing respiratory compromise. Retinoids, including isotretinoin and acitretin, promote desquamation, improving motion, respiration, ectropion, and eclabium. Acitretin is preferred for its fewer side effects and shorter half-life. Dosing should be 0.5–1 mg/kg/day. Retinoids are discontinued when the scale sheds and respiration improves. If oral retinoids cannot be tolerated, topical retinoids such as 0.1% tazarotene cream are also beneficial if used in limited areas, such as around the eyes, to relieve ectropion.

Infants (2 Months–1 Year)

Ichthyosis vulgaris (IV) and *X-linked ichthyosis* (XLI) are among the most common forms of ichthyosis. IV typically develops during infancy, revealing fine, rough, white scales most prominent on the extensor surfaces of the extremities with flexural sparing. XLI is sex-linked recessive and only affects males; the translucent, loosely adherent scales seen at birth are quickly replaced by adherent brown scales, most notably on the abdomen and extensor surfaces of lower limbs with flexural sparing. Baths and daily application of bland emollients to reduce scaling are preferred.

Rarely, infants may have normal skin at birth and subsequently develop ichthyosis. Disorders within the erythrokeratoderma variabilis et progressiva (EKVP) spectrum can present with migratory erythema and fixed, well-demarcated, hyperkeratotic plaques or symmetrically distributed, transient stationary, keratotic plaques on an erythematous base with palmoplantar keratoderma (PPK). Lesions appear on the extensor surfaces of extremities, buttocks, and face and can become confluent.

It is also essential to monitor growth and development because failure to thrive (FTT) is common among ichthyosis

patients. Appropriate consults and a gastrostomy feeding tube (G-tube) may be required. Infection and extracutaneous symptoms such as spastic diplegia in Sjögren–Larsson syndrome can also arise.

Children and Adults

Ichthyosis treatment in adults and children is tailored to age-specific needs. In infants and young children, treatment is focused on improving function and quality of life. In older children and adults, the significant impact of a visible disease motivates therapy. In such cases, first-line therapy includes baths and topical agents to reduce scaling and improve comfort. Since the skin of ichthyosis patients is susceptible to bacterial superinfection, dilute bleach baths can decrease risk of infection and improve odor. Bathing with two handfuls of baking soda is especially effective at removing scales, because the increased alkalinity may increase serine protease activity and promote desquamation. Despite its strong odor, topical 10% *N*-acetylcysteine with 5% urea has also demonstrated efficacy for scaling and ectropion and is another therapeutic option.

Emollients applied two to four times daily, ideally after bathing, can help retain moisture. Although discouraged in children because of stinging, adults can apply *keratolytics* including urea ($\geq 10\%$) and alpha-hydroxyacids (5–12%) to remove scale more effectively. Salicylic acid ($>2\%$) and topical tazarotene should be used on localized areas and can also relieve scaling.

Systemic retinoids, especially acitretin, are third-line therapeutics for scale-predominant disorders. For children and adults, we seek the lowest effective dose, and most respond to a dose between 0.5 and 1 mg/kg/day. Common side effects include dry lips, dry eyes, and photosensitivity. Rare side effects include long-term musculoskeletal effects, dyslipidemia, and liver injury. Therefore, serum vitamin D, lipid, and liver function tests are obtained at baseline, 1 month after initiating retinoids, and every 3 months afterwards. Retinoids should be used with caution in females of child-bearing potential; acitretin is relatively contraindicated in this population given the risk of retinoid embryopathy if conception occurs within 3 years of the last dose.

For epidermolytic ichthyoses, first-line therapies include emollients and bicarbonate baths to facilitate desquamation. Thick scales harbor a myriad of microorganisms, but antibiotics, antibacterial soaps, and bleach baths can control odor and reduce infection risk. Keratolytics and topical retinoids are second-line strategies that further reduce hyperkeratosis. Tolerance of keratolytics varies, and usage is limited to adolescents and adults. While topical retinoids and third-line systemic retinoids decrease infections and greatly improve skin appearance and function, they can exacerbate skin fragility. Therefore, it is important to initiate retinoids at a low dose and gradually increase to efficacy.

Exfoliative scale is seen in Netherton syndrome (NS) and treatment with emollients and focal use of topical steroids is standard of care. While corticosteroids can alleviate inflammation, impaired skin barrier increases risk of systemic toxicity of topical agents such as iatrogenic Cushing syndrome, especially among children. Therefore, monitoring serum drug levels is imperative, especially if using the topical immunomodulator, tacrolimus, to treat NS. Third-line therapies include biologics such as infliximab, a TNF- α inhibitor that targets inflammatory markers such as thymic stromal lymphopoietin (TSLP), interleukin-6, and interleukin-8 in the skin, resulting in clinical improvement in isolated case reports. Retinoids exacerbate desquamation and are contraindicated.

Psychosocial Management

The appearance of ichthyosis can be striking and intimidating, and families may feel guilty and reproachful. Without proper psychosocial support and education, there is a risk of delayed parental–infant bonding and child neglect after discharge. The ichthyoses profoundly impact quality of life from childhood to adulthood, and there is a high prevalence of depression and anxiety among affected individuals. Psychological assessment, support, and intervention is therefore crucial.

Resources

Foundation for Ichthyosis & Related Skin Types (for providers and patients): <http://www.firstskinfoundation.org/>

Free tele-ichthyosis service offering providers expert guidance on ichthyosis management: <https://www.firstskinfoundation.org/teleichthyosis>

Specific Investigations

Inherited ichthyosis

- Developmental milestones
- Growth and development, FTT
- Joint mobility
- Electrolyte balance (neonates and infants)
- Extracutaneous findings for syndromic ichthyoses (e.g., Sjögren–Larsson syndrome)
- Vitamin D status
- Mental health screening (depression, anxiety)
- Genetic testing

Acquired ichthyosis

- Malignancy screening
- Infection screen, including human immunodeficiency virus (HIV)
- Metabolic screening

Pathophysiologic basis for growth failure in children with ichthyosis: an evaluation of cutaneous ultrastructure, epidermal permeability barrier function, and energy expenditure. Moskowitz DG, Fowler AJ, Heyman MB, et al. *J Pediatr* 2004; 145(1): 82–92.

Growth failure and developmental delay have been observed in many types of ichthyosis. The abnormal skin barrier may contribute to FTT through chronic transepidermal water loss and calories.

Recognition and diagnosis of neuro-ichthyotic syndromes. Rizzo WB, Jenkins SM, Boucher P. *Semin Neurol* 2012; 32(1): 75–84.

This review describes the extracutaneous features of neuro-ichthyoses, including Sjögren–Larsson syndrome and trichothiodystrophy. Contractures and other joint mobility problems are common among these ichthyoses and must be considered in the diagnostic approach.

Ichthyosis in the newborn. Craiglow BG. *Seminars in perinatology* 2013; 37(1): 26–31.

A review of neonatal ichthyosis presentations and treatment options. Common complications mentioned include electrolyte imbalances and calorie malnutrition.

Vitamin D deficiency and rickets in children and adolescents with ichthyosiform erythroderma in type IV and V skin. Chouhan K, Sethuraman G, Gupta N, et al. *Br J Dermatol* 2012; 166: 608–15.

There is a potential for vitamin D deficiency in ichthyosis patients. All patients in this cross-sectional study had rickets.

Ichthyosis affects mental health in adults and children: a cross-sectional study. Sun Q, Ren I, Zaki T, et al. *J Am Acad Dermatol* 2020. doi:10.1016/j.jaad.2020.01.052.

Mental health problems such as depression and anxiety are prevalent among adults and children with ichthyosis.

Acquired ichthyosis. Patel N, Spencer LA, English JC, et al. *J Am Acad Dermatol* 2006; 55(4): 647–56.

A review of the assessment and treatment of acquired ichthyosis. The algorithm for evaluation includes malignancy, infection, and metabolic screening.

First-Line Therapies

• Bathing/soaking with or without bicarbonate and bleach	A
• Emollients	A

Rediscovering baking soda. Milstone LM. *J Am Acad Dermatol* 2010; 62(5): 885–6.

Sodium bicarbonate baths effectively remove scale in ichthyosis with no known risks.

Use of emollients in the treatment of dry skin conditions. Dyble T, Ashton J. *Br J Community Nurs* 2011; 16(5): 214–8.

Emollients are widely used to effectively treat dry skin conditions such as ichthyosis. This article discusses factors to consider when choosing the type of emollient in order to improve outcomes and compliance.

Association of glycerol and paraffin in the treatment of ichthyosis in children: an international, multicentric, randomized, controlled, double-blind study. Blanchet-Bardon C, Tadini G, Machado Matos M, et al. *J Eur Acad Dermatol Venerol* 2012; 26: 1014–9.

This large, double-blind study revealed that a 15% glycerol and 10% paraffin emollient significantly improved ichthyosis in children.

Efficacy of urea therapy in children with ichthyosis. A multicenter randomized, placebo-controlled, double-blind, semilateral study. Kuster W, Bohnsack K, Rippke F, et al. *Dermatology* 1998; 196: 217–22.

In this study, 60 children were treated with 10% urea lotion on one side and urea-free lotion on the other. After 8 weeks, 78% improved with 10% urea lotion and 72% improved without urea.

Second-Line Therapies

• Keratolytics (salicylic acid [avoid in infants, children under 12], urea, α -hydroxyacids, propylene glycol)	A
• Topical retinoids (tretinoin, tazarotene)	A
• Topical <i>N</i> -acetylcysteine	D

*Avoid for Netherton syndrome

Topical treatment of ichthyoses. Fleckman P, Newell BD, van Steensel MA, et al. *Dermatologic Therapy* 2013; 26(1): 16–25.

Discusses bathing, moisturization using emollients, keratolytics, retinoids, steroid ointments, calcineurin inhibitors, and future therapies in treating the ichthyoses.

Topical tazarotene for the treatment of ectropion in ichthyosis. Craiglow BG, Choate KA, Milstone LM. *JAMA Dermatol* 2013; 149(5): 598–600.

A 77-year-old woman with bilateral lower eyelid ectropion was successfully treated with 0.1% tazarotene cream.

Effect of topical tazarotene in the treatment of congenital ichthyoses. Hofmann B, Stege H, Ruzicka T, et al. *Br J Dermatol* 1999; 141(4): 642–6.

Twelve patients with congenital ichthyoses were treated with 0.05% tazarotene unilaterally and 10% urea cream on the contralateral side for 28 days. Tazarotene was more effective.

Successful treatment with topical *n*-acetylcysteine in urea in five children with congenital lamellar ichthyosis. Bassotti A, Moreno S, Criado E. *Pediatric Dermatology* 2011; 28(4): 451–5.

The authors reported 10% *N*-acetylcysteine and 5% urea markedly improved lamellar ichthyosis after 4 months.

Third-Line Therapies*

• Acitretin	A
• Isotretinoin	B
• Alitretinoin	D
• Dupilumab	E

*Avoid for Netherton syndrome

An appraisal of acitretin therapy in children with inherited disorders of keratinization. Lacour M, Mehta-Nikhar B, Atherton DJ, et al. *Br J Dermatol* 1996; 134(6): 1023–9.

In this review, 29 children with keratinization disorders received acitretin with an average dose of 0.47 mg/kg/day. Data supports long-term use.

Mutations in *KDSR* cause recessive progressive symmetric erythrokeratoderma. Boyden LM, Vincent NG, Zhou J, et al. *Am J Hum Genet* 2017; 100(6): 978–84.

Isotretinoin nearly resolved all features of progressive symmetric erythrokeratoderma (PSEK) caused by *KDSR* mutations.

Alitretinoin reduces erythema in inherited ichthyosis. Onnis G, Chiaverini C, Hickman G, et al. *Orphanet J Rare Dis* 2018; 13(1): 46.

While acitretin is the main retinoid used to treat severe ichthyosis, alitretinoin is a safer option for those who are pregnant or planning to become pregnant. Alitretinoin was shown to be more effective than acitretin at reducing erythema but less effective at reducing scaling.

Oral alitretinoin in congenital ichthyosis: a pilot study shows variable effects and risk of central hypothyroidism. Gånemo A, Sommerlund M, Vahlquist A. *Acta Derm Venerol* 2012; 92: 256–7.

Four patients with ichthyosis were treated with alitretinoin 10–30 mg once daily. Hypothyroidism was observed in two cases.

Treatment of Netherton syndrome with dupilumab. Steuer AB, Cohen DE. *JAMA Dermatol.* 2020 Mar 1;156(3):350–351.

A patient with Netherton syndrome reported 75% improvement of disease severity and functioning after two months of treatment with dupilumab and sustained improvement thereafter. Controlled trials are necessary to determine the role of dupilumab for treating Netherton syndrome.

Emerging Therapies

- Ex vivo cutaneous gene therapy
- Small molecule inhibitors (e.g., kallikrein inhibitors in NS)
- RNA interference (RNAi) for ichthyoses caused by dominant negative mutations (e.g., epidermolytic ichthyosis)

Congenital ichthyosis: an overview of current and emerging therapies. Vahlquist A, Gånemo A, Virtanen M. *Acta Derm Venereol* 2008; 88(1): 4–14.

Discusses emerging therapies such as gene therapy and RNAi technology in treating ichthyosis.

Pathogenesis-based therapies in ichthyoses. Lai-Cheong JE, Elias PM, Paller AS. *Dermatol Ther* 2013; 26(1): 46–54.

Discussed targeted treatment, such as delivering fragments of a deficient protease inhibitor, to treat NS.

Other

Life threatening salicylate poisoning caused by percutaneous absorption in severe ichthyosis vulgaris. Germann R, Schindera I, Kuch M, et al. *Hautarzt* 1996; 47(8): 624–7.

A 7-year-old boy with IV developed metabolic acidosis after topical 10% salicylic acid treatment.

Improved management of harlequin ichthyosis with advances in neonatal intensive care. Glick JB, Craiglow BG, Choate KA, et al. *Pediatrics* 2017; 139(1): e20161003.

A review of neonatal HI management, including family counseling.

Oral retinoid therapy for dermatologic conditions in children and adolescents. Brecher AR, Orlow SJ. *J Am Acad Dermatol* 2003; 49(2): 171–82.

A 0.45–1 mg/kg/day retinoid dosage is safe and efficacious in children.

Cushing syndrome from percutaneous absorption of 1% hydrocortisone ointment in Netherton syndrome. Halverstam CP, Vachharajani A, Mallory SB. *Pediatr Dermatol* 2007; 24(1): 42–5.

An 11-year-old boy with NS treated with 1% hydrocortisone for 1 year developed iatrogenic Cushing syndrome, emphasizing the necessity of proper monitoring.

Netherton syndrome: successful use of topical tacrolimus and pimecrolimus in four siblings. Bin Saif G, Al-Khenaizan S. *Int J Dermatol* 2007; 46(3): 290–4.

There was no significant difference in efficacy between tacrolimus and pimecrolimus.

Oral retinoid therapy for disorders of keratinization: single-center retrospective 25 years' experience on 23 patients. Katugampola RP, Finlay AY. *Br J Dermatol* 2006; 154: 267–76.

Children and adults with keratinization disorders taking oral retinoids developed skeletal, lipid, and liver abnormalities.

Oral liarozole versus acitretin in the treatment of ichthyosis: a phase II/III multicenter, double-blind, randomized, active-controlled study. Verfaillie CJ, Vanhoutte FP, Blanchet-Bardon C, et al. *Br J Dermatol* 2007; 156: 965–73.

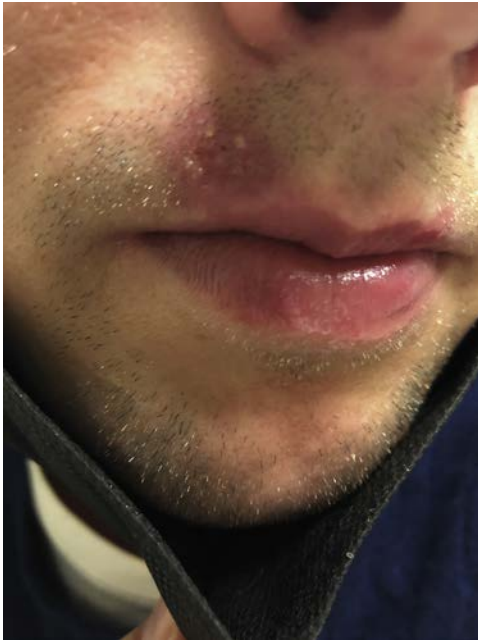
In this study, 32 patients were randomized to liarozole 75 mg twice daily or acitretin 10 mg in the morning and 25 mg at night for 12 weeks. Both groups improved, with fewer side effects in the former.

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Impetigo

R. Matthew McLarney, Warren R. Heymann



Impetigo is a common superficial bacterial infection of the skin, caused by *Staphylococcus aureus* or *Streptococcus pyogenes*. The infection is highly contagious and can easily spread to other body sites or close contacts. Impetigo usually affects children but can occur in people of any age. The worldwide population of children suffering from impetigo at any one time is estimated in excess of 162 million, making impetigo a global major public health problem.

Impetigo can be primary, with direct bacterial invasion of previously normal skin, or secondary, where infection develops when the skin barrier is disrupted by underlying disease, such as scabies.

Impetigo is classified as non-bullous or bullous. In the more common non-bullous form, thin-walled vesicles rupture to form superficial erosions with yellowish-brown crusts, which eventually heal without scarring. Bullous impetigo is characterized by larger bullae or blisters, which may continue to develop for several days.

Most cases of non-bullous impetigo are caused by *S. aureus*, but *S. pyogenes*, alone or in combination with *S. aureus*, may be implicated. In cooler climates, staphylococcal impetigo predominates, whereas in warmer and more humid climates, streptococcal impetigo is more common. Bullous impetigo is almost always caused by exfoliative toxin-producing strains of *S. aureus*. Secondary impetigo is usually caused by *S. aureus*.

MANAGEMENT STRATEGY

Impetigo is a self-limiting condition that will self-resolve in 2–3 weeks. The goal of treatment is to eradicate the infecting bacteria to allow rapid skin healing and control the spread of infection.

The ideal treatment should be effective, inexpensive, easily accessible, have limited adverse effects, and not promote bacterial resistance. This requires the use of an appropriate antimicrobial delivered in an effective manner. *Antibiotics may be administered either orally or topically.* The choice between topical or oral therapy depends on:

- The experience of the practitioner
- The preference of the patient
- The extent and severity of the disease
- The local bacterial resistance patterns
- The cost and availability of local resources

Topical or oral antibiotics with proven efficacy against *S. aureus* are the first choice of therapy. It is reasonable to use short courses of topical antibiotics for mild, limited impetigo, while reserving oral antibiotics for recalcitrant, extensive disease. In developing countries, topical agents are expensive and may be unavailable. Treatment strategies have to be sufficiently flexible to meet local needs.

Strains of bacteria causing impetigo are often extremely virulent. Patients therefore need to be educated on methods to avoid the spread of infection. Evidence regarding the value of disinfecting measures is limited; however, cleaning lesional skin with soap and water or a mild, non-irritant antiseptic will presumably aid the application of topical antibiotics and reduce the spread of infection.

Nasal carriage of *S. aureus* occurs in a high proportion of both patients, asymptomatic family members, and healthcare workers. Therefore, in recurrent, multiple familial, or nosocomial cases, treatment of nasal carriage may be necessary. Nasal swabs from the patient and immediate relatives should be performed to identify asymptomatic nasal carriers of *Staphylococcus aureus*. In the case of outbreaks on wards and in nurseries, healthcare professionals should also be swabbed. Eradication should be performed in asymptomatic carriers. The choice of antibiotic should be based on the sensitivities of organisms cultured from the pretreatment swab. This may require the use of a systemic antibiotic in conjunction with the nasal application of a topical antibiotic and an antiseptic skin cleanser.

Emerging antibiotic resistance has prompted the development of new therapies. Resistance to mupirocin and retapamulin is well-documented. Globally, the majority of isolates of *S. aureus* are resistant to penicillin; erythromycin resistance is also becoming more common. Methicillin-resistant *S. aureus* (MRSA) is an important cause of impetigo. MRSA poses a challenge because of its enhanced virulence and resistance to standard antibiotic therapy. Antibiotic treatment should be guided by knowledge of the likely causative agent and local resistance patterns, as well as bacterial susceptibility testing.

Specific Investigations

- Skin swabs for microbiologic assessment (Gram stain), culture, and sensitivity
- Nasal swabs from patients and immediate relatives in recalcitrant cases

A Gram stain of a swab from the lesion or exudate will reveal Gram-positive cocci, confirming the clinical diagnosis. Bacterial culture and sensitivity from a pretreatment swab are recommended to assess suitable alternative antibiotics for cases that do not respond to conventional treatment.

The global epidemiology of impetigo: a systematic review of the population prevalence of impetigo and pyoderma. Bowen AC, Mahé A, Hay RJ, et al. PLoS One 2015; 28; 10: e0136789.

The global prevalence of childhood impetigo is estimated to be in excess of 162 million.

Contemporary causes of skin and soft tissue infections in North America, Latin America, and Europe: report from the SENTRY Antimicrobial Surveillance Program (1998–2004). Moet GJ, Jones RN, Biedenbach DJ, et al. *Diagn Microbiol Infect Dis* 2007; 57: 7–13.

Antimicrobial surveillance confirms that *S. aureus* is the predominant pathogen causing skin and soft tissue infections in all studied geographic areas.

Impetigo in epidemic and nonepidemic phases: an incidence study over 4½ years in a general population. Rortveit S, Rortveit G. *Br J Dermatol* 2007; 157: 100–5.

S. aureus was the causal bacterium in 89% (117/132) and 68% (84/123) of impetigo cases during epidemic and non-epidemic periods, respectively ($p < 0.01$). *S. aureus* was resistant to fusidic acid in 84% (98/117) and 64% (54/84) of cases in epidemic and non-epidemic periods, respectively ($p < 0.01$).

DNA heterogeneity of *Staphylococcus aureus* strains evaluated by SmaI and SgrA1 pulsed field gel electrophoresis in patients with impetigo. Capoluongo E, Giglio A, Leonetti F, et al. *Res Microbiol* 2000; 151: 53–61.

Samples from lesional skin, nose, and pharynx were taken from 26 patients and their families, and the strain of *S. aureus* was typed; 54% of the patients had the same strain in both the nose and the lesion. In over half the families at least one other family member was found to be carrying the same strain as the patient's lesion.

High prevalence of mupirocin resistance in *Staphylococcus aureus* isolates from a pediatric population. Antonov NK, Garzon MC, Morel KD, et al. *J Antimicrob Chemother* 2015; 59(6): 3350–6.

In this study, 400 isolates from patients with skin infections from 2010 to 2012 were selected from a *S. aureus* surveillance study: 9.5% of isolates demonstrated retapamulin resistance, of which 58% were MRSA and 9.8% of isolates were found to have mupirocin resistance. *S. aureus* resistance to topical antimicrobials increased during the study period.

First-Line Therapies

• Topical mupirocin, fusidic acid, retapamulin, or ozenoxacin	A
• Oral flucloxacillin, cloxacillin, dicloxacillin, cephalexin, trimethoprim-sulfamethoxazole, or erythromycin	A
• Oral trimethoprim-sulfamethoxazole, clindamycin, fluoroquinolones, and tetracyclines in areas with high prevalence of MRSA	C
• Intravenous antibiotics	C
• Handwashing promotion for primary prevention	B

Interventions for impetigo (Cochrane Review). Koning S, van der Sande R, Verhagen AP, et al. *Cochrane Database Syst Rev* 2012; 1: D003261.

A systematic review of 68 trials, including 5578 participants, reporting on 50 different treatments, including placebo. There is good evidence that topical mupirocin and topical fusidic acid are equal to, or more effective than, oral antibiotics for people with limited impetigo. Fusidic acid, mupirocin, and retapamulin are

probably equally effective. Due to lack of studies in patients with extensive impetigo, it is unclear whether oral antibiotics are superior to topical antibiotics in this group.

No clear preference can be given for β -lactamase-resistant narrow-spectrum penicillins, broad-spectrum penicillins such as amoxicillin with clavulanic acid, cephalosporins, or macrolides. Penicillin was not as effective as most other antibiotics.

Treatment of impetigo in the pediatric population: consensus and future directions. Schachner LA, Torrelo A, Grada A, et al. *J Drugs Dermatol* 2020; 19: 281–90.

This review tabulates treatment regimens for impetigo.

Treatment of impetigo: oral antibiotics most commonly prescribed. Bolaji RS, Dabade TS, Gustafson CJ, et al. *J Drugs Dermatol* 2012; 11: 489–94.

Oral antibiotics are the most common class of medications used to treat impetigo in the United States. A shift toward topical antibiotics would likely decrease adverse effects associated with use of oral agents.

Short-course oral co-trimoxazole versus intramuscular benzathine benzylpenicillin for impetigo in a highly endemic region: an open-label, randomized, controlled, non-inferiority trial. Bowen AC, Tong SYC, Andrews RM, et al. *Lancet* 2014; 384(9960): 2132–40.

A total of 508 Australian children aged 3 months to 13 years with impetigo were assigned to receive a single dose of intramuscular benzathine benzylpenicillin, oral cotrimoxazole 4 mg/kg plus 20 mg/kg twice daily for 3 days, or oral cotrimoxazole 8 mg/kg plus 40 mg/kg once daily for 5 days. At day 7, 85% of patients were successfully treated, regardless of whether they received benzathine benzylpenicillin or pooled cotrimoxazole. There were similar results with 3-day and 5-day regimens of cotrimoxazole. Cotrimoxazole was better tolerated than benzathine benzylpenicillin.

Topical retapamulin ointment (1% wt/wt) twice daily for 5 days versus oral cephalexin twice daily for 10 days in the treatment of secondarily infected dermatitis: results of a randomized controlled trial. Parish LC, Jorizzo JL, Breton JJ, et al. *J Am Acad Dermatol* 2006; 55: 1003–13.

Retapamulin was as effective as cephalexin 500 mg BID (clinical success rates: 85.9% and 89.7%, respectively) in the treatment of patients with secondarily infected dermatitis. Microbiologic success rates were 87.2% for retapamulin and 91.8% for cephalexin. Retapamulin was well tolerated, and the topical formulation was preferred over the oral drug.

Ozenoxacin 1% cream in the treatment of impetigo: a multicenter, randomized, placebo- and retapamulin-controlled clinical trial. Gropper S, Albareda N, Chelius K, et al. *Future Microbiol* 2014; 9(9): 1013–23.

Patients received ozenoxacin 1% cream, retapamulin 1% ointment, or placebo cream twice daily for 5 days. At the final visit, the clinical success rate of ozenoxacin was 35%, retapamulin 38%, and placebo 19%. All treatments were well tolerated.

Topical mupirocin treatment of impetigo is equal to oral erythromycin therapy. Mertz PM, Marshall DA, Eaglstein WH, et al. *Arch Dermatol* 1989; 125: 1069–73.

Seventy-five patients were treated in an investigator-blinded study comparing topical mupirocin applied three times daily with oral erythromycin 30–50 mg/kg daily. The mupirocin-treated patients experienced similar clinical results to those treated with

oral erythromycin, although mupirocin was superior in the microbiological eradication of *S. aureus*.

The emergence of resistance to penicillin and erythromycin is so common in isolates of *S. aureus* that alternative antibiotics should be considered.

Disseminated bullous impetigo and atopic dermatitis: case series and literature review. Mannschreck D, Feig J, Selph J, et al. *Pediatr Dermatol* 2020; 37: 103–8.

Disseminated bullous impetigo was reported in 12 children, 11 of whom had atopic dermatitis. All children required IV or oral antibiotic therapy. Symptoms resolved in 24–72 hours for all except one child. The authors recommended cephalosporins as first-line for disseminated bullous impetigo.

Effect of handwashing on child health: a randomised controlled trial. Luby SP, Agboatwalla M, Feikin DR, et al. *Lancet* 2005; 366: 225–33.

In squatter settlements in Karachi, children younger than 15 years in households that received plain soap and handwashing promotion had a 34% lower incidence of impetigo than controls (95% CI, –52% to –16%).

Second-Line Therapies

• Addition of oral rifampin to standard oral antibiotic therapy	E
• Topical hydrogen peroxide	B
• Topical minocycline	B
• Topical gentian violet	C

Addition of rifampin to cephalexin therapy for recalcitrant staphylococcal skin infections – an observation. Feder HM Jr, Pond KE. *Clin Pediatr* 1996; 35: 205–8.

Two children with staphylococcal infections failing to respond to standard antibiotics responded when rifampin was added.

Topical gentian violet for cutaneous infection and nasal carriage with MRSA. Okano M, Noguchi S, Tabata K, et al. *Int J Dermatol* 2000; 39(12): 942–4.

In this study, 0.5% gentian violet was applied once daily to skin infections caused by MRSA in 28 patients, and 0.3% solution was applied to the anterior nares in nine cases of nasal MRSA colonization. Disinfection required a mean of 10.6 days for all cases (range 2–28). The only adverse reaction was purple color of the skin.

Hydrogen peroxide cream: an alternative to topical antibiotics in the treatment of impetigo contagiosa. Christensen OB, Anehus S. *Acta Dermatol Venereol* 1994; 74: 460–2.

A prospective comparison of hydrogen peroxide 1% cream with fusidic acid 2% cream (both applied 2–3 times daily) in 256 patients with impetigo. Over a 3-week treatment period, 92 patients of 128 (72%) in the hydrogen peroxide group were classified as healed, compared with 105 of 128 (82%) in the fusidic acid group. This difference was not statistically significant.

Topical minocycline foam for the treatment of impetigo in children: results of a randomized, double-blind, phase 2 study. Chamny S, Miron D, Lumelsky N, et al. *J Drugs Dermatol* 2016; 15(10): 1238–43.

Thirty-two children with impetigo were randomized to topical minocycline foam (TMF) 1% or TMF 4% twice daily for 7 days. Clinical cure was achieved in 57.1% of the TMF 1% and 50.0% of the TMF 4% groups. Both regimens were well tolerated.

Third-Line Therapy

• Povidone-iodine in controlling nosocomial spread of impetigo caused by MRSA	E

Prevention and control of nosocomial infection caused by methicillin-resistant *Staphylococcus aureus* in a premature infant ward: preventive effect of a povidone-iodine wipe of neonatal skin. Aihara M, Sakai M, Iwasaki M, et al. *Postgrad Med J* 1993; 69: S117–21.

An outbreak of MRSA causing impetigo was halted by wiping the body surface of the infants once daily with a diluted Iodine solution (10% povidone-iodine; 1:100 dilution).

Inducible urticarias, aquagenic pruritus, and cholinergic pruritus

Clive E.H. Grattan, Frances Lawlor



INDUCIBLE URTICARIAS

About 25% of patients with chronic urticaria have a definable and reproducible inducing trigger that distinguishes them from those with spontaneous urticaria and urticarial vasculitis. Inducible urticarias are defined by the predominant inducing stimulus (Table 114.1). More than one inducing stimulus elicits urticaria in some patients, and inducible urticarias can overlap with spontaneous urticaria. Physical urticarias caused by a physical stimulus (symptomatic dermatographism, delayed pressure, heat and cold contact and solar urticarias, and vibratory angioedema) are now included within the inducible urticarias.

MANAGEMENT STRATEGY

Pharmacologic

The presentation of inducible urticarias may vary in morphology and severity. Milder forms may require little more than *avoidance of triggers* and a preemptive dose of H_1 antihistamine around 1 hour before anticipated exposure, whereas a very severe attack involving anaphylaxis could potentially require emergency treatment with *intramuscular epinephrine (adrenaline)*. Acute presentations of severe inducible urticaria may require short courses of *oral corticosteroids* (e.g., prednisolone 0.5 mg/kg body weight daily for 5 days) in addition to regular non-sedating H_1 antihistamines. Drug management should be guided by the degree of disability or impairment in quality of life.

Non-pharmacologic

The triggering stimulus should be avoided where possible. Cold tolerance induction in cold urticaria and exercise tolerance induction in cholinergic urticaria has been described but is difficult to achieve and sustain. There is no evidence that exclusion diets are effective.

Specific Investigations

- Challenge (provocation) tests
- Blood tests (cryoproteins, specific IgE)

With the exceptions of testing for cryoglobulins in cold urticaria and specific IgE in food- and exercise-induced anaphylaxis, laboratory investigations are unnecessary and should not be undertaken except to monitor treatment or screen for eligibility (e.g., glucose-6-phosphatase dehydrogenase in patients being considered for dapsone or sulfasalazine).

The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Zuberbier T, Aberer W, Asero R, et al. *Allergy* 2018; 73(7): 1393–414.

The latest and most quoted European guideline on urticaria.

Chronic inducible urticaria: a systematic review of treatment options. Dressler C, Werner RN, Eisert L, et al. *J Allergy Clin Immunol* 2018; 141(5): 1726–34.

Thirty studies on chronic inducible urticarias were identified and reviewed to inform the 2017 EAACI guideline revision.

The definition, diagnostic testing, and management of chronic inducible urticarias – the EAACI/GA(2)LEN/EDF/UNEV consensus recommendations 2016 update and revision. Magerl M, Altrichter S, Borzova E, et al. *Allergy* 2016; 71(6): 780–802.

A comprehensive summary of provocation testing protocols.

Cold urticaria syndromes: historical background, diagnostic classification, clinical and laboratory characteristics, pathogenesis and management. Wanderer AA. *J Allergy Clin Immunol* 1990; 85: 965–81.

A classic review of cold urticaria and its investigation still relevant today.

Treatments of cold urticaria: a systematic review. Kulthanan K, Hunnangkul S, Tuchinda P, et al. *J Allergy Clin Immunol* 2019; 143(4): 1311–31.

A recent systematic review of treatment confirming the benefit of non-sedating antihistamines, up-dosing them to fourfold, and the place of omalizumab.

Heat urticaria: a revision of published cases with an update on classification and management. Pezzolo E, Peroni A, Gisondi P, et al. *Br J Dermatol* 2016; 175: 473–8.

A comprehensive review of this rare subtype of inducible urticaria.

First-Line Therapy

- Non-sedating ('second generation') H_1 antihistamines (can be used at up to fourfold the approved dose in the absence of contraindications) **A**

Non-sedating antihistamines (Table 114.2) should be prescribed in preference to classical antihistamines, which are often sedating and can impair psychomotor performance. Up-dosing of second-generation H_1 antihistamines is now widely practiced, although sedation at higher-than-licensed doses is a potential risk.

Table 114.1 Classification of inducible urticarias by the eliciting stimulus (in approximate reducing frequency of occurrence)

Symptomatic dermatographism	Stroking or rubbing the skin
Cholinergic urticaria (pale, papular wheals with red flares)	Rise in core temperature and other causes of sweating (exercise, hot baths, spicy food, and stress)
Cold urticaria	Rewarming of skin after cooling (localized or systemic)
Delayed pressure urticaria	Sustained perpendicular pressure
Solar urticaria	Ultraviolet or visible solar radiation
Heat urticaria	Local heat contact
Aquagenic urticaria	Water contact at any temperature
Vibratory angioedema	Vibration

Table 114.2 Examples of non-sedating and mildly sedating H₁ antihistamines

Acrivastine	Non-sedating, three-times-daily dosing
Bilastine	Non-sedating, once-daily dosing
Cetirizine	May be mildly sedating, once-daily dosing
Levocetirizine	Active enantiomer of cetirizine
Fexofenadine	Non-sedating, once-daily dosing
Loratadine	Non-sedating, once-daily dosing
Desloratadine	Active metabolite of loratadine
Mizolastine	Non-sedating, once-daily dosing
Rupatadine	Non-sedating, once-daily dosing

High-dose desloratadine decreases wheal volume and improves cold provocation thresholds compared with standard-dose treatment in patients with acquired cold urticaria: a randomized, placebo-controlled, cross-over study. Siebenhaar F, Degener F, Zuberbier T, et al. *J Allergy Clin Immunol* 2009; 123: 672–9.

Fourfold up-dosing a second-generation antihistamine has additional inhibitory effects on wheal formation in cold urticaria.

Rupatadine and its effects on symptom control, stimulation time, and temperature thresholds in patients with acquired cold urticaria. Metz M, Scholz E, Ferrán M, et al. *Ann Allergy Asthma Immunol* 2010; 104: 86–92.

A crossover, randomized, double-blind, placebo-controlled study of double-dose rupatadine, a second-generation H₁

antihistamine. Fifty-two percent of patients showed a complete response. There was also a significant improvement in critical cold stimulation time and critical temperature threshold.

Second-Line Therapies

Symptomatic dermatographism

- Omalizumab **B**
- Narrowband UVB (NB-UVB) phototherapy **C**
- H₂ antihistamines **B**

Cholinergic urticaria

- Omalizumab **B**
- Danazol **B**
- Anticholinergics **E**

Cold urticaria

- Omalizumab **B**
- Leukotriene receptor antagonists **E**
- Cold tolerance (desensitization) **E**

Heat urticaria

- Omalizumab **D**

Delayed pressure urticaria

- Omalizumab **D**
- Leukotriene receptor antagonists **B**
- Sulfasalazine **C**
- Dapsone **C**

Solar urticaria

- Omalizumab **C**
- Induction of tolerance (phototherapy and photochemotherapy) **D**

SYMPTOMATIC DERMOGRAPHISM

Omalizumab is effective in symptomatic dermatographism – results of a randomized placebo-controlled trial. Maurer M, Schütz A, Weller K, et al. *J Allergy Clin Immunol* 2017; 140(3): 870–3. e5.

Narrow-band ultraviolet B phototherapy is beneficial in antihistamine-resistant symptomatic dermatographism: a pilot study. Borzova E, Rutherford A, Konstantinou G, et al. *J Am Acad Dermatol* 2008; 59: 752–7.

A small, open study of H₁ antihistamine-unresponsive symptomatic dermatographism showing subjective and objective improvement in itch and whealing after 6 weeks' treatment, but relapse 6–12 weeks after stopping.

In dermatographic urticaria H₂ receptor antagonists have a small but therapeutically irrelevant additional effect compared with H₁ antagonists alone. Sharpe GR, Shuster S. *Br J Dermatol* 1993; 129: 575–9.

In this double-blind, crossover study, 19 patients were randomized to treatment with cetirizine 10 mg at night plus either ranitidine 150 mg twice daily or placebo. There was an increase in whealing threshold with additional H₂ blockade, but no subjective benefit on itch.

Addition of an H_2 to an H_1 antihistamine may provide better control of some inducible urticarias despite a lack of trial evidence. They may benefit wheal and erythema but not itch.

CHOLINERGIC URTICARIA

Efficacy and safety of omalizumab (Xolair) for cholinergic urticaria in patients unresponsive to a double dose of antihistamines: a randomized mixed double-blind and open-label placebo-controlled clinical trial. Gastaminza G, Azofra J, Nunez-Cordoba JM, et al. *J Allergy Clin Immunol Pract* 2019; 7(5): 1599–609. e1.

About a third of cholinergic urticaria patients became negative on an exercise challenge test after 48 weeks of treatment with omalizumab, demonstrating some benefit under conditions of the study but disappointing overall. Relapse of symptoms was seen in the majority 3 months after finishing treatment.

Real-life treatment of cholinergic urticaria with omalizumab. Altrichter S, Chuamanochan M, Knoth H, et al. *J Allergy Clin Immunol* 2019; 143(2): 788–91. e8.

In this retrospective analysis, six (37%) of 16 cholinergic urticaria patients had a complete response and five (31%) had useful benefit from omalizumab at different doses, the majority receiving 300 mg at some point in their treatment.

Beneficial effects of danazol on symptoms and laboratory changes in cholinergic urticaria. Wong E, Eftekhari N, Greaves MW, et al. *Br J Dermatol* 1987; 116: 553–6.

Seventeen male patients treated with danazol 200 mg three times daily in a double-blind, crossover study had sustained improvement in the number of exercise-induced wheals over 12 weeks.

Anabolic steroids should only be considered for severe cholinergic urticaria not responding adequately to up-dosed H_1 antihistamines, because of their potential for virilization and hepatotoxicity. Danazol should be reserved for severe cases and avoided during pregnancy. Androgenic adverse effects may be dose-limiting in women.

Severe cholinergic urticaria successfully treated with scopolamine butylbromide in addition to antihistamines. Ujiie H, Shimizu T, Natsuga K, et al. *Clin Exp Dermatol* 2006; 31: 978–81.

Although this case report suggests that anticholinergics may be successful for cholinergic urticaria, the general experience with this class of drugs is disappointing, and unwanted effects often outweigh any benefits.

Scopolamine butylbromide is better known as hyoscine butylbromide, approved for gastrointestinal spasm and not to be confused with hyoscine hydrobromide used for motion sickness.

COLD URTICARIA

Omalizumab is effective in cold urticaria-results of a randomized placebo-controlled trial. Metz M, Schütz A, Weller K, et al. *J Allergy Clin Immunol* 2017; 140(3): 864–7. e5.

Improvement of cold urticaria by treatment with the leukotriene receptor antagonist montelukast. Hani N, Hartmann K, Casper C, et al. *Acta Derm Venereol* 2000; 80: 229.

A case report of a patient with acquired cold-contact urticaria responding subjectively and objectively to montelukast 10 mg daily after only 4 days.

Cold urticaria: a clinico-therapeutic study in 30 patients, with special emphasis on cold desensitization. Henquet JM, Martens BPM, van Volten WA. *Eur J Dermatol* 1992; 2: 75–7.

Cold desensitization in four patients with severely disabling cold urticaria resulted in symptom-free follow-up ranging from 4 to 14 years. Induction of cold tolerance took 1–2 weeks.

Patients had to take cold showers (around 15°C) for 5 min twice a day to maintain the tolerance, so this approach is not for the faint-hearted. Cold tolerance is now outdated.

Cold urticaria: tolerance induction with cold baths. Von Mackensen YA, Sticherling M. *Br J Dermatol* 2007; 157: 799–846.

Nine of 23 patients desensitized with cold water immersions 15 years earlier responded to a questionnaire survey. Only one of them was able to continue the cold baths for 6 months, two for 3 months, and the others stopped almost immediately.

This report introduces a little realism concerning the likelihood of cold desensitization being an effective and well-tolerated long-term therapy for cold-contact urticaria.

HEAT URTICARIA

Treatment of severe heat urticaria with omalizumab – report of a case and review of the literature. Bonnekoh H, Terhorst-Molawi D, Buttgerit T, et al. *J Eur Acad Dermatol Venereol* 2020 Apr 1. doi: 10.1111/jdv.16407 [Epub ahead of print].

Heat urticaria is very rare. There are a small number of cases responding to omalizumab.

DELAYED PRESSURE URTICARIA

Rapid response to omalizumab in 3 cases of delayed pressure urticaria. Quintero OP, Arrondo AP, Veleiro B. *J Allergy Clin Immunol Pract* 2017; 5: 179–80.

Efficacy of montelukast, in combination with loratadine, in the treatment of delayed pressure urticaria. Nettis E, Pannafino A, Cavallo E, et al. *J Allergy Clin Immunol* 2003; 112: 212–3.

In a small, randomized study, objective pressure rechallenge after 15 days showed that montelukast 10 mg once daily with loratadine 10 mg once daily was more effective than either drug alone.

Desloratadine in combination with montelukast suppresses the dermatographometer challenge test papule, and is effective in the treatment of delayed pressure urticaria: a randomized, double-blind, placebo-controlled study. Nettis E, Colanardi MC, Soccio AL, et al. *Br J Dermatol* 2006; 155: 1279–82.

Although this study suggests that pressure urticaria can be controlled without steroids, clinical experience with montelukast in delayed pressure urticaria is usually disappointing.

Delayed pressure urticaria: response to treatment with sulfasalazine in a case series of seventeen patients. Swerlick RA, Puar N. *Dermatol Ther* 2015; 28: 318–22.

This open study supports the use of sulfasalazine in delayed pressure urticaria.

Potential side effects include bone marrow depression and hypersensitivity reactions, so patients need careful monitoring. Sulfasalazine should only be considered in patients who are not sensitive to aspirin and other non-steroidal drugs.

Delayed pressure urticaria – dapsons heading for first-line therapy. Grundmann SA, Kiefer S, Luger TA, et al. J Dstch Dermatol Ges 2011; 9: 908–12.

Of 31 patients with pressure urticaria treated with dapsons over a 6-year period surveyed retrospectively, 74% showed a good or very good response.

Dapsons can also be a useful and inexpensive treatment of delayed pressure urticaria.

SOLAR URTICARIA

Clinical and photobiological response in eight patients with solar urticaria under treatment with omalizumab, and review of the literature. Morgado-Carrasco D, Fustá-Novell X, Podlipnik S, et al. Photodermatol Photoimmunol Photomed 2018; 34(3): 194–9.

Omalizumab for the treatment of solar urticaria: case series and systematic review of the literature. Snast I, Kremer N, Lapidoth M, et al. J Allergy Clin Immunol Pract 2018; 6(4): 1198–204. e3.

Two small series of solar urticaria patients responding well to omalizumab, which can now be considered the treatment of choice after H₁ antihistamines for this rare condition before considering phototherapy or photochemotherapy.

Narrowband ultraviolet B phototherapy is a suitable treatment option for solar urticaria. Calzavara-Pinton P, Zane C, Rossi M, et al. J Am Acad Dermatol 2012; 67: e5–9.

Patients without an urticarial response to phototesting with NB-UVB were given an alternate-day exposure for 4 weeks. Those with an urticarial response to phototesting with NB-UVB were treated three times a day for 5 days in the first week and then subsequently the same as the first group for 3 weeks. Thirty-nine patients completed the study and reported good tolerance to the sun afterward.

Solar urticaria: long-term rush hardening by inhibition spectrum narrow-band UVB 311 nm. Wolf R, Herzinger T, Grathovac M, et al. Clin Exp Dermatol 2013; 38: 446–7.

UVA rush hardening for the treatment of solar urticaria. Beissert S, Ständer H, Schwarz T. J Am Acad Dermatol 2000; 42: 1030–2.

Protection was achieved within 3 days of exposing three patients to multiple incremental UVA irradiations at 1-hour intervals. Rush hardening with UVA did not cause sunburn reactions and provided protection against visible light and UVB-induced urticaria in two of the three patients.

UV-induced tolerance should be considered for patients who need more than antihistamines.

Successful and long-lasting treatment of solar urticaria with UVA rush hardening therapy. Masuoka E, Fukunga A, Kishigami K, et al. Br J Dermatol 2012; 167: 198–201.

Two patients with solar urticaria who reacted to intradermal injection of their own serum that had been preirradiated with visible light were treated with multiple UVA incremental exposures at 1-hour intervals for 2–3 days and became symptom free, and their postirradiation skin tests became negative. Maintenance UVA exposures were performed every 1 or 2 weeks for 4 months in one patient and 5 months in the other. The first patient remained clear off treatment for 6 months.

Successful treatment with UVA rush hardening in a case of solar urticaria. Mori N, Makino T, Matsui K, et al. Eur J Dermatol 2014; 24: 117–9.

A direct comparison between NB-UVB, psoralen UVA (PUVA), and UVA hardening for solar urticaria has not been performed to date.

Third-Line Therapies

• Intravenous immunoglobulins	D
• Ciclosporin	E
• Plasmapheresis	E
• Etanercept	E

Effect of high-dose intravenous immunoglobulin in delayed pressure urticaria. Dawn G, Urcelay M, Ah-Weng A, et al. Br J Dermatol 2003; 149: 836–40.

Three of eight patients went into remission after one or more infusions of intravenous immunoglobulin (IVIG) at 2g/kg and two improved, but confirmation of pressure-induced wheals by objective testing was not done, and all patients had spontaneous chronic urticaria. It was not clear whether the benefit of treatment was mainly on the pressure urticaria or the spontaneous urticaria.

Cold urticaria responding to systemic ciclosporine. Marsland AM, Beck MH. Br J Dermatol 2003; 149: 214.

One patient with acquired cold-contact urticaria of over 1 year's duration and unresponsive to antihistamines improved within a week of starting ciclosporin at 3 mg/kg daily, and the improvement was maintained at 1.7 mg/kg/day. It was not stated what happened on stopping treatment.

There is currently no good evidence that acquired cold-contact urticaria is an autoimmune disease, so the use of immunomodulating drugs should be regarded as speculative and of unproven benefit. The benefit seen in some patients probably relates to partial inhibition of histamine release. H₁ antihistamines should be given concurrently.

Ciclosporin A therapy for severe solar urticaria. Edström DW, Ros AM. Photodermatol Photoimmunol Photomed 1997; 13: 61–3.

A clinically useful reduction in sensitivity to visible or ultraviolet (UV) light occurred while taking ciclosporin at 4.5 mg/kg daily, but the symptoms recurred within 1–2 weeks of stopping treatment. The authors suggest that this treatment might be appropriate for severe disease when other treatments have failed, especially in countries where treatment is necessary only for a few months during summer.

Solar urticaria—effective treatment by plasmapheresis. Duschet P, Leyen P, Schwarz T, et al. Clin Exp Dermatol 1987; 12: 185–8.

A refractory period of at least 12 months followed a single treatment with 3 L plasmapheresis.

Successful treatment of delayed pressure urticaria with anti-TNF- α . Magerl M, Philipp S, Manasterski M, et al. J Allergy Clin Immunol 2007; 119: 752–4.

Single case report of a complete response of pressure urticaria symptoms within a week of starting etanercept for concurrent psoriasis.

Successful treatment of systemic cold contact urticaria with etanercept in a patient with psoriasis. Gualdi G, Monari P, Rossi MT, et al. Br J Dermatol 2012; 166: 1373–4.

A patient with longstanding cold-contact urticaria and psoriasis treated with etanercept underwent resolution of both conditions within weeks of starting treatment, relapsed on withdrawal, and improved on reintroduction.

AQUAGENIC PRURITUS

Aquagenic pruritus is diagnosed when itching, prickling, burning, buzzing, or other skin discomfort, which may be intense, are provoked by contact with water. There are no visible skin changes. The sensation is associated with feelings of anger, irritability, or depression in approximately half of patients. The symptoms are provoked at any water temperature and degree of salinity. They occur within minutes rather than hours and start either during a bath or shower or soon afterward. The discomfort may be present for between 10 min and 2 hours. Any part of the body may be affected. Patients may also itch when the ambient temperature changes. Spontaneous remission is rare. The pathogenesis of the condition is not clear.

MANAGEMENT STRATEGY

Other chronic skin diseases must be ruled out by taking a full history and by clinical examination (particularly aquagenic pruritus of the elderly manifesting as xerosis and other inducible urticarias). Direct questioning is necessary regarding cold-induced symptoms and whealing; water-induced whealing or syncope; exercise-, heat-, or emotion-induced symptoms and whealing; and friction-induced itching and whealing. Familial cases occur. The well-recognized 'bath itch' that occurs in approximately 40% of patients with polycythemia vera must be ruled out before aquagenic pruritus is diagnosed. Rarely, other hematologic abnormalities have also been associated including myeloproliferative, myelodysplastic, hypereosinophilic conditions and juvenile xanthogranuloma, hepatitis C, and lactose intolerance. Occasionally, antimalarial drugs have induced an aquagenic pruritus-like picture in patients with lupus erythematosus. When the diagnosis is reached, it is important to explain that aquagenic pruritus is a recognized skin condition, which, although very unpleasant and difficult to manage, has no immediate implications with regard to the patient's general health. Drug treatment is usually based on the use of *antihistamines*, *adding sodium bicarbonate to the water*, and *phototherapy*. β -Blockers have been used. Treatment directed against chronic, generalized pruritus may help. *Topical mild cleansers and emollients* may be used in patients unresponsive to treatment. *Gabapentin* starting at low dose and increasing is an option. Mirtazapine 15 mg daily can be given either alone or added to gabapentin.

Specific Investigations

- Complete blood count (repeated yearly)
- Water induction

First-Line Therapies

• Explanation	E
• Minimally sedating antihistamine	C
• Sodium bicarbonate added to bath water	D
• Mild cleaner/soap substitute	D
• Emollients	D

Antihistamines are used by these authors in the management of aquagenic pruritus. There is no consensus regarding the first-line

treatment, as the response of each patient is individual and no single treatment is effective in all cases; however, it would seem reasonable to start by advising a minimally sedating antihistamine 2 hours before the bath or shower on a regular basis. Patients may have a good response to antihistamines. Not all patients respond to antihistamine treatment, however, and, of those who do, the response may consist of a diminution rather than an abolition of symptoms.

Aquagenic pruritus. Greaves MW, Black AK, Eady RAJ, et al. *Lancet* 1981; 282: 2008–11.

Aquagenic pruritus. Steinman HK, Greaves MW. *J Am Acad Dermatol* 1985; 13: 91–6.

Aquagenic pruritus: pharmacological findings and treatment. Greaves MW, Handfield-Jones SE. *Eur J Dermatol* 1992; 2: 482–4.

Aquagenic pruritus may respond to the addition of sodium bicarbonate to the bath water. Advice about the amount of sodium bicarbonate to be added varies. In those who have responded, amounts of 200 g, 100 g, and 25 g have been added. The most practical approach might be to start with approximately 200 g per bath, and if there is a satisfactory response, to reduce gradually to a level that continues to suppress the itching. In a series of 25 patients, 25% improved with this treatment; however, in some cases the response may be temporary. Large quantities of sodium bicarbonate may be purchased economically at bakers' wholesalers.

Baking soda baths for aquagenic pruritus. Bayoumi AHM, Highet AS. *Lancet* 1986; 11: 464.

Clinical practice. Chronic pruritus. Yosopovitch G, Bernard JD. *New Engl J Med* 2013; 368(17): 1625–34.

Second-Line Therapies

• UVB	C
• NB-UVB	E
• Combined UVA/NB-UVB therapy	E

Due to the necessity for hospital attendance, UVB should be considered a second-line treatment for aquagenic pruritus. A response usually occurs between 2 and 4 weeks of treatment, but relapse normally occurs within months of stopping treatment, which may then be repeated as necessary or maintenance therapy instituted as the condition is ongoing.

A good response to NB-UVB is described in two patients to whom it was administered three times per week. The improvement occurred at about 2 months of treatment and was maintained on weekly treatment in the ensuing months. In one of the patients desloratadine was added during the maintenance period. NB-UVB may prove to be effective.

Combined UVA and UVB treatment was used to treat one patient with good response.

Ultraviolet phototherapy for pruritus. Rivard J, Lim HW. *Dermatol Ther* 2005; 18: 344–54.

Narrow band ultraviolet B in aquagenic pruritus. Xifra A, Carrascosa JM, Ferrandiz C. *Br J Dermatol* 2005; 158: 1233.

Aquagenic pruritus responding to combined ultraviolet A/narrowband UVB therapy. Jean M, Koh A, Chong WS. *Photodermatol Photoimmunol Photomed* 2009; 25: 169.

Third-Line Therapies

• Bath oil	E
• Emulsifying ointment in the bath water	E
• PUVA	E
• Propranolol	E, C
• Transdermal nitroglycerin	E
• Naltrexone	E
• Gabapentin	E
• Mirtazapine	E

PUVA treatment has been effective in the bath itch of polycythemia vera and has been used successfully both in a series of five patients and in individual patients, although either maintenance or repeated courses of therapy are necessary to maintain control of the condition. PUVA with oral psoralens may be regarded as a third-line treatment for practical reasons.

Aquagenic pruritus responding to intermittent phototherapy. Holme SA, Anstey AV. Clin Exp Dermatol 2001; 26: 40–1.

Repeated PUVA treatment of aquagenic pruritus. Goodkin R, Bernhard JD. Clin Exp Dermatol 2002; 27: 164–5.

Aquagenic pruritus responds to propranolol. Thomsen K. J Am Acad Dermatol 1990; 22: 697.

Treatment with propranolol of six patients with idiopathic aquagenic pruritus. Nosbaum A, Pecquet C, Bayrow O, et al. J Allergy Clin Immunol 2011; 28: 113.

After a report of successful treatment of two patients with propranolol, six patients were treated with propranolol 10–40 mg/day for 3 months depending on their tolerance of the drug. Either relief or elimination of symptoms occurred in five after 7 days. Relapse took place after stopping, and one patient needed retreatment, which was effective.

Aquagenic pruritus response to the exogenous nitric oxide donor, transdermal nitroglycerin. Goiha Yahr M. Int J Dermatol 1994; 33: 752.

Transdermal nitroglycerin has been used effectively in one patient.

Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus and dermatological diseases. Metze D, Reinmann S, Beissert S, et al. J Am Acad Dermatol 1999; 41: 533–9.

Successful treatment of refractory aquagenic pruritus with naltrexone. Ingber S, Cohen PD. J Cutan Med Surg 2005; 9: 215–6.

Naltrexone at a dose of 50 mg daily controlled the condition in the two patients with aquagenic pruritus to whom it was given.

Clinical practice. Chronic pruritus. Yosopovitch G, Bernard JD. New Engl J Med 2013; 368(17): 1625–34.

CHOLINERGIC PRURITUS

Cholinergic pruritus occurs when patients itch, sting, or prickle after a rise in body temperature. The provoking stimuli are exercise (walking, running, dancing, going to the gym), including housework (ironing, vacuuming), heat (hot room, hot food, hot bath,

sunny day), and emotion (excitement, stress, embarrassment) or fever. A combination of factors may cause a more pronounced itch (e.g., walking on a sunny day). The intensity, extent, and duration of the itching seem to be directly proportional to the strength of the eliciting stimulus. By definition, no whealing occurs on the skin during an attack. Although the prevalence of this condition is not known, it is the authors' impression that many people itch when they become warm, although this itching is frequently insufficiently severe or incapacitating to present at a dermatology clinic. Cholinergic pruritus can be regarded as a variant of cholinergic urticaria. There is one case report that describes a patient presenting initially with cholinergic pruritus who progressed to cholinergic urticaria. Because there are no visible skin lesions, it is important to be aware of the condition and to differentiate it from aquagenic pruritus in those who describe itching after a bath or shower.

MANAGEMENT STRATEGY

Explaining the provoking factors and stressing that the condition is not an allergy, not related to diet, nor related to any underlying disease is helpful. If possible, *minimizing situations in which the itching occurs* can be helpful, and cooling the skin as quickly as possible may lessen the duration of the itching. It is impossible to tell the patient how long the condition will be present before remission takes place. Therapeutic agents typically utilized are *antihistamines*, although *danazol* has been reported to be beneficial. In the severely affected patient unresponsive to the standard recommended treatments, systemic drugs recommended for cholinergic urticaria can be used.

Specific Investigations

- Exercise induction
- Warm bath induction (40–41°C)

First-Line Therapies

• Explanation	E
• Second generation H ₁ antihistamines	E

An explanation is the most important part of treatment. The patient needs to understand the relationship between the itching and heat and the importance of keeping cool. Treatment with minimally sedating antihistamines generally produces an improvement, although they are unlikely to suppress the condition completely. Antihistamines should be taken regularly every morning or 2 hours before an expected stimulus in order to assess any response. If the antihistamine proves helpful, the same dose could be repeated 9–12 hours later if necessary.

Second-Line Therapy

• Danazol	C

Cholinergic pruritus, erythema, and urticaria: a disease spectrum responding to danazol. Berth-Jones J, Graham Brown RAC. Br J Dermatol 1989; 121: 235–7.

Danazol, which has been used in cholinergic urticaria, may rarely be effective in very severely affected individuals. The recommended dose is 200 mg three times daily. This dose could be continued for approximately 1 month and reduced to the minimum that controls the condition.

Irritant contact dermatitis

Mary Kathryn Abel, Jenny E. Murase



Irritant contact dermatitis (ICD) is the most common form of contact dermatitis and is defined as the reaction to an exogenous substance – the irritant – that damages the epidermis through physical or chemical mechanisms, triggering an innate immunologic response. Clinical manifestations of ICD vary according to multiple factors, including the preexisting status of the skin (atopy, barrier disruption), the nature and number of irritants (corrosive or caustic), the duration and frequency of contact, and the conditions of exposure (moisture, occlusion, temperature). Acute ICD is usually attributable to a single irritant, while chronic ICD results from repeated exposure to multiple irritants and often involves the hands.

MANAGEMENT STRATEGY

Correct diagnosis is essential in the management of ICD. A thorough evaluation will include patch testing to rule out allergic contact dermatitis (ACD), a family history (including history of atopy, psoriasis, or other skin conditions), and history of work, habits, hobbies, and exposures to determine the possible causative irritants. Irritant avoidance is key to treatment and prevention. Minimizing contact with the irritant and using protective equipment such as gloves and aprons are necessary, as is appropriate patient and employer education. However, even with avoidance and education, further treatment for ICD is often required. These treatments have not been rigorously evaluated in patients with ICD despite their widespread use; rather, the majority of the literature includes patients with chronic hand dermatitis (CHD), ACD, or atopic dermatitis.

Moisturizers, emollients, and barrier creams are used as first-line therapy. While the terms 'moisturizer' and 'emollient' are often used synonymously, moisturizers include humectants like lactic acid, urea, glycerin, or sorbic acid, which attract water to hydrate the stratum corneum. Moisturizers come in different

consistencies (from light to heavy): lotions, creams (Vanicream, Eucerin, CeraVe cream, Cetaphil cream), or ointments (Aquaphor, Vaseline petroleum jelly, shea butter). Emollients (petrolatum, lanolin, mineral oil) work by slowing transepidermal water loss, and also hydrating the skin like moisturizers. Barrier creams, on the other hand, are designed to repair the skin barrier to allow for healing. Moisturizers, emollients, and barrier creams can be used liberally multiple times a day on the affected or exposed areas.

Topical corticosteroids can also be used to aid in the treatment of ICD if avoidance and moisturizing are not sufficient. For severe acute ICD or chronic ICD with skin thickening, a super high-potency steroid can be applied 1–2 times daily for the acute phase, with expeditious transition to medium-to-high potency steroids. ICD involving the face or flexural areas should be treated with a medium- or low-potency corticosteroid applied 1–2 times daily. Additionally, topical calcineurin inhibitors (tacrolimus 0.1% or pimecrolimus 1% cream) can be used 1–2 times daily for refractory ICD when topical therapy is required for an extended period of time to avoid the atrophy that accompanies chronic topical corticosteroid use.

Second-line therapies for ICD include narrowband ultraviolet light (NB-UVB) or broadband UVB therapy. UV therapy can be administered 2–4 times per week from home with devices like the M Series unit from Daavlin or Handisol II from National Biological. Hand psoralen plus UVA (PUVA) photochemotherapy can be delivered using oral or topical psoralen administration. PUVA is considered inferior to UVB due to its phototoxic effects in overdose or if the topical solution is not applied evenly.

Dupilumab is a monoclonal antibody injection that acts as a dual inhibitor of IL-4 and IL-13 signaling. The recommended dose for an adult patient is 600 mg (two 300 mg injections), then 300 mg injections every other week. At the time of this publication, dupilumab is approved for moderate-to-severe atopic dermatitis, asthma, and nasal polyps; however, even in its early stages of testing, the medication is showing extremely promising results with CHD.

Finally, steroid-sparing immunosuppressants like methotrexate (10–25 mg/week) and ciclosporin (3–5 mg/kg/day), or acitretin (10–50 mg)/alitretinoin (30 mg), can be used but are not recommended unless the ICD is refractory to all other conventional therapies.

Specific Investigations

- Patch testing to environmentally relevant allergens
- Detailed case history of patient's work, habits, hobbies, and exposures

Irritant dermatitis. Chew AL, Maibach HI, eds. Berlin/Heidelberg, Springer, 2005.

In addition to a detailed clinical, family, and occupational history including the patient's chemical environment, patch testing can aid in differentiating between ICD and ACD.

Contact dermatitis: a practice parameter – update 2015. Fonacier L, Bernstein DI, Pacheco K, et al. J Allergy Clin Immunol Pract 2015; 3: S1–39.

All patients suspected of having a combination of ICD and ACD should undergo patch testing to rule out ACD. Patch testing is the gold standard to confirm the diagnosis of ACD.

First-Line Therapies

- Physical skin protection **A**
- Emollients, moisturizers, keratolytics (β -hydroxyacid [salicylic acid] and alpha hydroxyacid), and humectants (urea, glycerin, sodium lactate; includes occlusives like mineral oil, petrolatum, lanolin, dimethicone, shea butter) **A**
- Barrier creams (Cavilon, Baza Protect, PeriShield) **A**
- Topical corticosteroids **B**
- Topical calcineurin inhibitors **A**

High-fat petrolatum-based moisturizers and prevention of work-related skin problems in wet-work occupations. Mygind K, Sell L, Flyvholm MA, et al. *Contact Dermatitis* 2006; 54: 35–41.

In this randomized controlled study of 644 gut cleaners in Danish swine slaughterhouses, protective gloves were most effective at reducing the frequency of eczema and could not be replaced by high-fat petrolatum moisturizers.

Effect of glove-occlusion on human skin (II). Long-term experimental exposure. Ramsing DW, Agner T. *Contact Dermatitis* 1996; 34: 258–62.

Hypoallergenic, non-latex, occlusive gloves (Elastyren) worn for prolonged periods may impair skin barrier function. Wearing cotton gloves under the occlusive gloves can prevent this effect.

Efficacies of a barrier cream and an after work emollient cream against cutting fluid dermatitis in metalworkers: a prospective study. Goh CL, Gan SL. *Contact Dermatitis* 1994; 31: 176–80.

In this randomized controlled trial of 54 metal workers, participants received either a barrier cream (Arretil), an afterwork emollient cream (Keri lotion), or no cream. There was no significant difference in the prevalence of cutting fluid dermatitis or transepidermal water vapor loss; however, afterwork emollient cream reduced the prevalence of cutting fluid irritation.

A randomized comparison of an emollient containing skin-related lipids with a petrolatum-based emollient as adjunct in the treatment of chronic hand dermatitis. Kucharekova M, Van de Kerkhof PCM, Van de Valk PGM. *Contact Dermatitis* 2003; 48: 293–9.

The use of either Locobase Repair emollient (containing skin-related lipids) or petrolatum-based emollient was associated with significant improvement in CHD. No significant difference in the improvement was demonstrated for the emollient containing skin-related lipids.

Double-blind, randomized study to assess the effectiveness of different moisturizers in preventing dermatitis induced by hand washing to simulate healthcare use. Williams C, Wilkinson SM, McShane P, et al. *Br J Dermatol* 2010; 162: 1088–92.

A total of 132 patients were enrolled in this double-blind, randomized study to evaluate the effect of five different moisturizers on skin barrier function. Three of the five moisturizers led to a statistically significant decrease in transepidermal water loss and increase in subclinical assessment of epidermal hydration. These results suggest that regular application of moisturizers offers

protective effects against repeated exposure to irritants without the loss in barrier efficacy.

Interventions for preventing occupational irritant hand dermatitis. Bauer A, Ronsch H, Elsner P, et al. *Cochrane Database Syst Rev* 2018; Art. No. CD004414.

In this systematic review and meta-analysis of nine randomized controlled trials involving 2,888 patients in different occupational settings, rates of ICD were lower among individuals who used barrier creams (risk ratio 0.87, 95% CI 0.72–1.06) and moisturizers (risk ratio 0.71, 95% CI 0.46–1.09), although this difference was not statistically significant.

Effectiveness of skin protection measures in prevention of occupational hand eczema: Results of a prospective randomized controlled trial over a follow-up period of 1 year. Kütting B, Baumeister T, Weistenhöfer W, et al. *Br J Dermatol* 2010; 162: 362–70.

In this randomized controlled trial of 800 healthy metalworkers over 1 year, the use of barrier creams significantly contributed to the development of favorable skin status from baseline, whereas the application of moisturizers alone did not.

Double-blind, randomized trial of scheduled use of a novel barrier cream and an oil-containing lotion for protecting the hands of health care workers. McCormick RD, Buchman TL, et al. *Am J Infect Control* 2000; 28: 302–10.

In this randomized, double-blind trial, 54 healthcare workers with irritant CHD received either a petrolatum oil-containing lotion (Lubriderm) or a barrier cream (Hand Sense [emulsion with glycerin and isopropyl dimethicone]) and saw improvement (69% and 52%, respectively).

Barrier creams can cause irritation and sensitization to their ingredients, and patch testing of emollients and barrier creams may be needed to exclude ACD.

Efficacy of topical corticosteroids on irritant skin reactions. Ramsing DW, Agner T. *Contact Dermatitis* 1995; 32: 293–7.

To evaluate the effect of topical corticosteroids on experimentally induced irritant skin reactions in a double-blind, vehicle-controlled study, 16 volunteers had sodium lauryl sulfate patch tests applied to the arms. Patients treated with betamethasone-17-valerate saw significant lower transepidermal water loss and erythema at day 7 compared with vehicle-treated skin reactions.

Efficacy and safety of pimecrolimus cream 1% in mild-to-moderate chronic hand dermatitis: a randomized, double-blind trial. Hordinsky M, Fleischer A, Rivers JK, et al. *Dermatology* 2010; 221: 71–7.

A total of 652 patients with CHD were randomized to pimecrolimus 1% cream or vehicle cream twice daily. The treatment success and proportion of patients experiencing pruritus relief was higher in the pimecrolimus group compared with the vehicle group.

Topical tacrolimus 0.1% improves symptoms of hand dermatitis in patients treated with a prednisone taper. Krejci-Manwaring J, McCarthy MA, Camacho F, et al. *J Drugs Dermatol* 2008; 7: 643–6.

In this randomized, double-blind, controlled trial, 32 patients with moderate-to-severe CHD received a 3-week taper of prednisone followed by tacrolimus 0.1% ointment or vehicle for 12 weeks. Tacrolimus significantly improved induration and scaling compared to the vehicle.

Second-Line Therapies

• Narrowband ultraviolet light therapy (NB-UVB therapy)	A
• Dupilumab	C
• Methotrexate	C
• Hand psoralen plus UVA (PUVA) therapy	A
• Ciclosporin	C

An observer-blinded randomized controlled pilot trial comparing localized immersion psoralen-ultraviolet A with localized narrowband ultraviolet B for the treatment of palmar hand eczema. Brass D, Fouweather T, Stocken DD, et al. *Br J Dermatol* 2018; 179: 63–71.

In this randomized controlled trial testing the efficacy of soak PUVA (0.5 mL of 8-methoxypsoralen for 15 min followed by UVA radiation [0.5 J/cm² with increase to 6 J/cm² maximum]) or NB-UVB treatment (initial dose 0.5 J/cm² increase by 20% to 10 J/cm²) twice weekly for 12 weeks, 23 patients in both groups saw a reduction in severity of palmar CHD.

Chronic eczematous dermatitis of the hands: a comparison of PUVA and UVB treatment. Rosen K, Mobacken H, Swanbeck G. *Acta Derm Venereol* 1987; 67: 48–54.

The efficacy of PUVA and UVB was assessed in a randomized controlled trial of 35 patients with eczematous hand dermatitis (six with ICD). All patients treated with PUVA cleared but most relapsed after 3 months. UVB-treated patients showed clinical improvement but no resolution of hand dermatitis.

Local narrowband UVB phototherapy vs local PUVA in the treatment of chronic hand eczema. Sezer E, Etikan I. *Photodermatol Photoimmunol Photomed* 2007; 23: 10–4.

In this randomized controlled trial, 12 patients with CHD received local NB-UVB therapy with Philips TL-01 lamps (initial dose of 150 mJ/cm² with increase by 20% until 2000 mJ/cm²) on one hand and paint PUVA gel (0.1% 8-methoxypsoralen followed by UVA radiation using Daavlin system [initial dose of 1.0 J/cm² with a 0.5 J/cm² increase every session until final dose of 7.5 J/cm²]) on the other hand. NB-UVB therapy was as effective as PUVA therapy with similar tolerance.

A retrospective review of dupilumab for hand dermatitis. Lee N, Chipalkatti N, Zancanaro P, et al. *Dermatology* 2019; 235: 187–8.

In a retrospective review of 66 patients prescribed dupilumab for CHD, 96.7% of patients reported improvement in pruritus. On average, the patients tried over four other therapies prior to initiating dupilumab, most frequently prednisone.

Although dupilumab is a new and understudied drug at the time of this publication, retrospective reports and case studies have been extremely promising. Clinical trials are studying the efficacy of dupilumab as a therapeutic option in many dermatologic conditions, including moderate-to-severe CHD refractory to topical steroids.

Methotrexate versus acitretin in the treatment of chronic hand dermatitis. O'Shea PM, Lugo-Somolinos A. *J Drugs Dermatol* 2015; 14: 1389–91.

In this retrospective study of 21 patients treated with methotrexate (average dose 12.8 mg/week) and/or acitretin (average dose 27.5 mg/day), 100% of patients treated with acitretin achieved clearance compared with 40% treated with methotrexate.

Comparison of cyclosporine and topical betamethasone 17,21-dipropionate in the treatment of severe chronic hand eczema. Granlund H, Erkkö P, Eriksson E, et al. *Acta Derm Venereol* 1996; 76: 371–6.

Oral ciclosporin (3 mg/kg/day) was compared with topical 0.05% betamethasone dipropionate in a randomized, double-blind study of 41 patients with refractory CHD. Both treatments significantly decreased total disease activity score, but there was no difference in efficacy. Both ciclosporin and betamethasone dipropionate had similar adverse event rates.

Due to systemic effects of immunosuppression, steroid-sparing immune modulators can cause an increased risk of renal failure, hepatitis, serious infections, and lymphoma. Patients should be transitioned expeditiously from systemic to topical therapy to maintain remission.

Third-Line Therapies

• Oral alitretinoin or acitretin	B

Oral alitretinoin (9-cis-retinoic acid) therapy for chronic hand dermatitis in patients refractory to standard therapy: results of a randomized, double-blind, placebo-controlled, multicenter trial. Ruzicka T, Larsen FG, Galewicz D, et al. *Arch Dermatol* 2004; 140: 1453–9.

In a randomized controlled trial of 319 patients with CHD refractory to conventional therapy, oral alitretinoin at 10, 20, and 40 mg led to significant and dose-dependent improvement. The rate of relapse was 26% at 3 months following discontinuation.

Extended treatment with oral alitretinoin for patients with chronic hand eczema not fully responding to initial treatment. Lynde C, Cambazard F, Ruzicka T, et al. *Clin Exp Dermatol* 2012; 37: 712–7.

This multicenter, clinical trial of 243 patients showed that extended treatment by 12–24 weeks with alitretinoin 30 mg after initial 24-week treatment course was beneficial and well-tolerated.

Jellyfish stings

Lawrence Scerri



Jellyfish are members of the phylum Cnidaria, which consists of five classes: Cubozoa (box jellyfish), Hydrozoa (Portuguese man-of-war and bluebottle), Scyphozoa (true jellyfish), Anthozoa (corals and sea anemones), and Staurozoa (staromedusans). They have a worldwide marine distribution. They often consist of a bell-shaped body, ranging from 1 mm to over 2 m in diameter, with tentacles up to 60 m long. Most are harmless but several species may cause local and systemic toxic reactions in humans.

Jellyfish envenomings can occur during recreational and commercial pursuits, both in the water and when encountering living or dead animals on shore. Jellyfish sting their prey using nematocysts: stinging structures located in specialized cells called *cnidocytes*. The nematocyst is a highly coiled, hollow, harpoon-like microtubule responsible for venom injection. Contact with a jellyfish tentacle can trigger millions of nematocysts to pierce the skin and inject venom. Those providing care to sting victims should avoid being stung by adherent tentacles on the victim.

The severity of jellyfish stings depends on many factors. These include the species and age of the jellyfish involved, the geographic location, the location of the nematocysts involved (bell or tentacle), patient age and general health, the amount of skin involved, and the number of nematocysts triggered.

Most jellyfish stings are self-limiting, causing localized pain and skin lesions. However, symptoms can range from local discomfort to severe pain, through to cardiorespiratory distress, shock, and death.

Management of jellyfish envenomation is directed at alleviating local effects of venom; preventing further nematocyst discharges; and controlling systemic reactions, which may vary according to species. With a few exceptions, evidence of efficacy of treatments is largely based on uncontrolled studies, in-vitro studies, anecdotal evidence, case reports, and expert opinions.

In this chapter we discuss the most important types of jellyfish stings, and the different symptoms and management of these stings, as well as preventive strategies.

CLINICAL AND DEMOGRAPHIC FEATURES

Cubozoa (Box Jellyfish)

These are almost invisible in water and represent the most significant hazard among jellyfish classes. They are often found in shallow coastal waters and harbors.

Chironex fleckeri (Australian box jellyfish/sea wasp), belonging to the order of multitentacled chirodropids, is only found in northern Australian waters. However, several other species of chirodropids found throughout non-Australian tropical realms are also capable of inflicting life-threatening envenomings. The toxin is dermonecrotic, cardiotoxic, and neurotoxic. Though the majority of victims suffer minimal symptoms, stings can cause immediate and excruciating pain. Skin manifestations include large welts and whiplike purple-red plaques. Severe envenomation is rare but can cause rapid cardiovascular collapse and death.

Carukia barnesi (Irukandji jellyfish), belonging to the order of smaller four-tentacled carybdeids, is notorious for the Irukandji syndrome. This is a poorly defined set of symptoms induced particularly by this species. The initial sting is often trivial. The symptoms of Irukandji syndrome develop after 20–30 minutes with victims showing three patterns of symptoms: pain, catecholamine-like effects, and cardiopulmonary decompensation. Symptoms range from headaches, through severe pain, nausea, vomiting, and cardiopulmonary distress, sometimes resulting in death. Although the syndrome was originally documented in coastal northern Australia, it has subsequently been reported in other areas.

Hydrozoa

Physalia physalis (Portuguese man-of-war) and the smaller *Physalia utriculus* (bluebottle) mostly inhabit ocean waters and are particularly notable for their floating bladder-like pneumatophore, long tentacles, and the immediate, intense cutaneous pain of their sting resulting in possible necrosis and systemic reactions, with potentially fatal outcomes.

Scyphozoa (True Jellyfish)

The majority of jellyfish envenomings throughout the world occur from the scyphozoans.

Pelagia noctiluca (mauve stinger), found worldwide but most commonly in warmer waters like the Mediterranean, is capable of inflicting an excruciatingly painful, severe inflammatory reaction with possible cutaneous necrosis, but systemic reactions are rare.

Chrysaora quinquecirrha (sea nettle), mostly found in ocean waters, causes a mild-to-moderately painful sting.

Cyanea capillata (lion's mane) prefers cooler northern oceans and seas and can claim to achieve the biggest size within the Medusozoa subphylum, reaching a weight of up to a metric ton. Its sting produces minor to severely painful local reactions with occasional self-limiting systemic reactions.

Anthozoa (Corals and Sea Anemones)

Sea anemone stings range from mild erythema and tingling to painful urticarial and vesiculobullous lesions. Stings from corals are usually mild. 'Coral cuts' from the hard coral exoskeleton are more serious and may introduce debris, bacteria, and other infections into the wound.

Seabather's Eruption (Sea Lice)

This is an acute dermatitis caused by larvae of thimble jellyfish (*Linuche unguiculata*) and sea anemone (*Edwardsiella lineata*). It has been reported along the west Atlantic coast and in southeast Asia. The rash, usually confined to underneath the bathing suit, is a highly pruritic erythematous papular eruption. Symptoms usually begin within hours to 15 days after exposure.

CUTANEOUS MANIFESTATIONS OF JELLYFISH STINGS

Immediate cutaneous reactions include wheals and blisters at the site of the sting. In more severe stings, partial- or full-thickness skin necrosis can occur. Delayed, persistent, or recurrent eruptions have been reported at the initial envenomation site, consisting of erythema, urticarial lesions, papules, and plaques up to several months later due to delayed venom release from residual nematocysts or type IV delayed hypersensitivity. Other sequelae include granulomatous dermatitis, secondary infections, postinflammatory hyperpigmentation, scarring, and erythema nodosum.

MANAGEMENT STRATEGY

First-Line Therapies

Prevention of jellyfish stings

- Lycra stinger suits to protect skin from contact with jellyfish **E**
- Beach/ocean stinger nets to provide physical barrier between jellyfish and swimmers (NB: These are only effective on jellyfish that are larger than the net mesh size) **E**
- Proprietary Safe Sea jellyfish sting inhibitor cream (NB: This treatment may cause discharge of more nematocysts in some species) **A**
- Removing (and washing) bathing suits and showering to reduce/prevent seabather's eruption **E**

Immediate management of stings

- Remove sting victims from the water **E**
- Those providing care to sting victims must avoid being stung by jellyfish **E**
- Immediately remove any tentacles, preferably wearing gloves (though dermis of fingers is usually thick enough to prevent significant envenoming to first-aider) **E**
- Avoid rubbing sting site **E**
- Wash sting site with sea water (not fresh water) **E**
- Identify type of jellyfish involved **E**
- Cardiopulmonary resuscitation if needed (especially for box jellyfish) **E**
- Topical agents to provide analgesia or reduce further nematocyst discharge
- Lignocaine/benzocaine **C**
- Hot water (not for Australian box jellyfish stings) **A**
- Ice (not for *Physalia* stings) **C**
- Proprietary Stingose solution (aqueous solution of 20% aluminum sulfate and 1.1% surfactant) for *Physalia* stings **D**

- Vinegar (4–6% acetic acid) for box jellyfish and *Pelagia noctiluca* stings **C**
- Baking soda slurry (paste made of 50% baking soda and 50% sea water) for *Cyanea capillata* and *Chrysaora* sp. **E**

Box jellyfish stings

- Liberal amounts of vinegar to sting site **C**
- Oral and parenteral analgesia as required **C**
- Intravenous antivenom (only for Australian box jellyfish) **D**
- Intravenous magnesium (only for Australian box jellyfish) **D**
- Cardiac monitoring, supportive care, and cardiopulmonary resuscitation as required **D**

America and Hawaii. Ward NT, Darracq MA, Tomaszewski C, et al. *Ann Emerg Med* 2012; 60: 399–414.

Systematic review of the evidence supporting various treatments for envenomation by jellyfish (cnidarian) and related organisms in North America and Hawaii. Hot water and topical lidocaine seem beneficial in improving pain symptoms. If not available, remove nematocysts and wash the area with salt water. Vinegar causes pain exacerbation or nematocyst discharge in the majority of species (but is useful in box jellyfish stings).

Prophylactic treatment of jellyfish stings – a randomized trial. Tønseth KA, Anderson TS, Pripp AH, et al. *Tidsskr Nor Laegeforen* 2012; 132 (12–13): 1446–9. English, Norwegian.

In this randomized, controlled study involving 38 subjects, sunscreen containing Safe Sea jellyfish sting inhibitor was significantly more protective than conventional sunscreen or no application against the sting-related pain and skin changes induced by lion's mane jellyfish tentacles.

A randomised controlled trial of hot water (45 degrees C) immersion versus ice packs for pain relief in bluebottle stings. Loten C, Stokes B, Worsley D, et al. *Med J Aust* 2006; 184: 329–33.

Hot-water immersion was more effective than cold packs at reducing pain in nematocyst-confirmed stings. Immersion in water at 45°C for 20 minutes provides effective and practical analgesia from bluebottle stings.

Heated debates: hot-water immersion or ice packs as first aid for cnidarian envenomations? Wilcox CL, Yanagihara AA. *Toxins* 2016; 8: 97.

This systematic review found that the majority of studies to date support the use of hot-water immersion for pain relief and improved health outcomes with the exception of Australian box jellyfish stings, which respond better to ice packs.

To pee, or not to pee: a review on envenomation and treatment in European jellyfish species. Montgomery L, Seys J, Mees J. *Drugs* 2016; 14, 127.

An extensive systematic review incorporating papers on 37 scyphozoans, one cubozoan, and three hydrozoan species. Treatments displaying only positive outcomes comprised analgesics, anesthetic agents, nerve channel blockers, sea water, and Stingose. Vinegar had an overall marginally negative effect (16 vs. 15 papers). Antiinflammatories, baking soda slurry, and temperature treatment portrayed an overall greater positive effect than negative.

First aid treatment of jellyfish stings in Australia. Response to a newly differentiated species. Fenner PJ, Williamson JA, Burnett JW, et al. *Med J Aust* 1993; 158: 498–501.

Vinegar inhibits nematocyst discharge in box jellyfish stings and is an accepted first aid treatment. However, it should not be used in *Physalia* (bluebottles) because it causes discharge of nematocysts.

Nematocyst discharge in *Pelagia noctiluca* oral arms can be affected by lidocaine, ethanol, ammonia and acetic acid. Morabito R, Marino A, Dossena S, et al. *Toxicon* 2014; 83: 52–8.

In-situ nematocyst discharge was dramatically impaired by 1% lidocaine, 70% alcohol, 5% acetic acid, or 20% ammonia.

Is there a role for the use of pressure immobilization bandages in the treatment of jellyfish envenomation in Australia? Little M. *Emerg Med (Fremantle)* 2002; 14: 171–4.

A review of the literature indicates no benefit from applying compression bandages in jellyfish stings as recommended in some other envenomations.

Antivenom efficacy or effectiveness: the Australian experience. Isbister GK. *Toxicology* 2010; 268: 148–54.

A number of recent studies in Australia bring into question the effectiveness of some antivenoms, including box jellyfish antivenoms. The author notes this does not prove ineffectiveness but suggests the need for more studies.

Australian venomous jellyfish, envenomation syndromes, toxins and therapy. Tibballs J. *Toxicon* 2006; 48: 830–59.

Case studies suggest antivenom for Australian box jellyfish may be moderately efficacious.

Secondary Infections and Long-Term Treatment

Dermonecrosis is a frequent outcome of jellyfish stings; however, many resolve spontaneously. Treating dermonecrosis from these envenomings as a burn, with specific attention to avoiding secondary bacterial infection, significantly decreases the risk of permanent scarring.

Clinical perspectives on seabather's eruption, also known as 'sea lice'. Tomchik RS, Russell MT, Szmant AM, et al. *JAMA* 1993; 269: 1669–72.

Seabather's eruption is usually a benign, clinical syndrome that resolves spontaneously. Treatment is symptomatic and involves the use of antihistamines and steroids.

Successful management of a delayed and persistent cutaneous reaction to jellyfish with pimecrolimus. Di Costanzo L, Balato N, Zagaria O, et al. *J Dermatolog Treat* 2009; 20: 179–80.

Topical pimecrolimus produced improvement in dermatitis.

Delayed cutaneous reaction to jellyfish. Veraldi S, Carrera C. *Int J Dermatol* 2000; 39: 28–9.

Oral hydroxyzine and topical hydrocortisone butyrate provided relief and reduced duration of a delayed dermatitis secondary to contact with an unknown jellyfish.

Granulomatous jellyfish dermatitis. Ulrich H, Landthaler M, Vogt T. *J Dtsch Dermatol Ges* 2007; 5: 493–5.

Topical therapy with tacrolimus 0.1% for two 2-week treatment periods led to healing of the skin changes with a slight scar in a patient with granulomatous dermatitis.

Treatment of a pigmented lesion induced by a *Pelagia noctiluca* sting. Kokelj F, Burnett JW. *Cutis* 1990; 46: 62–4.

Hyperpigmentation, present 4 years after a jellyfish sting, was successfully treated within 4 days of using 1.8% hydroquinone.

Second-Line Therapies

Seabather's eruption

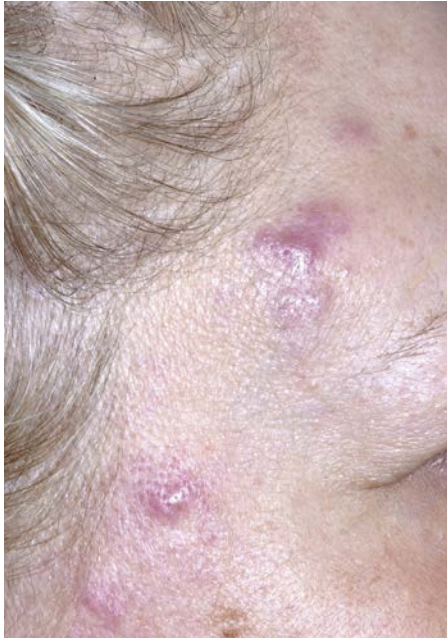
- Topical and oral antihistamines E
- Topical and oral corticosteroids E

Treatment of dermatitis and hyperpigmentation due to jellyfish stings

- Oral antihistamines E
- Topical, intralesional, and oral corticosteroids E
- Topical immunomodulators (tacrolimus and pimecrolimus) E
- Topical hydroquinone E

Jessner lymphocytic infiltrate

Joanna E. Gach



Jessner lymphocytic infiltrate (JLI) is a chronic, inflammatory condition presenting with erythematous or reddish-brown papules or annular or arciform plaques, which can expand peripherally and sometimes develop central healing. The lesions are usually seen in adults and affect the face, neck, or upper trunk. Although they are frequently asymptomatic, some patients report itch or burning. A case report noted ectropion as a complication. The lesions can persist from weeks to years and disappear without sequelae but may recur. Additionally, JLI has been reported as a manifestation of borreliosis and due to treatment with ramipril, TNF- α inhibitors, the IL-12/23 inhibitor ustekinumab, duloxetine, leflunomide, glatiramer acetate, and bee venom immunotherapy.

MANAGEMENT STRATEGY

JLI runs a waxing and waning course marked by intermittent improvement and subsequent exacerbations, which makes the evaluations of therapeutic effectiveness difficult. Patients demand treatment because they find the lesions disfiguring or itchy.

Potent topical steroids applied once or twice daily for 4 weeks are the first-line treatment for many dermatologists. Unfortunately, the results of treatment are variable and, most importantly, only short lasting. If the response is inadequate, injection of intralesional corticosteroids into localized lesions or the use of *potent topical steroids under occlusive dressing* may be beneficial but is associated with a greater risk of skin atrophy. *Topical tacrolimus* may be a safer alternative.

In cases where ultraviolet (UV) exposure has been reported to induce or exacerbate lesions, additional therapy with broad spectrum UVA and UVB protection all year round may be needed. This group of patients may respond to *antimalarials*, in particular, hydroxychloroquine.

A variety of other therapies have been reported to be effective in the management of JLI. *Thalidomide*, *retinoids*, and *laser* proved to be helpful in some cases, but their use may be limited by the adverse effects, which may be difficult for the patient and physician to accept, especially as JLI is harmless.

Many other treatments, including nicotinamide, vitamin E, penicillin, chlortetracycline, minocycline, dapsone, and radiotherapy, have been tried unsuccessfully.

Specific Investigations

- Skin biopsy
- Lesional skin for direct immunofluorescence
- Antinuclear antibodies/extractable nuclear antigen

The diagnosis can be made on clinical grounds. The investigations are helpful in differentiating the condition from discoid lupus erythematosus, lupus erythematosus tumidus, and cutaneous lymphoma.

The heterogeneity of Jessner's lymphocytic infiltration of the skin. Immunohistochemical studies suggesting one form of perivascular lymphocytoma. Cerio R, Oliver GF, Jones EW, et al. *J Am Acad Dermatol* 1990; 23: 63-7.

Skin biopsy of the lesion shows normal epidermis and a moderate, dense, sleeve-like perivascular and periadnexal infiltrate in the middle dermis. This consists of normal-looking lymphocytes with the B cells grouped in close proximity to the superficial vessels and T cells at the periphery, and, occasionally, plasma cells.

Could Jessner's lymphocytic infiltrate of the skin be a dermal variant of lupus erythematosus? An analysis of 210 cases. Lipsker D, Mitschler A, Grosshans E, et al. *Dermatology* 2006; 213: 15-22.

Immunofluorescence studies of lesional skin showed a lupus band with IgG, IgM $\pm$ C3 in 9.5% of cases of JLI. Antinuclear antibodies were present in 45% of cases.

Plasmacytoid dendritic cells: an overview of their presence and distribution in different inflammatory diseases, with special emphasis on Jessner's lymphocytic infiltrate of the skin and cutaneous lupus erythematosus. Tomasini D, Mentzel T, Hantschke M, et al. *J Cutan Pathol* 2010; 37: 1132-9.

Distribution of distinct perivascular and periadnexal clusters of plasmacytoid dendritic cells in JLI and tumid lupus erythematosus is identical.

First-Line Therapies

• Potent topical/intralesional corticosteroids	C
• Topical immunomodulators	D

Jessner's lymphocytic infiltration of the skin. A clinical study of 100 patients. Toonstra J, Wildschut A, Boer J, et al. *Arch Dermatol* 1989; 125: 1525-30.

A series of 100 patients with JLI assessing clinical manifestations, duration, clinical course, and treatments. Of 91 patients treated with topical steroids, 43 had an excellent ($n = 13$) or good

(*n* = 30) response, with temporary regression of the lesions. Many patients had no response.

Jessner-Kanof lymphocyte infiltration responded well to impulse intralesional corticosteroid. Zhang S, Li S, Wang T, et al. *Dermatol Ther* 2018; 31(6): e12730. doi: 10.1111/dth.12730.

A 20-year-old female with JLI responded after three intralesional steroid injections.

Effective treatment of chronic inflammatory skin diseases. Once a week occlusion therapy with clobetasol propionate and DuoDERM. Volden G. *Tidsskr Nor Laegeforen* 1992; 112: 1272–4.

JLI was among other chronic skin diseases that were treated once a week with clobetasol propionate lotion left under the completely occlusive hydrocolloid dressing DuoDERM. The lesions cleared within a few weeks.

Topical calcineurin inhibitors in treating Jessner's lymphocytic infiltration of the skin: report of a case. Tzung TY, Wu JC. *Br J Dermatol* 2005; 152: 383–4.

Tacrolimus 0.1% ointment twice daily produced an improvement after 2 weeks but had to be withdrawn because of diffuse erythema and desquamation that occurred 2 weeks later. The same effect occurred on rechallenge and settled with a single 5-mg dose of dexamethasone administered by intramuscular injection. Subsequently, pimecrolimus 1% cream cleared the rash within 6 weeks, with no relapse 2 months later.

Second-Line Therapies

• Systemic corticosteroids	E
• Antimalarials	C
• Retinoids	E
• Photodynamic therapy	D
• Methotrexate	E
• Laser therapy	D

Jessner's lymphocytic infiltration of the skin. A clinical study of 100 patients. Toonstra J, Wildschut A, Boer J, et al. *Arch Dermatol* 1989; 125: 1525–30.

Antimalarial drugs (chloroquine sulfate and hydroxychloroquine sulfate) were used in 15 patients, with a good response in six. There were no details given regarding doses or treatment regimens.

Hydroxychloroquine 200 mg once or twice a day or chloroquine 200 mg daily was used in other case reports.

Mepacrine as successful monotherapy for refractory Jessner-Kanof disease: still an important drug in the dermatologic armamentarium. Wuyts L, Dandelooy J, Siozopolou V, et al. *J Dermatolog Treat* 2017; 28(3): 276–8.

Mepacrine 100 mg daily is recommended as monotherapy or as an add-on to hydroxychloroquine.

Satisfactory resolution of Jessner's lymphocytic infiltration of the skin following treatment with etretinate. Morgan J, Adams J. *Br J Dermatol* 1990; 122: 570.

One case of JLI was treated with etretinate 50 mg daily for 3 months and 25 mg daily for another 3 months. The rash subsided within 4 weeks of treatment and did not recur for 9 months after stopping treatment.

Isotretinoin 20 mg daily was used in other case reports but was not helpful. Etretinate is no longer available. To date there are no reports of utilizing acitretin in patients with JLI.

Photodynamic therapy: new treatment for refractory lymphocytic infiltration of the skin. Park KY, Kim HK, Li K, et al. *Clin Exp Dermatol* 2012; 3: 235–7.

Remission was observed after two sessions of methyl 5-aminolevulinic acid cream photodynamic therapy with Aklilite 1 lamp, 630 nm.

Successful treatment of Jessner's lymphocytic infiltration of the skin with methotrexate. Laurinaviciene R, Clemmensen O, Bygum A. *Acta Derm Venereol* 2009; 89: 542–3.

Oral methotrexate 15 mg weekly for 6 months produced clearance. No recurrence 2 years after withdrawal of the drug.

Nonconventional use of flash-lamp pulsed-dye laser in dermatology. Nisticò S, Campolmi P, Moretti S, et al. *Biomed Res Int* 2016; 2016: 7981640. doi: 10.1155/2016/7981640.

Single treatment with 595-nm pulsed-dye laser used on four patients. All lesions were cleared.

Third-Line Therapies

• Auranofin	E
• Thalidomide	A

Jessner's lymphocytic infiltrate treated with auranofin. Farrell AM, McGregor JM, Staughton RC, et al. *Clin Exp Dermatol* 1999; 24: 500.

A marked improvement within 3 weeks of starting auranofin 3 mg orally twice daily. This case was unresponsive to chloroquine, hydroxychloroquine, minocycline, dapsone, and isotretinoin. Monitoring of the therapy includes monthly full blood count for thrombocytopenia and urinalysis to detect nephritis.

Crossover study of thalidomide vs. placebo in Jessner's lymphocytic infiltration of the skin. Guillaume JC, Moulin G, Dieng MT, et al. *Arch Dermatol* 1995; 131: 1032–5.

In a group of 27 patients, 20 achieved complete remission after 2 months of therapy with thalidomide 100 mg daily; 16 (59%) patients were in complete remission 1 month after stopping therapy. Side effects included sleepiness, constipation, dry mouth, and sensorimotor neuropathy in two patients.

Juvenile plantar dermatosis

Ian H. Coulson



Juvenile plantar dermatosis (JPD) is a symmetrical, scaly, and fissured eruption affecting the ball of the foot, heels, and occasionally the finger pulps. The instep and interdigital skin are rarely affected. The condition occurs almost exclusively in children and clears around puberty.

MANAGEMENT STRATEGY

JPD usually presents between 4 and 7 years of age. Spontaneous resolution occurs in most patients around puberty.

The main etiologic factor is thought to be the occlusive effect of 'trainer' sports shoes and manmade fibers in hosiery, resulting in hyperhidrosis. This, some suggest, washes away surface lipids, which are already reduced because of the relative lack of sebaceous glands on the plantar surface of the foot. This hyperhidrosis is, therefore, followed by rapid dehydration of the skin on removal of footwear. It is proposed that this maceration/dehydration renders the skin susceptible to trauma (e.g., from sport). Avoidance of vigorous exercise may therefore be helpful in these patients.

The role of atopy is debated. Some series have found an increased incidence of atopy in patients and families, and, indeed, this condition was first referred to as 'atopic winter feet.' It has been argued that the atopic diathesis and the associated filaggrin mutation predisposes the skin of the foot to the traumatic effects of sport and vigorous activity, and to the effects of alternating hyperhidrosis and dehydration.

Mycology should be undertaken if tinea pedis is considered. Patch testing may produce positive results in between 10% and 29% of cases. Even when these are to footwear-related allergens, however, there is debate as to whether allergen avoidance affects clinical outcome. Increased numbers of bacteria have been suggested to cause inflammation of the sweat ducts and thereby inhibit sweat secretion, but this has not been a consistent finding.

Changing to non-occlusive footwear along with cotton or woolen socks or open footwear has been proposed as a therapeutic maneuver. *Rotating leather or cork insoles* so that the sole of the shoe never becomes saturated with sweat may help. *Emollients and lubricants containing dimethicone*, both to reduce fissuring and to reduce the dehydration occurring on removing occlusive footwear, are reported to be helpful. *Topical corticosteroids and tacrolimus* may be beneficial if there is an inflammatory component. *Occlusive bandages* containing zinc ointment, ichthammol, or tar may help if hyperkeratosis and fissuring are a prominent feature. All these often only help temporarily, and regular rotation of emollients may be required.

It is the impression of most dermatologists that this condition has become less common in recent years, possibly related to changes in teenage fashion and footwear materials.

Specific Investigation

- Patch tests

Juvenile plantar dermatosis: a new entity. Mackie RM, Husain SL. Clin Exp Dermatol 1976; 1: 253–60.

Thirteen of 102 patients showed a positive patch test. Eight were reactions to footwear constituents, but subsequent changes in footwear did not affect the clinical outcome.

Common pediatric foot dermatoses. Guentz BJ. J Pediatr Health Care 1999; 13: 68–71.

A practical review differentiating the various forms of tinea pedis and shoe dermatitis from JPD.

Sole dermatitis in children: patch testing revisited. Darling MI, Horn HM, McCormack SK, et al. Pediatr Dermatol 2011; 29: 254–7.

Of 14 children with JPD, 29% had clinically relevant reactions.

Epidemiologic and clinical features of foot dermatitis in 389 children. Ortiz-Salvador JM, Esteve-Martínez A, García-Rabasco A, et al. Pediatr Dermatol 2017; 34: 535–9.

A retrospective study of 389 children referred for patch testing over a 9-year period with exclusively foot eczema. A diagnosis after patch testing was allergic contact dermatitis in 23 children, atopic eczema in 12, JPD in 8, dyshidrotic eczema in 6, irritant contact dermatitis in 2, and tinea pedis in 1. The most frequent allergens were potassium dichromate, thimerosal, cobalt chloride, mercapto mix, colophonium, mercury, and nickel sulfate.

First-Line Therapy

- Await spontaneous resolution

C

Juvenile plantar dermatosis – an 8 year follow-up of 102 patients. Jones SK, English JSC, Forsyth A, et al. Clin Exp Dermatol 1987; 12: 5–7.

Of 50 patients traced, the condition had resolved in 38. The mean age of remission was 14 years.

Second-Line Therapies

• Change to non-occlusive footwear	C
• Sport avoidance	C
• Emollients	C
• Topical corticosteroids	C
• Rotation of topical agents	C
• Topical tacrolimus	C

Juvenile plantar dermatosis. Can sweat cause foot rash and peeling?

Gibbs NF. Postgrad Med 2004; 115: 73–5.

A review of the disease, its etiology, and its treatment.

Juvenile plantar dermatosis. Graham RM, Verbov JL, Vickers CFH. Br J Dermatol 1987; 12: 468–70.

Although there was no association with any particular sport, intensive exercise causing skin cracking, soreness, and bleeding was a common complaint; 75% of parents said that a change in footwear had not been helpful.

In contrast to Jones et al. earlier, only 30% of cases in this series had resolved (mean age 11.8 years), though the ages of the remaining 70% were not stated.

Juvenile plantar dermatosis responding to topical tacrolimus.

Shiple DR, Kennedy CTC. Clin Exp Dermatol 2005; 31: 453–4.

Topical 0.1% tacrolimus twice daily in conjunction with a regular emollient produced improvement within 4 weeks, with the feet appearing almost normal after 2 months. Intermittent tacrolimus was useful for relapses.

Third-Line Therapies

• Zinc oxide/impregnated bandages	C
• Bed rest/footwear avoidance	E

Juvenile plantar dermatosis. Graham RM, Verbov JL, Vickers CFH. Br J Dermatol 1987; 12: 468–70.

Occlusion with zinc paste or ichthammol-impregnated bandages was among the most beneficial of treatments.

The etiology of juvenile plantar dermatosis. Shrank AB. Br J Dermatol 1979; 100: 641–8.

Bed rest or avoidance of shoes/hosiery for 3 weeks resulted in disease clearance (thought to be related to the time taken for the sweat duct apparatus in the foot to regrow).

Juvenile xanthogranuloma

Maria Rosa Noliza Encarnacion, Nanette Silverberg



The non-Langerhans cell histiocytosis juvenile xanthogranuloma (JXG) is a benign disease common in infancy and early childhood but may affect adults as well. JXG presents as single or multiple rubbery, firm, round to oval yellow-red to orange cutaneous papules or nodules. The most common sites are the head and neck followed by the upper trunk and extremities.

JXG is usually limited to the skin and is self-healing within months to years. Treatment is recommended for systemic lesions if their location interferes with organ function.

MANAGEMENT STRATEGY

The clinical and radiological presentation is non-specific. Correlation with histopathology is the gold standard for the diagnosis.

In approximately 5% of children, JXG may be a systemic disease with involvement of $\geq$ two organs. Skin lesions may precede the development of other organ complications with a latent period of months to years. Clinicians should remain alert to the development of suspicious clinical or laboratory findings needing further investigation (see below).

1. Eye involvement. The eye is the most frequent site of extracutaneous involvement. Ocular JXG seems to occur more commonly as an isolated site. Only 0.3–0.5% of patients with cutaneous JXG develop ocular JXG (usually during the first 2 years of life). Most frequent complications are hyphema, glaucoma, and anterior uveitis, with the risk of loss of visual acuity. Ocular JXG is the most frequent cause of spontaneous hyphema in children.

- 2. Systemic juvenile xanthogranuloma.** Systemic JXG accounts for 4–10% of JXG cases, but only 50% of systemic JXG cases demonstrate skin lesions. Age under 2 years and having multiple cutaneous lesions may be risk factors for systemic involvement, and these may give a high degree of clinical suspicion. The disease may involve internal organs such as the lungs, kidneys, heart, central nervous system, adrenal glands, pituitary gland, bones, and bone marrow.
- 3. An association between JXG, neurofibromatosis type 1 (NF1), and juvenile myelomonocytic leukemia (JMML).** The presence of JXG in patients with NF1 is considered a warning sign for JMML. A study by Zvulunov et al. concluded that the risk of JMML was 20–32 times greater in children with NF1 and JXG as in those without JXG. Because JMML is an aggressive disease with a median survival of approximately 1 year if not treated with stem cell transplantation, early diagnosis may be crucial for a positive outcome.
- 4. Other diseases associated with JXG:** urticaria pigmentosa, insulin-dependent diabetes mellitus, aquagenic pruritus, cytomegalovirus infection, cutaneous tuberculosis, and neoplasia. A case of tuberculosis presenting with generalized xanthogranulomas in an adult Filipino male by Caro-Chang and Cubillan concluded that tuberculosis, together with other infectious disorders, should also be investigated in patients presenting with generalized xanthogranulomas.

Specific Investigations

- In most cases, no specific investigations are required
- Correlation with histopathology and immunostaining
- Ophthalmology evaluation (recommended for <2 yo with multiple micronodular lesions)
- Dermoscopy
- Reflectance confocal microscopy
- Fine-needle aspiration cytology (FNAC) smears
- Further evaluation warranted for symptoms of affected organs

The various clinical spectra of juvenile xanthogranuloma: imaging for two case reports and review of literature. Höck M, Zelger B, Schweigmann G, et al. BMC Pediatr 2019. doi <https://doi.org/10.1186/s12887-019-1490-y>.

Immunostaining is important in establishing the diagnosis: JXG stains positive for factor XIIIa, CD68, CD163, CD14, and fascin, and is mostly negative for S100 protein and regularly negative for CD1a and anti-langerin (CD207), which are specific for Langerhans cells.

Giant juvenile xanthogranuloma: case report, literature review, and algorithm for classification. Ladha MA, Haber RM. J Cutan Med Surg 2018; 22(5): 488-94. [10.1177/1203475418777734](https://doi.org/10.1177/1203475418777734).

The dermoscopic features of classic JXG were first reported by Palmer and Bowling: (1) an orange-yellow base called setting sun sign; (2) clouds of diffuse yellow deposits, likely histiocytes; and (3) branched linear vessels at the periphery.

Reflectance confocal microscopy for the noninvasive diagnosis of cutaneous juvenile xanthogranuloma. Pimenta R, Leal-Filipe P, Oliveira A. Skin Res Technol 2018. <https://doi.org/10.1111/srt.12616>.

Epidermal examination revealed a normal honeycomb pattern. At the dermal-epidermal junction level, dilated papillae

filled with clustered, large and refractile, multinucleated roundish structures were found. They were also found at the superficial dermis, together with discoid-shaped structures with a peripheral bright ring. The former atypical cells corresponded to Touton cells, while the latter corresponded to foamy histiocytes. These in vivo features allowed the diagnosis of cutaneous juvenile xanthogranuloma. A skin biopsy was no longer required.

Cytological diagnosis of juvenile xanthogranuloma: a rare histiocytic disorder. Chauhan S, Diwaker P, Singh A, et al. 2019. Wiley Periodicals. <https://doi.org/10.1002/dc.24310>.

FNAC smears may be another option and may save patients from unnecessary surgical biopsy or excision. FNAC shows foamy macrophages along with mixed inflammatory infiltrate and few Touton giant cells. This cytological diagnosis requires a high index of suspicion by a cytopathologist.

Neurofibromatosis type 1 diagnosed in a child based on multiple juvenile xanthogranulomas and juvenile myelomonocytic leukemia. Jans SRR, Schomerus E, Bygum A. 2014. Wiley Periodicals, Inc. <https://doi.org/10.1111/pde.12478>.

Diagnostic hints to neurofibromatosis type 1:

- Café au lait spots, macrocephaly with axillary or inguinal freckling, Lisch nodules and neurofibromas
 - Wood's lamp examination to look for café au lait spots and nevus anemicus.
- Diagnostic hints to juvenile myelomonocytic leukemia (JMML):
- Peripheral blood samples may show leukocytosis with immature granulocytes, monocytosis, anemia, and thrombocytopenia
 - Splenomegaly, hepatomegaly, and lymphadenopathy (splenomegaly is a necessary diagnostic criterion)
 - Pallor, skin bleeding, infections, coughing, or unexplained fever should be tested.

Systemic juvenile xanthogranuloma: a case report and brief review. Meyer M, Grimes A, Becker E, et al. 2018. British Association of Dermatologists. <https://doi.org/10.1111/ced.13403>.

Diagnostic hints to JMML:

- Complete blood count (leading to bone marrow aspiration/biopsy if cytopenias are present)
- Comprehensive metabolic profile to include renal panel and liver function tests and coagulation profile.

Successful treatment of systemic juvenile xanthogranulomatosis with cytarabine and 2-chlorodeoxyadenosine: a case report and review of the literature. Maintz L, Wenzel J, Irnich M, et al. Br J Dermatol 2017; 176: 481–7. <https://doi.org/10.1111/bjd.14813>.

Depending on the history, diagnostics may include a laboratory analysis, sonography of lymph nodes and abdomen, chest X-ray, radiographic skeletal survey or radionuclide bone scan, CT or MRI of the brain, and ophthalmologic examination.

First-Line Therapies

- None ("wait and see")
- Surgical resection for symptomatic extracutaneous lesions
- Ocular lesions treated with topical or intralesional corticosteroid

Giant juvenile xanthogranuloma: case report, literature review, and algorithm for classification. Ladha MA, Haber RM. Journal of Cutaneous Medicine and Surgery 2018; 22: 488–94 [10.1177/1203475418777734](https://doi.org/10.1177/1203475418777734).

The natural history of JXG is spontaneous regression within 6 months to 3 years of first appearance. However, once resolved, they can leave anetoderma, residual hyperpigmentation, or atrophy. Treatment is not recommended for cutaneous lesions given their benign nature. However, ocular lesions or systemic manifestations may require treatment for symptom control.

Aggressive surgical management of recurrent intracranial juvenile xanthogranuloma: case report and review of literature. AlQazlan S, Albakr A, Al Twoim A, et al. Childs Nerv Syst 2020; 36(1): 213–217. <https://doi.org/10.1007/s00381-019-04323-9>.

Intracranial JXG is not as sensitive to chemotherapy as cutaneous lesions. Therefore, surgical management is recommended for symptomatic patients with solitary lesions.

Eyelid juvenile xanthogranuloma: a case report and literature review. Hassan A, Talib N, Adzman S. Cureus 2019; 11(6): e5008 <https://doi.org/10.7759/cureus.5008>.

In non-sight-threatening conditions, it can be treated with high-dose topical steroid, periocular steroid, and systemic corticosteroid.

Second-Line Therapies

- Cutaneous surgery
- Ocular surgery
- Ocular lesions treated with systemic corticosteroids and/or low-dose radiotherapy

Juvenile xanthogranuloma: a case report. da Silva SP, Viveiros C, Almeida R, et al. Rev Paul Pediatr 2019 Feb 25. <https://doi.org/10.1590/1984-0462/2019/37;2/00013>.

Lesions are expected to heal well; therefore, surgical removal may be considered only for cosmetic reasons, especially in cases of giant JXG.

Therapeutic options include immunosuppression and chemotherapy, using corticosteroids, ciclosporin or methotrexate, radiotherapy, and surgical excision, which should be considered carefully in the setting of systemic disease.

Ocular juvenile xanthogranuloma. Niu L, Zhang C, Meng F, et al. American Academy of Optometry 2015. <https://doi.org/10.1097/oxp.0000000000000609>.

The cases with ocular surface involvement were successfully treated by excision and the case with iris involvement spontaneously regressed without any treatment. Early excision may be the better choice for ocular surface lesions, especially when corneal involvement is a possibility.

Successful treatment of systemic juvenile xanthogranulomatosis with cytarabine and 2-chlorodeoxyadenosine: a case report and review of the literature. Maintz L, Wenzel J, Irnich M, et al. Br J Dermatol 2017; 176: 481–487. <https://doi.org/10.1111/bjd.14813>.

In case of rapid progress, systemic corticosteroids are valuable, e.g., in cases with ocular JXG to prevent glaucoma and amblyopia. Therapies with radiation and/or chemotherapy alone or in combination with systemic corticosteroid therapy have been reported, but should be reserved for unresectable disease with serious complications and/

or progressive course due to the possibility of spontaneous remission, uncertain efficacy, and high risk of toxic side effects in the usually very young patients. However, there is growing evidence to support the use of chemotherapeutics in the treatment of symptomatic multisystem JXG with vital organ involvement.

Third-Line Therapies

- For unresectable systemic lesions with compromised organ function, radiotherapy, chemotherapy, or stem cell transplantation

Successful treatment of systemic juvenile xanthogranulomatosis with cytarabine and 2-chlorodeoxyadenosine: a case report and review of the literature. Maintz L, Wenzel J, Irnich M, et al. *Br J Dermatol* 2017; 176: 481–7. <https://doi.org/10.1111/bjd.14813>.

Further therapy with cytarabine (ARA-C; 1000 mg/m²/day) and 2-chlorodeoxyadenosine (2CDA 9 mg/m²/day), four cycles of 5 days/week every 28 days, followed by a consolidation phase with 2-chlorodeoxyadenosine alone (5 mg/m²/day, seven cycles of 3 days every 21 days) was successful and the patient is in his fourth year in remission.

Systemic juvenile xanthogranuloma: a case report and brief review. Meyer M, Grimes A, Becker E, et al. 2018. *British Association of Dermatologists*. <https://doi.org/10.1111/ced.13403>.

After 6 weeks of chemotherapy (vinblastine and prednisolone), all cutaneous lesions had halted in growth, with some decreasing in size. Several months into therapy, vinblastine-related toxicities led to a transition to cytarabine. After 1 year of therapy, only residual hepatic lesions remained, with involution of all pulmonary lesions and skin nodules, prompting discontinuation of treatment for observation. At 2 years off treatment, imaging and physical examination revealed no evidence of progression or relapse.

Haploidentical stem cell transplantation with posttransplant cyclophosphamide for refractory systemic juvenile xanthogranuloma. Ito J, Shima H, Inoue K, et al. 2019. *Wiley Periodicals, Inc.* <https://doi.org/10.1002/pbc.27926>.

Allogeneic hematopoietic stem cell transplantation (HSCT) is a salvage therapy for children with refractory Langerhans cell histiocytosis (LCH). However, for non-LCH, there is only one case reported of a patient with cutaneous JXG with NF1 and JMML who was successfully treated with HSCT with posttransplant cyclophosphamide.

Kaposi sarcoma

Michael A. Renzi Jr., Rachel Mancini, Steven Manders



Kaposi sarcoma (KS) is a distinct, often multifocal, endothelial neoplasm etiologically linked to Kaposi sarcoma herpesvirus (KSHV) or human herpesvirus 8 (HHV8), predominantly transmitted via saliva but also by solid organ transplantation. In the United States, epidemic or acquired immunodeficiency syndrome (AIDS)-associated KS is the most common presentation; however, transplant or iatrogenic immunosuppression-related KS is on the increase. In clinical practice, classic and endemic KSs are also encountered. Therapy is similar for each type.

MANAGEMENT STRATEGY

Therapy goals include cosmetic improvement, palliation, or cessation of progression. Dermatologists most often encounter limited cutaneous KS, defined as fewer than 10 skin lesions, a lack of oral or visceral involvement, and the absence of tumor-associated lymphedema. Treatment options include *cryotherapy*, *intralesional vinblastine*, *radiotherapy*, and *alitretinoin gel*. Because treatment is essentially for cosmesis, side effects such as pigmentary changes and pain become important in therapeutic decisions.

For patients with resistant limited disease, extensive cutaneous involvement, systemic KS, or tumor-associated lymphedema, treatment modalities include liposomal anthracyclines (pegylated liposomal doxorubicin or liposomal daunorubicin), taxanes (paclitaxel), and interferon- α . For epidemic KS, effective antiretroviral therapy (ART) can by itself be sufficient to halt disease

progression and has been found to have a synergistic effect with the *liposomal anthracyclines*, *paclitaxel*, and *interferon- α* . However, several cases of worsening of KS with the initiation of ART have been reported as part of an immune reconstitution syndrome. Iatrogenic immunosuppression-associated KS can respond to decreased dosing of the immunosuppressive regimen or change to *sirolimus*. *Radiotherapy* remains an alternative treatment option for this group of patients.

Treatment of oral lesions is problematic because of inaccessibility to cryotherapy and radiation-induced mucositis. Options include *intralesional vinblastine*, sclerosing agents such as *sodium tetradeceyl sulfate*, or systemic treatments.

An increasing number of investigational therapeutics have been explored for the treatment and prevention of KS, including *antiangiogenic agents*, *antiviral agents*, *matrix metalloproteinase inhibitors*, *tyrosine kinase inhibitors*, *laser therapy*, *PD-1 inhibitors*, and *agents targeting interleukin (IL)-12*.

Specific Investigations

- Serology for human immunodeficiency virus (HIV), CD4+ T-lymphocyte counts, viral load (if HIV positive)
- Complete blood count, renal and hepatic function
- Chest radiograph
- Stool for occult blood

Management of AIDS-related Kaposi's sarcoma. Di Lorenzo G, Konstantinopoulos PA, Pantanowitz L, et al. *Lancet Oncol* 2007; 8: 167–76.

Review of current treatment strategies and ongoing investigations.

First-Line Therapies

• Pegylated liposomal doxorubicin	A
• Paclitaxel	A
• Antiretroviral therapy	B
• Cryotherapy	C
• Radiotherapy	B
• Alitretinoin gel	A

PEGylated liposomal doxorubicin plus highly active antiretroviral therapy versus highly active antiretroviral therapy alone in HIV patients with Kaposi's sarcoma. Martin-Carbonero L, Barrios A, Saballs P, et al.; Caelyx/KS Spanish Group. *AIDS* 2004; 18: 1737–40.

Randomized study comparing pegylated liposomal doxorubicin plus ART vs. ART alone showed a greater response rate in the former group.

A randomized controlled trial of highly active antiretroviral therapy versus highly active antiretroviral therapy and chemotherapy in therapy-naïve patients with HIV-associated Kaposi sarcoma in South Africa. Mosam A, Shaik F, Uldrick TS, et al. *JAIDS* 2012; 60: 150–7.

Fifty-nine treatment-naïve patients were randomized to ART (stavudine, lamivudine, and nevirapine) and 53 to ART and chemotherapy (Triomune plus bleomycin, doxorubicin, and vincristine). Overall KS response was 39% in the ART arm and 66% in the combination therapy arm. There was no survival difference.

Randomized trial of paclitaxel versus pegylated liposomal doxorubicin for advanced human immunodeficiency virus-associated Kaposi sarcoma. Cianfrocca M, Lee S, Von Roenn J, et al. *Cancer* 2010; 116: 3969–77.

Seventy-three patients with advanced HIV-associated KS were randomized to paclitaxel vs. pegylated liposomal doxorubicin, both of which resulted in significant improvement of pain and swelling. Overall incidence of toxicity was greater in those treated with paclitaxel.

Highly active antiretroviral therapy in AIDS-associated Kaposi's sarcoma: implications for the design of therapeutic trials in patients with advanced, symptomatic Kaposi's sarcoma. Krown SE. *J Clin Oncol* 2004; 22: 399–402.

In patients with early disease (stage T₀), 80% of patients who had not previously received ART showed regression with ART alone.

Imiquimod 5% cream versus cryotherapy in classic Kaposi sarcoma. Odvakmaz DE, Bayramugurler D, Caglayan C. *J Cutan Med Surg* 2019; 23: 488–95.

Single-blinded, non-controlled study. Of the patients receiving cryotherapy, 50% had complete response compared with 42.3% in the imiquimod group.

Radiotherapy in the management of classic Kaposi sarcoma: a single institution experience in northeast Turkey. Kandaz M, Bahat Z, Guler OC. *Dermatol Ther* 2018; 31: e12605.

For non-HIV-associated KS, the complete response rate at 5 years was 91.6% for radiotherapy with >20 Gy and 89.6% with 8 Gy.

Phase III vehicle-controlled, multicentered study of topical alitretinoin gel 0.1% in cutaneous AIDS-related Kaposi's sarcoma. Bodsworth NJ, Bloch M, Bower M, et al.; International Panretin Gel KS Study Group. *Am J Clin Dermatol* 2001; 2: 77–87.

Response rate was 37% (compared with 7% treated with vehicle).

Second-Line Therapies

• Intralesional interferon	C
• Interferon- α_{2b}	C
• Intralesional vinblastine	C

Interferon-alpha2b with protease inhibitor-based antiretroviral therapy in patients with AIDS-associated Kaposi sarcoma: an AIDS malignancy consortium phase I trial. Krown SE, Lee JY, Lin L, et al. *AIDS* 2006; 41: 149–53.

Administration of interferon- α_{2b} led to limited improvement in KS lesions. The maximum tolerated dose was 5 million IU/day.

Intralesional vinblastine for cutaneous Kaposi's sarcoma associated with acquired immunodeficiency syndrome. Boudreaux AA, Smith LL, Cosby CD, et al. *J Am Acad Dermatol* 1993; 28: 61–5.

Responses were achieved in 88% of treated lesions, but pain and hyperpigmentation are common. Pain was minimized by the addition of bicarbonate-buffered lidocaine to the diluent.

Third-Line Therapies

• Bevacizumab	C
• Sorafenib	C
• Gemcitabine	B
• Lenalidomide	E
• Thalidomide	B
• Liposomal all-trans retinoic acid, intravenous	B
• Photodynamic therapy	B
• 9- <i>cis</i> -retinoic acid	B
• Etoposide	B
• Mechanistic target of rapamycin (mTOR) inhibitors (sirolimus/rapamycin)	C
• IL-12	C
• Matrix metalloproteinase inhibitor COL-3	C
• Halofuginone	C
• Imiquimod 5% cream	C
• Sodium tetradecyl sulfate 3%	C
• Surgical excision	E
• Antiviral agents (ganciclovir, valganciclovir, foscarnet)	B
• Intramuscular immunoglobulin	E
• Electrochemotherapy	B
• ND:YAG laser	D
• Timolol	E
• Diphenycprone	E
• Nivolumab	E
• Pazopanib	E

A pilot study of liposomal doxorubicin combined with bevacizumab followed by bevacizumab monotherapy in patients with advanced Kaposi sarcoma. Ramaswami R, Uldrick TS, Polizzotto MN, et al. *Clin Cancer Res* 2019; 25: 4238–47.

Sixteen patients were treated with bevacizumab and liposomal doxorubicin, followed by bevacizumab monotherapy maintenance. Overall response rate was 56%, with a median time to response of 1.5 years.

A phase Ib study of sorafenib (BAY 43-9006) in patients with Kaposi sarcoma. Uldrick TS, Goncalves PH, Wyvill KM, et al. *Oncologist* 2017; 22(5): 505–49.

Minimal clinical response with only 2/7 patients experiencing a partial response.

Randomized phase IIA trial of gemcitabine compared with bleomycin plus vincristine for treatment of Kaposi sarcoma in patients on combination antiretroviral therapy in western Kenya. Busakhala NW, Waako PJ, Strother MR, et al. *J Glob Oncol* 2018; 4: 1–9.

Complete response was achieved in 33.3% of patients receiving gemcitabine, and in 17.6% of patients receiving bleomycin plus vincristine.

Lenalidomide in treating AIDS-related Kaposi's sarcoma. Martinez V, Tateo M, Castilla MA, et al. *AIDS* 2011; 25: 878–80.

Three cases of HIV-associated KS were successfully treated by lenalidomide, a thalidomide analog.

A retrospective analysis of thalidomide therapy in non-HIV-related Kaposi's sarcoma. Ben M'barek L, Fardet L, Mebazaa A, et al. *Dermatology* 2007; 215: 202–5.

Only three of 11 patients achieved remission, with sensory neuropathy and vertigo limiting therapy in 27%.

A multicenter phase II study of the intravenous administration of liposomal tretinoin in patients with acquired immunodeficiency syndrome-associated Kaposi's sarcoma. Bernstein ZP, Chanan-Khan A, Miller KC, et al. *Cancer* 2002; 95: 2555–61.

A thrice-weekly dosing schedule (60 mg/m² escalating to 90 mg/m² and then to 120 mg/m² if tolerated) was more effective than once a week, without any significant difference in toxicity.

New photodynamic therapy protocol to treat AIDS-related Kaposi's sarcoma. Tardivo JP, Del Giglio A, Paschoal LH, et al. *Photomed Laser Surg* 2006; 24: 528–31.

Case report describing successful treatment of a solitary patient with epidemic KS.

9-cis-retinoic acid capsules in the treatment of AIDS-related Kaposi sarcoma: results of a phase 2 multicenter clinical trial. Aboulafia DM, Norris D, Henry D, et al. *Arch Dermatol* 2003; 139: 178–86.

Overall response was 19%. Moderate efficacy and substantial toxicity at higher doses limit use.

As needed vs immediate etoposide chemotherapy in combination with antiretroviral therapy for mild-to-moderate AIDS-associated Kaposi sarcoma in resource-limited settings: A5264/AMC-067 randomized clinical trial. Hosseinipour MC, Kang M, Krown SE, et al. *Clin Infect Dis* 2018; 67: 251–60.

Etoposide plus ART slowed time to KS progression (24.1 vs. 96.6 weeks). There was no difference between as needed administration and immediate etoposide after 48 weeks of treatment.

Sirolimus for Kaposi's sarcoma in renal-transplant recipients. Stallone G, Schena A, Infante B, et al. *N Engl J Med* 2005; 352: 1317–23.

Fifteen transplant patients achieved total remission when switched from ciclosporin to sirolimus for immunosuppression.

Classic Kaposi's sarcoma treated with topical rapamycin. Diaz-Ley B, Grillo E, Rios-Buceta L, et al. *Dermatol Ther* 2015; 28: 40–3.

An immunocompetent patient improved after 16 weeks of treatment with topical rapamycin.

Phase 2 study of pegylated liposomal doxorubicin in combination with interleukin-12 for AIDS-related Kaposi sarcoma. Little RE, Aleman K, Kumar P, et al. *Blood* 2007; 110: 4165–71.

Thirty of 36 patients had a good response to liposomal doxorubicin with IL-12 for six 3-week cycles followed by twice-weekly IL-12 for maintenance for 3 years. No control group was included, and patients received highly active antiretroviral therapy (HAART) in addition to the experimental regimen.

Activity of subcutaneous interleukin-12 in AIDS-related Kaposi sarcoma. Little RE, Pluda JM, Wyvill KM, et al. *Blood* 2006; 107: 4650–7.

IL-12 was administered twice weekly with significant results observed at doses >100 ng/mg; side effects limited dosing above 500 ng/kg.

Randomized phase II trial of matrix metalloproteinase inhibitor COL-3 in AIDS-related Kaposi's sarcoma: an AIDS Malignancy Consortium Study. Dezube BJ, Krown SE, Lee JY, et al. *J Clin Oncol* 2006; 24: 1389–94.

A response rate of 41% was observed at a dose of 50 mg/day.

Phase II AIDS malignancy consortium trial of topical halofuginone in AIDS-related Kaposi's sarcoma. Koon HB, Fingleton B, Lee JY, et al. *JAIDS* 2011; 56: 64–8.

Twenty-six patients with HIV and KS limited to the skin were treated with halofuginone (angiogenesis inhibitor) with a response rate of 35%.

Imiquimod 5% cream for treatment of HIV-negative Kaposi's sarcoma skin lesions: a phase I to II, open-label trial in 17 patients. Célestin Schartz NE, Chevret S, Paz C, et al. *J Am Acad Dermatol* 2008; 58: 585–91.

Imiquimod was applied under occlusion three times a week for 24 weeks. Eight of 17 patients showed some response, with six of 17 demonstrating tumor progression.

Intralesional vinblastine vs 3% sodium tetradecyl sulfate for the treatment of oral Kaposi's sarcoma A double blind, randomized clinical trial. Ramírez-Amador V, Esquivel-Pedraza L, Lozada-Nur F, et al. *Oral Oncol* 2002; 38: 460–7.

Sixteen patients were randomized to each arm. Results were equivocal but suggested a possibly greater tolerability of sodium tetradecyl sulfate.

Local therapy for mucocutaneous Kaposi's sarcoma in patients with acquired immunodeficiency syndrome. Webster GF. *Dermatol Surg* 1995; 21: 205–8.

Surgery can occasionally be helpful for isolated lesions, but recurrence is frequent; therefore, this modality is of limited value.

Mohs micrographic surgery for exophytic Kaposi sarcoma. Solevami T, Bennett RG. *Dermatol Surg* 2020; 6(9): 1232–5.

Case report of successful treatment of KS lesions with Mohs micrographic surgery (MMS). MMS was used when the patient did not qualify for other non-surgical treatments options, so MMS may have use in patients that do not qualify for other treatment modalities.

Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. Martin DE, Kupperman BD, Wolitz RA, et al. *N Engl J Med* 1999; 340: 1063–70.

In this randomized, controlled trial, intravenous and oral ganciclovir resulted in a decrease in the development of KS.

Effect of antiviral drugs used to treat cytomegalovirus end organ disease on subsequent course of previously diagnosed Kaposi's sarcoma in patients with AIDS. Robles R, Lugo D, Gee L, et al. *J AIDS Hum Retrovirol* 1999; 20: 34–8.

In patients being treated for cytomegalovirus with foscarnet, progression of KS was markedly delayed.

Valganciclovir for suppression of human herpesvirus 8 replication: a randomized, double-blind, placebo-controlled, crossover trial. Casper C, Krantz EM, Corey L, et al. *J Infect Dis* 2008; 198: 23–30.

Valganciclovir was noted to reduce the shedding frequency and quantity of HHV-8.

Successful treatment of classical Kaposi sarcoma with low-dose intramuscular immunoglobulins. Thoms KM, Hellriegel S, Krone B, et al. *Br J Dermatol* 2011; 164: 1107–9.

Improvement was noted in a patient treated with intramuscular immunoglobulins.

Effects of electrochemotherapy on human herpesvirus 8 kinetics in classic Kaposi sarcoma. Starita N, DiMonta G, Cerasuolo A, et al. *Infect Agent Cancer* 2017; 12: 35.

Complete response was achieved in 73.6% of patients, with a significant decline in HHV8 viral load after a single electrochemotherapy (ECT) treatment.

Successful treatment of classic Kaposi sarcoma with long-pulse neodymium-doped yttrium aluminum garnet laser: a preliminary study. Ozdemir M, Balevi A. *Dermatol Surg* 2017; 43(3): 366–70.

Treatment of classic KS with long-pulse neodymium:yttrium-aluminum-garnet (Nd:YAG) laser resulted in clinical and histological improvement. Nd:YAG was especially effective for papulonodular and deeper lesions located on bony structures.

Topical timolol for treatment of penile Kaposi sarcoma in HIV-negative patient. Sainz-Gaspar L, Suarez-Penaranda JM, Poussa-Martinez M, et al. *Dermatol Ther* 2017; 30.

Moderate treatment response to topical timolol twice per day was noted in an HIV-negative patient.

Topical diphencyprone immunotherapy for painful nodular acral recurrence of Kaposi sarcoma. Pagliarello C, Stanganelli I, Fabrizi G, et al. *JAMA Dermatol* 2017; 153(2): 234–5.

Two patients achieved clinical clearance within 3 months utilizing diphencyprone 0.2% solution under occlusion for 24 hours once weekly.

PD-1 blockade with nivolumab in endemic Kaposi sarcoma. Delyon J, Bizot A, Battistella M, et al. *Ann Oncol* 2018; 29: 1067–69.

Two cases of non-HIV-associated KS with bone and lymph node involvement. Patients received nivolumab 3 mg/kg every 2 weeks. After six cycles, significant partial response was seen for both patients.

Ring a ring o'roses, a patient with Kaposi's? Pazopanib, pazopanib, it might go away. Mediterranean (classic) Kaposi sarcoma responds to the tyrosine kinase inhibitor pazopanib after multiple lines of standard therapy. Harris BHL, Walsh JL, Neciunaite R, et al. *Clin Exp Dermatol* 2018; 42: 234–6.

Case report demonstrating complete clearance of all KS lesions with oral pazopanib 400 mg once daily for 2 weeks, followed by 800 mg once daily for 6 months.

Kawasaki disease

Dirk Van Gysel, Hannelore De Maeseneer



Kawasaki disease (KD), seen primarily in infants and children, is an acute, febrile, multiorgan vasculitic process known for its mucocutaneous and nodal involvement. Although KD was described in Japan several decades ago, its pathogenesis has yet to be clarified.

MANAGEMENT STRATEGIES

The goal of therapy in the acute phase is to reduce inflammation and arterial damage and to prevent thrombosis in those with coronary artery lesions (CALs). The mainstay of initial treatment is intravenous immunoglobulin (IVIG) together with acetylsalicylic acid (ASA).

Meta-analyses of IVIG compared with placebo have shown a conclusive decrease in new CALs among IVIG-treated patients. IVIG appears to have a generalized antiinflammatory effect and should be given as a single intravenous infusion: 2 g/kg, over 10–12 hours, within 10 days of illness onset but preferably as soon as possible after diagnosis.

In the acute inflammatory phase, ASA, a potent inhibitor of prostaglandin synthesis, is administered orally every 6 hours. The recommended total daily dose ranges from moderate (30–50 mg/kg/day in Japan and Western Europe) to high-dose (80–100 mg/kg/day in the United States). There are no data to suggest that either dose of ASA is superior. After the patient is afebrile for 48 hours, the dose is reduced to low (3–5 mg/kg orally daily) and continued for 6–8 weeks after onset of illness until the patient has no evidence of coronary changes.

However, approximately 10%–20% of patients do not respond to such treatment. In Japanese patients who were predicted at baseline to have a high risk of IVIG resistance, primary therapy with IVIG + corticosteroids showed a more advantageous effect than IVIG alone regarding coronary artery abnormality prevention.

As for second-line therapy in IVIG-refractory KD, neither infliximab nor corticosteroids were significantly more effective than

a second IVIG infusion with respect to lowering CALs and treatment resistance.

New discoveries related to the genetics and pathophysiology of KD have suggested a more disease-specific therapeutic role for calcineurin inhibitors (e.g., ciclosporin), tumor necrosis factor inhibitors (e.g., infliximab, etanercept), and interleukin-1 inhibitors (e.g., anakinra).

Thromboprophylaxis and careful surveillance for coronary artery stenoses/obstructions and myocardial ischemia are the cornerstones of long-term management. Selected patients with myocardial ischemia may be candidates for revascularization with catheter interventions or coronary artery bypass surgery or, rarely, cardiac transplantation.

Specific Investigations

Laboratory tests:

- Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count, electrolytes, renal function, liver function (including bilirubin, aspartate aminotransferase (AST) or alanine aminotransferase (ALT), and albumin) and urinalysis

Evaluation for cardiovascular abnormalities:

- Echocardiography
- CT angiography, cardiac MRI, or invasive angiography

KAWASAKI DISEASE: AN OVERVIEW

There is no single diagnostic test for KD; diagnosis rests on clinical criteria and laboratory findings. The diagnosis of 'complete KD' should be made during the acute phase and is based on clinical criteria. The diagnosis can be established in the presence of prolonged refractory fever (≥ 5 days and minimally responsive to antipyretics) and with the fulfillment of at least four of the following five criteria: non-specific exanthema; bilateral bulbar conjunctival injection without exudate; changes in extremities: erythema and edema of the hands and feet in acute phase and/or periungual and perineal desquamation in subacute phase; oral erythema, cracking of lips, and strawberry tongue; cervical lymphadenopathy (≥ 1.5 cm diameter, mainly unilateral), although not all symptoms are always present at the same time.

The diagnosis of 'incomplete KD' is made if fewer than four of the above five diagnostic criteria are met. For these patients, the American Heart Association created an algorithm based on echocardiographic and laboratory abnormalities (Vervoort D, Donné M, Van Gysel D. Pitfalls in the diagnosis and management of KD: an update for the pediatric dermatologist. *Pediatr Dermatol* 2018; 35(6): 743–7).

KAWASAKI DISEASE: AN UPDATE ON TREATMENT

First-Line Therapies

• Intravenous immunoglobulin (IVIG)	A
• Acetylsalicylic acid (ASA)	B
• Corticosteroids (IVMP)	B

IVIG

The effects of early intravenous immunoglobulin therapy for Kawasaki disease: the 22nd nationwide survey in Japan. Kuwabara M, Yashiro M, Ae R, et al. *Int J Cardiol* 2018; 269: 334–8.

In this Japanese cohort study 20,933 patients were assessed with echocardiography and divided into three groups according to the start of the IVIG therapy: (1) early: ≤ 4 days; (2) conventional: 5–7 days; and (3) late: 8–10 days after start of the symptoms.

After multiple adjustments, conventional therapy had similar risks for coronary dilatation or aneurysm compared with early therapy, whereas late therapy had a higher risk.

A comparison of efficacy of six prediction models for IVIG resistance in Kawasaki disease. Qian W, Tang Y, Yan W, et al. *Ital J Pediatr* 2018; 44: 33.

In this retrospective, Chinese, single center study the authors aimed to evaluate the efficacy of six prediction models using the medical data of 504 patients with a diagnosis of KD.

Their own prediction model (with age < 6 months, rash, edema of extremities, % neutrophils, and serum albumin as independent risk factors for IVIG non-responders) had a sensitivity of 0.72 and a specificity of 0.75. Sensitivity of Kobayashi, Egami, Kawamura, Sano, and Formosa were 0.72, 0.44, 0.48, 0.20, and 0.68, respectively. Specificity of these models were 0.62, 0.82, 0.66, 0.91, and 0.48, respectively.

Defining the risk of first intravenous immunoglobulin unresponsiveness in non-Asian patients with Kawasaki disease. Piram M, Darce Bello M, Tellier S, et al. *Sci Rep* 2020; 10(1): 3125.

This study investigated the accuracy of three Japanese scoring systems (Kobayashi, Egami, and Sano scores) and studied factors associated with IVIG unresponsiveness in a large multiethnic French population of children with KD to build a new scoring system. Japanese scores had poor performance in the whole population (sensitivity 14%–61%). Predictors of secondary treatment after initial IVIG were hepatomegaly, ALT level ≥ 30 IU/L, lymphocyte count $< 2400/\text{mm}^3$, and time to treatment < 5 days. The sensitivity remained good in the three main ethnic subgroups (74%–88%).

Acetylsalicylic acid

What dose of aspirin should be used in the initial treatment of Kawasaki disease? A meta-analysis. Jia X, Du X, Bie S, et al. *Rheumatology (Oxford)* 2020 Mar 11. pii: keaa050.

The aim of this study was to evaluate the efficacy of IVIG plus high-dose aspirin compared with IVIG plus low-dose aspirin in the treatment of KD. Eight retrospective cohort studies were included, characterizing 12,176 patients.

No significant difference was found in the incidence of CALs between the high- and low-dose aspirin groups. The patients treated with high-dose aspirin had slightly faster resolution of fever, but the rates of IVIG resistance and days in hospital were similar.

Efficacy between low and high dose aspirin for the initial treatment of Kawasaki disease: current evidence based on a meta-analysis. Zheng X, Yue P, Liu L, et al. *PLoS One* 2019; 14(5): e0217274.

This meta-analysis evaluates the efficacy of low-dose aspirin compared with high-dose for the initial treatment of KD. No

significant differences were found in the incidence of CALs, the risk of IVIG-resistant KD, and duration of fever and hospitalization. The authors conclude that low-dose aspirin (3–5 mg/kg/day) may be as effective as the use of high-dose aspirin (≥ 30 mg/kg/day) for the initial treatment of KD.

Is aspirin necessary in the acute phase of Kawasaki disease? Huang X, Huang P, Zhang L, et al. *J Paediatr Child Health* 2018; 54: 661–4.

In this retrospective study, 910 KD patients with a follow-up of at least 2 years were classified into three groups according to the doses of aspirin. Group 1 included 152 cases treated with IVIG only in the acute phase. Group 2 included 672 cases treated with IVIG plus 3–5 mg/kg/day aspirin as the low-dose group, and group 3 included 86 cases treated with IVIG plus 30–50 mg/kg/day aspirin as the moderate-dose group.

There was no significant difference among the three groups in terms of the antiinflammation effect revealed by CRP level, white blood cell count, percentage of neutrophils in white blood cells, decreasing platelet count or prevention of the formation of CALs. The authors conclude that the role of aspirin in the treatment of the acute phase of KD should be questioned as a definite benefit has not been shown in their study.

Efficacy and safety of intravenous immunoglobulin plus prednisolone therapy in patients with Kawasaki disease (Post RAISE): a multicentre, prospective cohort study. Miyata K, Kaneko T, Morikawa Y, et al. *Lancet Child Adolesc Health* 2018; 2: 855–62.

In this study the efficacy and safety of primary IVIG plus prednisolone were verified. For predicted non-responders, each hospital independently decided whether to add IVMP to the primary IVIG treatment, according to their respective treatment policy. Primary IVIG plus prednisolone therapy in this study resulted in a reduced non-response rate and decreased incidence of CALs.

Second-Line Therapies

• Second IVIG dose	B
• Corticosteroids (IVMP)	B
• Infliximab (IFX)	B

Comparison of second-line therapy in IVIG-refractory Kawasaki disease: a systematic review. Crayne CB, Mitchell C, Beukelman T. *Pediatr Rheumatol Online J* 2019; 17(1): 77.

In this systematic review the efficacy and safety of three treatments (i.e., a second IVIG infusion, intravenous pulse methylprednisolone [IVMP], and infliximab [IFX]) in patients with refractory KD were evaluated. Of the 388 patients included from the eight studies analyzed, a majority received a second IVIG dose ($n = 263$, 68%). Fever resolution was comparable between IVIG (72%) and IVMP (73%). IFX (88%) significantly increased fever resolution by approximately 20% compared with IVIG redose. Clinical significance of differences in coronary outcomes remains unclear.

Indirect-comparison meta-analysis of treatment options for patients with refractory Kawasaki disease. Chan H, Chi H, You H, et al. *BMC Pediatr* 2019; 19: 158.

This meta-analysis analyzed 12 studies involving 372 IVIG-resistant KD patients. Neither IFX nor IVMP was significantly more effective than second IVIG infusion with respect to lowering CALs and treatment resistance. No significant differences

were found between IFX and IVMP in the incidence rate of CALs, the treatment resistance, the rates of coronary artery aneurysm, and the coronary artery dilatation. Compared with second IVIG infusion, both IFX and IVMP showed significant effectiveness in antipyretic effects. IVMP treatment showed significant association with fewer adverse events than second IVIG infusion and IFX.

Corticosteroids

Corticosteroids for the treatment of Kawasaki disease in children. Wardle AJ, Connolly GM, Seager MJ, et al. Cochrane Database Syst Rev 2017 Jan 27; 1: CD011188.

This Cochrane review includes seven trials consisting of 922 children with all severities of KD who were treated with corticosteroids, including different types of corticosteroid and different durations of treatment.

On pooled analysis, corticosteroids reduced the subsequent occurrence of CALs without resultant serious adverse events and mortality. Corticosteroids also reduced the duration of fever, the time for ESR and CRP to normalize, and the length of hospital stay. Evidence was considered high quality for the incidence of serious adverse events, mortality, and time for laboratory parameters to normalize. Evidence was considered moderate for the incidence of CALs, duration of clinical symptoms (fever, rash), and length of hospital stay.

The prevention of coronary arterial abnormalities in Kawasaki disease: a meta-analysis of the corticosteroid effectiveness. Yang TJ, Lin MT, Lu CY, et al. J Microbiol Immunol Infect 2018; 51: 321–31.

This meta-analysis includes 19 studies that compared incidence of CALs between regimens with corticosteroid and regimens without it; 3591 patients were included for analysis. The incidence of CALs was significantly lower in patients treated with a regimen with corticosteroid. In general, a greater effect was seen in the patients who received corticosteroid as initial and adjuvant therapy with IVIG than those who received corticosteroid as rescue therapy. The risk reduction was statistically significant in Japanese groups but not significant in non-Japanese groups.

TNF- α Blockers

TNF- α blockers for the treatment of Kawasaki disease in children. Yamaji N, da Silva Lopes K, Shoda T, et al. Cochrane Database Syst Rev 2019 Aug 16; 8: CD012448.

This Cochrane review included five randomized controlled trials (RCTs) that compared TNF- α blockers to placebo or other drugs (including retreatment with IVIG) in children with KD, with a total of 494 participants. TNF- α blockers reduced the incidence of treatment resistance. There was no clear difference between groups in the incidence of CALs. The TNF- α blocker intervention decreased infusion reactions, and there was no clear difference for incidence of ‘infections’ after treatment initiation, rash or contact dermatitis. The authors conclude that low-certainty evidence indicates that TNF- α blockers have beneficial effects on treatment

resistance and the adverse effect ‘infusion reaction’ after treatment initiation for KD when compared with no treatment or additional treatment with IVIG.

Third-Line Therapies

• Ciclosporin	B
• Anakinra	C
• Plasma exchange	D

Ciclosporin

Efficacy of primary treatment with immunoglobulin plus ciclosporin for prevention of coronary artery abnormalities in patients with Kawasaki disease predicted to be at increased risk of non-response to intravenous immunoglobulin (KAICA): a randomised controlled, open-label, blinded-endpoints, phase 3 trial. Hamada H, Suzuki H, Onouchi Y, et al. Lancet 2019; 393(10176): 1128–37.

In this RCT, 175 KD patients from 22 hospitals in Japan, who were predicted to be unresponsive to IVIG, were enrolled and randomly assigned to IVIG plus ciclosporin (5 mg/kg/day for 5 days) or IVIG groups. The analysis showed that combined primary therapy with IVIG and ciclosporin was safe and effective as the incidence of coronary artery abnormalities was lower in the study treatment group than in the conventional treatment group.

Anakinra

The use of interleukin 1 receptor antagonist (anakinra) in Kawasaki disease: a retrospective cases series. Kone-Paut I, Cimaz R, Herberg J, et al. Autoimmun Rev 2018; 17: 768–74.

In their retrospective case series, Kone-Paut et al. analyzed the efficacy of anakinra (doses from 2 to 8 mg/kg) in terms of fever resolution (100%), decrease of CRP (100%), and effect on coronary artery dilatation (Z scores, which decreased in 10/11 patients and increased in one who died suddenly of pericardial hemorrhage). They concluded that anakinra used late in the disease course led to a rapid and sustained improvement in clinical and biological inflammation. Their retrospective analysis did show neither a striking nor a rapid decrease of coronary dilatations, and they could not determine if anakinra itself had an effect on coronary artery dimensions.

Plasma Exchange

Safety and efficacy of plasma exchange therapy for Kawasaki disease in children in intensive care unit: case series. Noguchi S, Saito J, Kudo T, et al. JA Clin Rep 2018; 4: 25.

In the four reviewed cases of refractory KD, plasma exchange treatment with 5% albumin in electrolyte-balanced solution was performed. The plasma levels of CRP were significantly decreased after plasma exchange. The two cases in which dilatations of the coronary artery were found were ameliorated until 1 month after the onset. However, one case showed marked decreases in coagulation factors, especially in fibrinogen after each plasma exchange even with a transfusion of fresh frozen plasma.

Keloids

Brian Berman



Keloids are dermal hyperproliferative growths of dense fibrous tissue that extend beyond the borders of the original wound and do not regress spontaneously. In addition to the cosmetic disfigurement and negative psychological impact that keloids may cause the patient, these scars can often present with intense pain and pruritus.

MANAGEMENT STRATEGY

The therapeutic options for keloids are numerous; however, there is no one modality that is considered to be universally safe and effective. Prevention of initial development and prevention of recurrence should be the main determinants in treatment selection. The initial rule of treatment involves *prevention* and *patient education*. It is of the utmost importance to close wounds with minimal tension and inflammation. Non-essential surgery, tattoos, and piercings should be avoided as keloids commonly develop in areas of high skin tension and incision sites in the mid-chest skin. Surgery overlying joints should be avoided, and surgical wounds should parallel skin creases. Areas of inflammatory skin diseases such as acne and folliculitis need to be treated.

Common therapeutic modalities include occlusive dressings, compression therapy, intralesional corticosteroid injections, intralesional interferon injections, intralesional 5-fluorouracil injections, cryosurgery, surgical excision, radiation therapy, and laser therapy. Because no single therapy is vastly superior or universally efficacious, combination therapies have led to the greater success rates. Radiation, occlusive dressings, topical imiquimod, and corticosteroid injections vary in effectiveness to reduce the high rate of keloid recurrence postsurgical excision (about 70%).

Intralesional corticosteroids have been the mainstay of treatment for keloids. The most commonly used is triamcinolone acetonide in concentrations of 10–40 mg/mL administered intralesionally with a 25- to 27-gauge needle at 4–6-week intervals. *Topical corticosteroids* and *topically applied corticosteroid-impregnated tape* are

also used frequently; the basis for the latter involves recent data demonstrating that occlusion enhances percutaneous penetration of steroids by the formation of a drug reservoir within the stratum corneum. *Silicone gel sheets* and *silicone occlusive dressings* have anti-keloidal effects, which appear to be a result of hydration.

Pressure devices are thought to induce local tissue hypoxia and have been shown to have a thinning effect on keloids. A novel idea in the treatment of keloids and hypertrophic scars is the use of *intralesional interferon- α_{2b}* , which has been used successfully to reduce scar height and postoperative recurrences via a mechanism of collagen synthesis inhibition. *Interferon- γ* has also been evaluated in the treatment of keloids, with modest results.

Cryotherapy can be used as monotherapy or in conjunction with other treatment modalities, most commonly triamcinolone, with reported efficacy. Its mechanism of action involves the induction of vascular damage and tissue anoxia that ultimately leads to necrosis. However, some reported side effects have included hypopigmentation and postoperative pain. A specialized intralesional needle cryoprobe method has been recently reported to result in better efficacy and fewer side effects.

Radiation therapy has been used as monotherapy or as an adjunct to surgical excision. The carcinogenesis risks of radiotherapy are extremely small; however, the concept of using potentially harmful radiation to treat benign lesions is a persistent and important issue.

Surgical excision alone yields widely varying results with high (55–100%) recurrence rates. The *combination of surgical excision with other modalities, such as intralesional corticosteroids or with pressure dressings, X-ray therapy, interstitial radiation, and brachytherapy*, reduces recurrence rates to a range of 10–50%.

CO₂ and argon lasers were used in the treatment of keloids but have recently been replaced by the Nd:YAG and 585-nm *pulsed-dye lasers* because of their better efficacy and fewer adverse effects. *Intralesional injection of 5-fluorouracil* has been beneficial for hypertrophic scars and for keloids. *Bleomycin, retinoic acid, intralesional verapamil, and mitomycin C* have all been reported to have good efficacy in small clinical trials, but more clinical experience with these agents is needed.

Specific Investigation

- Skin biopsy

Dermatofibrosarcoma protuberans is a unique fibrohistiocytic tumor expressing CD34. Aiba S, Tabata N, Ishii H, et al. *Br J Dermatol* 1992; 127: 79–84.

Dermatofibrosarcoma protuberans can be easily misdiagnosed as a keloid. Histopathology may help differentiate the two, but expression of CD34 by tumor cells occurs only in dermatofibrosarcoma protuberans.

First-Line Therapies

• Intralesional corticosteroids	B
• Compression	B
• Occlusive dressing	B
• Intralesional 5-fluorouracil	B

A new uniform protocol of combined corticosteroid injections and ointment application reduces recurrence rates after surgical keloid/hypertrophic scar excision. Hayashi T, Furukawa H, Oyama A, et al. *Dermatol Surg* 2012; 38: 893–7.

Twenty-one keloids were treated with surgical excision, then corticosteroid injections (a mixture of 1 mL of triamcinolone acetonide, 40 mg/mL, and 1 mL of procaine hydrochloride intradermally on both sides of the suture line at the rate of 0.1 mL every 1 cm up to 2 mL) after removal of the sutures and every 2 weeks (for five more times) thereafter. In addition, all postsurgical wounds received self-administered steroid ointment (diflorasone diacetate) application twice daily for 6 months after suture removal. Recurrence occurred in three of the 21 keloid cases (14.3%) and one of the six hypertrophic scar cases (16.7%).

Keloids treated with topical injections of triamcinolone acetonide. Immediate and long term results. Kiil J. *Scand J Plast Reconstruct Surg* 1977; 11: 169–72.

In a prospective clinical trial of 52 patients, intralesional injections of triamcinolone acetonide (1 mL triamcinolone acetonide 40 mg/cc) alone resulted in significant flattening and reduction of pruritus in 93% of the keloids. One-third had partial recurrence at 1 year, and at 5 years, more than 50% had recurred. All recurrences were successfully treated with further triamcinolone acetonide injections.

Outcomes of surgical excision with pressure therapy using magnets and identification of risk factors for recurrent keloids. Park TH, Seo SW, Kim JK, et al. *Plast Reconstr Surg* 2011; 128: 431–9.

In this study, 1436 ear keloids in 883 patients were treated with surgical excision followed by pressure therapy using magnets. The overall recurrence-free rate was 89.4% after a follow-up period of 18 months. Keloid recurrence was significantly associated with the presence of prior treatment history, keloid low growth rate, and high patient body mass index.

A surgical approach for earlobe keloid: keloid fillet flap. Kim DY. *Plast Reconstr Surg* 2004; 113: 1668–74.

Surgical revision of keloids on earlobes followed by intradermal scaffold/linear surgical incision was performed in 19 subjects (26 earlobe keloids). At 12 months, the recurrence rate was 19.2%. There were no device-related adverse events.

Comparison of a silicone gel-filled cushion and silicone gel sheeting for the treatment of hypertrophic or keloid scars. Berman B, Flores F. *Dermatol Surg* 1999; 25: 484–6.

In this study of 32 keloid patients, 53% treated with silicone gel cushion and 36.3% treated with silicone gel sheeting had a reduction in keloid volume.

Clinical evaluation of a new self-drying silicone gel in the treatment of scars: a preliminary report. Signorini M, Clementoni MT. *Aesthet Plast Surg* 2007; 31: 183–7.

A prospective trial involving 160 patients that compared postoperative treatment with a self-drying transparent silicone gel with no treatment. Sixty-seven percent of patients in the treatment group had a significant improvement in scar quality.

Intralesional 5-fluorouracil in keloid treatment: a systemic review. Bijlard E, Steltenpool S, Niessen FB. *Acta Derm Venereol* 2015; 95: 778–82.

Systematic review of 18 publications with 482 patients. 5-fluorouracil treatment was effective in 45–96% of patients, but only triamcinolone with 5-fluorouracil (50 mg/mL; 20–150 mg maximum per lesion) performed better than triamcinolone alone.

Second-Line Therapies

• Intralesional interferon- α_{2b}	B
• Cryosurgery	B
• Radiation	B

Recurrence rates of excised keloids treated with postoperative triamcinolone acetonide injections or interferon alfa-2b injections. Berman B, Flores F. *J Am Acad Dermatol* 1997; 37: 755–7.

There was a statistically significant reduction in the recurrence of 124 excised keloids with postexcision interferon- α_{2b} (18.7% recurrence) versus excision alone (51.1%) and versus treatment with postoperative intralesional triamcinolone (58.4%).

Effects of interferon- α_{2b} on keloid treatment with triamcinolone acetonide intralesional injection. Lee JH, Kim SE, Lee A-Y. *Int J Dermatol* 2008; 47: 183–6.

Forty keloid lesions from 19 patients were treated either with triamcinolone acetonide (concentration and volume not noted) intralesional (TAIL) combined with interferon- α_{2b} (0.5 MU IFN- α_{2b} /cm² of keloid up to 0.5 mL twice a week for 24 weeks) or with TAIL alone. Superior results were obtained with combination therapy, with more than 80% improvement in lesion depth and volume in most patients.

Cryotherapy in the treatment of keloids. Rusciani L, Rossi G, Bono R. *J Dermatol Surg Oncol* 1993; 19: 529–34.

Of 65 keloids treated with 2–10 sessions of 2–3 freeze-thaw cycles/session of cryotherapy using liquid nitrogen at a distance of approximately 2 cm, 48 had complete flattening. The most common adverse effects included atrophic depressed scars, residual hypopigmentation, and depigmentation.

Treatment of keloids with laser-assisted topical steroid delivery: a retrospective study of 23 cases. Cavalie M, Sillard L, Montaudie H, et al. *Dermatol Ther* 2015; 28(2): 74–8.

Retrospective study of 23 patients with 70 keloids, with three keloids/patient treated with ablative fractional erbium laser every other week for a median of nine treatments with topical betamethasone cream BID under occlusion. The median improvement was 50% (range 43–84) with none completely improved.

Hypofractionated electron-beam radiation therapy for keloids: retrospective study of 568 cases with 834 lesions. Shen J, Lian X, Sun Y, et al. *J Radiat Res* 2015; 56: 811–7.

Retrospective study of 568 patients with 834 keloids treated with radiotherapy – 18 Gy external electron beam at 6 or 7 MeV in two fractions a week apart. Relapse rate was 9.59% and time to relapse 6–28 months. No radiation-induced cancers were observed.

A retrospective registry study evaluating the long-term efficacy and safety of superficial radiation therapy following excision of keloid scars. Berman B, Nestor MS, Gold MH, et al. *J Clin Aesthetic Dermatol* 2020; 13: 12–16.

A retrospective, chart review study of 96 excised keloids receiving postoperative superficial radiation therapy (SRT; 61 patients) with ≥ 1 -year follow-up (or with a recurrence noted prior to 1 year). Keloidectomy sites usually received three 6-Gy fractions of SRT (biological effective dose of 30, 70, or 100 kV) on postoperative days 1, 2, and 3 to the suture closure line, with a 5 mm margin. It was noted that 10.4% of treated keloids recur within 12 months, with 5/10 recurrences being clinically significant. The

Kaplan–Meier survival probability estimate cure rate was 85.6% from 24 months post-SRT treatment end.

Consensus guidelines on the use of superficial radiation therapy for treating nonmelanoma skin cancers and keloids. Nestor M, Berman B, Goldberg D, et al. *J Clin Aesthet Dermatol.* 2019; 12(2): 12–8.

Based on a search of the literature and expert clinical expertise, the following consensus guidelines were established: postsurgical treatment of keloid excision suture lines with several fractions of SRT significantly reduces keloid recurrence rates; fractionation of the SRT dose reduces the risk of hyperpigmentation and other adverse events. The optimal treatment protocol is a biologically effective dose of 3000cGy in three fractions of 600cGy on postoperative days 1, 2, and 3; and there is little evidence that exposing keloid or surrounding healthy skin to SRT at a 3000cGy dosing causes skin cancer.

Surgical excision with adjuvant irradiation for treatment of keloid scars: a systemic review. van Leeuwen MC, Stokmans SC, Bulstra AE, et al. *Plast Reconstr Surg Glob Open* 2015; 3: e440.

Systematic review of 33 articles that contained 3130 patients with 3470 keloid scars treated with excision followed by low-dose or high-dose brachytherapy. High-dose brachytherapy showed lower recurrence rates compared with low-dose brachytherapy and external radiation, and a short time (<7 hours) interval post-excision was associated with a lower recurrence rate compared with a long time interval (>24 hours).

Third-Line Therapies

• Laser surgery	C
• Imiquimod	B
• Mitomycin C	B
• Intralesional interferon- γ	C
• Topical retinoic acid	B
• Intralesional bleomycin	B
• Verapamil	B
• Surgery	B

Management of ear lobule keloids using 980-nm diode laser. Kassab AN, El Kharbotly A. *Eur Arch Otorhinolaryngol* 2012; 269: 419–23.

Twelve patients with a total of 16 lobule keloids were treated with 980-nm diode laser and subsequent intralesional triamcinolone acetate injection. Between two and five treatment sessions led to 75% of patients with more than 75% reduction of keloid size, with no recurrence in the past 12 months.

The effect of carbon dioxide laser surgery on the recurrence of keloids. Norris JEC. *Plast Reconstruct Surg* 1991; 87: 44–9.

In this retrospective study, 23 patients had adequate follow-up. One had no recurrence, nine required corticosteroids to suppress recurrence, and 13 were considered to be treatment failures.

Pilot study of the effect of postoperative imiquimod 5% cream on the recurrence rate of excised keloids. Berman B, Kaufman J. *J Am Acad Dermatol* 2002; 47: S209–11.

Thirteen keloids were surgically excised and closed primarily and suture lines treated with imiquimod 5% cream every night for 8 weeks. Ten patients with 11 keloids completed the 6-month study, and there were no recurrences.

Effects of imiquimod 5% cream in the prevention of excised keloid recurrence. Frias J, Vargas R, Paez P, et al. *Skin* 2018; 2: 44–6.

Forty-one keloids in 25 patients were *tangentially shaved* and the base curetted. Twenty-four hours postsurgery, imiquimod 5% cream was applied to site OD $\times$ 8 weeks. Of ear keloids, 3/20 (15%) relapsed at 1 year and 4/20 (20%) in 5 years.

Role of mitomycin C in reducing keloid recurrence: patient series and literature review. Gupta M, Narang T. *J Laryngol Otol* 2011; 125: 297–300.

Twenty patients with 26 earlobe keloids were treated with surgical shave excision and topical mitomycin C (1 mg/mL applied twice 3 weeks apart). No recurrences were noted after 24 months.

Intralesional interferon gamma treatment for keloids and hypertrophic scars. Larrabee WF, East CA, Jaffe HS, et al. *Arch Otolaryngol Head Neck Surg* 1990; 116: 1159–62.

Five of the 10 study patients had a reduction in their scar size by at least 50% in linear dimensions. The treatment protocol was one treatment per week for 10 weeks. Up to 0.05 mg of interferon- γ was injected weekly.

The local treatment of hypertrophic scars and keloids with topical retinoic acid. Janssen de Limpens AMP. *Br J Dermatol* 1980; 103: 319–23.

There was a reduction in keloid size and symptoms in 77% of 28 intractable keloids treated with topical retinoic acid.

Treatment of keloids and hypertrophic scars using bleomycin. Huu ND, Huu SN, Thi XL, et al. *Open Access Maced J Med Sci* 2019; 7(2): 298–9.

Fifty-five patients with 120 keloids of different sizes and locations received an average of four treatments with intralesional bleomycin (1.5 U/mL; 0.2–0.4 mL/cm²; maximum volume per session 3.5 mL). Complete flattening was achieved in 70.8% and highly significant flattening in 8.3%. Local side effects included pain (100%), blisters (78.3%), ulceration (5.8%), and hyperpigmentation (56.7%). Keloid recurrence rate was 14% by 18 months.

Comparison of intralesional verapamil with intralesional triamcinolone in the treatment of hypertrophic scars and keloids. Margaret Shanthi FX, Ernest K, Dhanraj P. *Indian J Dermatol Venereol Leprol* 2008; 74: 343–8.

In this randomized, single-blind, parallel group study in which 54 patients were allocated to receive either verapamil (2.5 mg) or triamcinolone (40 mg) every 3 weeks up to 6 months, there was a reduction in vascularity, pliability, height, and width of the scar with both drugs after 3 weeks of treatment. Triamcinolone had a faster reduction rate, but verapamil had a lower rate of hypopigmentation.

Keratoacanthoma

Sybil Keena T. Que, Chrysalyne D. Schmults



A keratoacanthoma (KA) is a form of well-differentiated squamous cell carcinoma characterized by its low metastatic potential and capacity for spontaneous regression. Clinically, a KA appears as a rapidly growing nodule sharply circumscribed and often crateriform. Untreated, it can self-resolve and involute slowly over months. Histologically, KAs have a crateriform appearance, a central keratin plug, and a proliferating well-differentiated squamous epithelium showing epidermal pallor.

There are several clinical presentations of KA, including solitary, multiple, keratoacanthoma centrifugum marginatum, subungual, intraoral, generalized eruptive (Grzybowski), KAs associated with Muir-Torre syndrome, and KAs related to chemical exposure, immunosuppression, and human papillomavirus (HPV) infection.

MANAGEMENT STRATEGY

The management strategy of the KA can be tailored to clinical findings, specifically the presence of a solitary lesion versus multiple generalized KAs.

Although solitary KAs will often resolve spontaneously, it is difficult to predict the clinical course and larger lesions involute with scarring. Thus, solitary KAs should be managed like any other well-differentiated squamous cell carcinoma. The first-line treatment is definitive excisional surgery (including Mohs micrographic surgery for high-risk sites, cosmetically sensitive areas, and large KAs).

Second-line treatment for small KAs includes destructive modalities such as cryotherapy or electrodesiccation and curettage. Cryotherapy with three freeze-thaw cycles of liquid nitrogen can be used, either alone or after first debulking the KA. For

lesions treated with electrodesiccation and curettage, fragments of the curetted tumor can be sent to pathology for diagnostic confirmation if not previously biopsied; however, the disadvantage is that this sample does not represent the full-thickness specimen, which hinders the interpretation of histologic margins.

Intralesional chemotherapies like intralesional 5-fluorouracil (IL 5-FU) and intralesional methotrexate (IL MTX) can be used prior to surgery to decrease the size of a large KA. They can also be used to treat small KAs, although close follow-up is needed in this case to evaluate for incomplete treatment or recurrence. Patients who have numerous KAs, however, may prefer less invasive therapies such as curettage or intralesional chemotherapy over multiple, repeated excisions.

Intralesional 5-fluorouracil (IL 5-FU) at 50 mg/mL is injected directly into the KA (after ring block with local anesthesia) until the lesion blanches in color. This typically requires 0.1 mL–1 mL, depending on the size of the KA. During follow-up, repeat treatments with IL 5-FU can be administered to lesions not fully resolved. When using IL 5-FU or other non-definitive treatments, it is important to follow up every 4–8 weeks. For lesions that do not resolve or are enlarging despite treatment, consider obtaining a biopsy to rule out high-grade SCC.

Intralesional methotrexate (IL MTX) at 12.5 mg/mL or 25 mg/mL is an alternative chemotherapeutic agent available for intralesional injection. Tumor blanching is likewise the clinical endpoint for injection. Similar to IL 5-FU, patients treated with IL MTX require close follow-up and often need a second injection.

Topical 5-FU can also be effective in treating generalized KAs but should be treated under occlusion to increase their efficacy. We advise applying a thin layer of topical 5-FU twice daily and occluding with a plastic wrap overnight for 4 weeks. It may also be necessary to debulk tumors prior to application of topical 5-FU to facilitate absorption of the medication.

Since KAs can originate at sites of trauma, including pruritic areas that are constantly scratched, there is some benefit to applying *topical or intralesional corticosteroids* to treat existing KAs and to prevent the emergence of new KAs. Topical clobetasol 0.05% ointment can be applied broadly over the area with generalized KA and covered with a plastic wrap overnight for 2 weeks or until the lesions resolve. Intralesional triamcinolone (Kenalog) 40 mg/mL can be injected into each KA until blanching of the lesion is observed. Repeat treatments may be needed at follow-up visits.

For patients with refractory or severe disease, oral acitretin can be prescribed to decrease the number of new KAs. It be started at 10 mg PO every other day for 1 month, with the dose increased monthly until the patient is on 20 mg PO daily.

Specific Investigations

- Detailed clinical history
- Full body skin examination
- Skin biopsy

First-Line Therapies

• Standard surgical excision	E
• Mohs micrographic surgery	E
• Acitretin	A

Keratoacanthoma centrifugum marginatum: unresponsive to oral retinoid and successfully treated with wide local excision. Das K, Das NK, Rathore VS, et al. Dermatol Reports 2010; 2: e1.

This case report describes a rare variant of KA, which grows large and never involutes spontaneously. After failure of retinoid therapy, this KA was excised with a wide local excision.

Though evidence is limited to small case reports, complete surgical excision is the first-line and provides definitive treatment of the KA. While there is no literature specifically about the use of Mohs surgery for KAs, Mohs surgery provides margin-controlled clearance of skin cancer and can be considered as the form of excision on cosmetically sensitive areas, large KAs, and high-risk sites, such as the head and neck, hands, or feet.

Multiple keratoacanthomas treated with oral retinoids. Street ML, White JW Jr., Gibson LE. *J Am Acad Dermatol* 1990; 23: 862–6.

Two patients with multiple keratoacanthomas were treated with oral retinoids (etretinate and 13-*cis*-retinoic acid, respectively). Both patients had hundreds of follicular papules on the trunk and extremities. Oral retinoids resulted in regression of the larger, more atypical keratoacanthomas.

Acetretin is the current retinoid of choice for KAs.

Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. Bavinck JN, Tieben LM, Van der Woude FJ, et al. *J Clin Oncol* 1995; 13: 1933–8.

Forty-four renal transplant recipients with more than 10 keratotic skin lesions on the hands and forearms were enrolled in a randomized, double-blind, placebo-controlled trial. During the 6-month period, there was a 13.4% relative decrease in the number of keratotic lesions in the acitretin group in comparison to the placebo group, which experienced a 28.2% relative increase in keratotic lesions.

Second-Line Therapies

• Electrodesiccation and curettage	B
• Topical 5-fluorouracil	E
• Intralesional 5-fluorouracil	D
• Intralesional methotrexate	B
• Intralesional corticosteroids	E

Controversies in skin surgery: electrodesiccation and curettage versus excision for low-risk, small, well-differentiated squamous cell carcinomas. Reschly MJ, Shenefelt PD. *J Drugs Dermatol* 2010; 9: 773–6.

A small controlled study compared cure rates of electrodesiccation and curettage (ED&C) versus excision of low-risk cutaneous squamous cell carcinomas, both in a Veterans Affairs (VA) hospital and in a private practice. There was no significant difference in cure rates and recurrences during 1-year follow-up for patients at the VA hospital (ED&C: 14 of 14 cases successfully treated vs. excision: 15 of 16 successfully treated and one recurrence; $p = 0.1711$). At the private practice, all 106 KAs were successfully treated on 1-year follow-up.

Evaluation of curettage and electrodesiccation in treatment of keratoacanthoma. Nedwich JA. *Australas J Dermatol* 1991; 32: 137–41.

Reports from all KA curettages submitted to a pathology practice in Brisbane, Australia, were reviewed. Of the 111 KAs studied, only four recurred over periods ranging from 3 to 26 months. The authors conclude that curettage and electrodesiccation is efficient and effective.

Eruptive squamous atypia (also known as eruptive keratoacanthoma): definition of the disease entity and successful

management via intralesional 5-fluorouracil. Que SKT, Compton LA, Schmults CD. *J Am Acad Dermatol* 2019; 81: 111–22.

Thirty patients with 136 eruptive keratoacanthoma(s) received treatment with intralesional 5-fluorouracil (IL 5-FU). In 67% of cases, eruptive keratoacanthoma(s) resolved with IL 5-FU monotherapy. The remainder required additional therapies such as topical 5-FU, steroids, cryotherapy, or acitretin and resolved with these adjunctive therapies.

Successful treatment of keratoacanthoma with intralesional fluorouracil. Goette DK, Odom RB. *J Am Acad Dermatol* 1980; 2: 212–6.

Thirty patients with 41 keratoacanthomas were treated with weekly intralesional 5-FU. Forty lesions (97.5%) cleared after an average of three injections in an average of 3.4 weeks.

Management of keratoacanthoma: 157 tumors treated with surgery or intralesional methotrexate. Moss M, Weber E, Hoverson K, et al. *Dermatol Surg* 2019; 45: 877–83.

The authors document the treatment of 73 KAs with intralesional methotrexate (MTX). The use of intralesional MTX monotherapy resulted in an 88% cure rate (9 out of 73 treated KAs did not resolve). Non-resolving KAs were excised, with no recurrences or complications.

Intralesional methotrexate treatment for keratoacanthoma tumors: a retrospective study and review of the literature. Annet NM, VanBeek MJ, Arpey CJ, et al. *J Am Acad Dermatol* 2007; 56: 989–93.

A total of 38 cases of KA treated with MTX were identified: 18 from the authors' institution and 20 from the literature. Intralesional MTX achieved resolution in 92% and required an average of 2.1 injections given about 18 days apart. Adverse events were rare, including two reports of pancytopenia in patients with chronic renal failure.

Intralesional methotrexate treatment for keratoacanthoma tumors: a retrospective case series. Aubut N, Alain J, Claveau J. *J Cutan Med Surg* 2012; 16: 212–7.

The authors identified 46 cases of KA treated with IL MTX. Complete resolution was achieved in 74% of patients, requiring an average of 1.8 injection sessions. Adverse events did not occur.

Intralesional infusion of methotrexate as neoadjuvant therapy improves the cosmetic and functional results of surgery to treat keratoacanthoma: results of a randomized trial. Martorell-Calatayud A, Requena C, Nagore E, et al. *Actas Dermosifiliogr* 2011; 102: 605–15.

A prospective, randomized study on patients with KA at least 1.5 cm included 10 patients who received neoadjuvant IL MTX and 15 patients who underwent surgery without prior IL MTX. The patients who received neoadjuvant IL MTX displayed a reduction of between 50% and 80% in the size of the lesion prior to surgery. No complications were observed in either group.

Topical 5-fluorouracil as primary therapy for keratoacanthoma. Gray RJ, Meland NB. *Ann Plast Surg* 2000; 44: 82–5.

Two patients with KAs were treated with topical 5-fluorouracil and had complete resolution of their lesions within 8 weeks.

Multiple reactive keratoacanthomas treated with zinc oxide wraps and intralesional corticosteroids. West L, Ayoade K, Vandergriff T, et al. *JAAD Case Rep* 2018; 4: 701–4.

A case report of a patient with multiple KAs on the legs showed resolution of KAs unresponsive to other therapies (including

systemic antibiotics, topical steroids, topical 5-fluorouracil). Successful resolution was achieved using intralesional injection of triamcinolone 40 mg/mL followed by zinc oxide wraps (Unna boots) to provide barrier protection, reduce inflammation, and minimize lower extremity edema.

Third-Line Therapies	
• Lasers	D
• Radiation therapy	D
• Photodynamic therapy	D

Argon laser treatment of small keratoacanthomas in difficult locations. Neumann RA, Knobler RM. *Int J Dermatol* 1990; 29: 733–6.

Seventeen patients with biopsy-confirmed, small, solitary KAs on the face and extremities were treated with the argon laser. All lesions were less than 10 mm in diameter. Excellent treatment results were achieved in 65% of patients and 35% healed

with mild scarring. There were no recurrences during the 2-year follow-up.

Radiation therapy of keratoacanthomas: results in 55 patients. Caccialanza M, Sopelana N. *Int J Radiat Oncol Biol Phys* 1989; 16: 475–7.

Fifty-five patients were treated with radiation therapy using orthovoltage X-rays delivered as 40 Gy in twice weekly fractions of 4 Gy. All cases achieved complete regression of KAs.

Efficacy of topical photodynamic therapy for keratoacanthomas: a case-series of four patients. Farias MM, Hasson A, Navarrete C, et al. *Indian J Dermatol Venereol Leprol* 2012; 78: 172–4.

A case series of four patients with solitary KA confirmed by histology were treated with topical photodynamic therapy (PDT) with methylaminolevulinic acid (MAL) cream. After three sessions of PDT, the lesions completely disappeared. No evidence of recurrence and excellent cosmetic outcome was achieved after 3 years of follow-up.

Keratosis lichenoides chronica

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INTRODUCTION

Keratosis lichenoides chronica (KLC), also known as Nekam disease, is a rare, chronic disorder characterized by erythematous to violaceous keratotic papules and plaques arranged in a linear and reticular pattern over the trunk and extremities. Patients may also have a seborrheic dermatitis-like or rosacea-like eruption on the face. KLC can be associated with oral manifestations (recurrent aphthous-like ulcers). Other manifestations, such as palmoplantar keratoderma, ocular manifestations (including blepharitis, conjunctivitis, uveitis, and iridocyclitis), alopecia, and nail dystrophy, have been reported in 20%–30% of patients. KLC has a chronic and progressive course and is often resistant to many therapies. The pathophysiology of KLC is not well understood. Histopathologically, KLC has features of interface dermatitis with lichenoid infiltrate adherent to epidermis, usually consisting of lymphocytes, histiocytes, plasma cells, and few eosinophils, as well as hyperkeratosis, focal parakeratosis, and irregular acanthosis.

MANAGEMENT STRATEGY

Treatment of KLC represents a significant challenge because of the rarity of the condition. It is also resistant to most therapies. No controlled trials are available, but many case series and case reports suggest that *phototherapy* and *systemic retinoids*, alone or in combination, may provide the best treatment option with nearly half of patients reaching complete remission. Other reported treatments

include *systemic steroids*, *sulfones*, *methotrexate*, *antimalarial agents*, and *ciclosporin*. Topical treatments are usually ineffective. Oral retinoids (mostly acitretin) given at a dose of 0.3–0.6 mg/kg/day have been the most effective treatment for KLC.

Specific Investigations

- Skin biopsy
- ANA (if discoid lupus is suspected)

First-Line Therapies

• Oral retinoids (acitretin)	E
• Phototherapy (psoralen and ultraviolet A [PUVA] or UVB)	E
• Re-PUVA	E
• Re-UVB	E
• Acitretin in combination with other systemic agents	E

Keratosis lichenoides chronica: case-based review of treatment options. Pistoni F, Peroni A, et al. *J Dermatolog Treat* 2016; 27: 383–8.

A review of all 71 cases reported in literature between 1972 and 2014. Significant clinical response, defined as complete or partial clearance, was seen in 42% (5/12) patients treated with NB-UVB, 50% (6/12) of patients treated with PUVA, and 56.6% (17/30) of patients treated with systemic retinoids. Combination of oral retinoids plus phototherapy resulted in complete remission in 50% (5/10) of patients treated with Re-PUVA and 100% (3/3) of patients treated with Re-UVB.

Keratosis lichenoides chronica: characteristics and response to acitretin. Avermaete A, Kreuter JA, Stücker M, et al. *Br J Dermatol* 2001; 144: 422–4.

A case report describing a patient with KLC who failed treatment with systemic and topical corticosteroids and PUVA. When given acitretin 0.5 mg/kg, all his lesions flattened considerably after 3 weeks and completely resolved after 6 months of therapy.

A case of pediatric keratosis lichenoides chronica with unusual presentation of severe oral erosions. Nasimi M, Azizpour A, Lajevardi V, et al. *JAAD Case Rep* 2018; 6: 4: 267–9.

A pediatric patient with KLC with oral aphthous-like ulcers was treated with oral acitretin at a dose of 10 mg daily. After 2 months of retinoid therapy, the keratotic plaques on her extremities flattened, and the erythema was much reduced, but not the oral lesions.

Keratosis lichenoides chronica and eruptive keratoacanthoma-like lesions in a patient with multiple myeloma. Marzano AV, Bellinva M, Caputo R, et al. *J Eur Acad Dermatol Venereol* 2005; 19: 129–33.

A case report of patient who developed KLC and multiple keratoacanthomas. Treatment with oral acitretin 25 mg daily for 3 months led to regression of the keratoacanthomas and good improvement of the KLC skin lesions.

Keratosis lichenoides chronica mimicking verrucous secondary syphilis. Jayaraman AG, Pomerantz D, Robinson-Bostom L. *J Am Acad Dermatol* 2003; 49: 511.

A case report of a patient who developed thick keratotic lesions of KLC. Treatment with 25 mg of acitretin daily resulted in partial improvement in his skin lesions.

Keratosis lichenoides chronica treated with acitretin plus narrowband ultraviolet B phototherapy. Koseoglu RD, Sezer E, Yuksek J. *J Dermatol* 2008; 35: 172–4.

A case of a 19-year-old male patient with KLC. Complete clearance of the facial lesions and regression of the body lesions noted 2 months after initiation of treatment with oral acitretin (1 mg/kg/day) plus narrowband ultraviolet B (NB-UVB) treatment, thrice weekly. There was no recurrence of the lesions during a 12-month follow-up period.

Keratosis lichenoides chronica: marked response to PUVA in combination with acitretin. Demirci E, Boyvat A, Arica IE, et al. *Acta Derm Venereol* 2005; 85: 552–3.

A case report of a patient with KLC who had partial improvement after 3 months' PUVA therapy three times per week. Complete clearance was noted 2 months after adding acitretin 35 mg/day to PUVA.

Easy to diagnose, difficult to treat: keratosis lichenoides chronica. Adisen E, Erdem O, Celepci S, et al. *Clin Exp Dermatol* 2010; 35: 47–50.

A case report of a 20-year-old patient with KLC. Treatment with PUVA three times per week in combination with acitretin (25 mg daily) resulted in flattening of the lesions with total resolution in some areas in 2 months. Of note, patient was also using calcipotriol ointment.

Keratosis lichenoides chronica. Bath PUVA therapy. Remling R, Schnopp C, Schmidt T, et al. *Hautarzt* 2002; 53: 550–3.

A case report of a patient who responded to bath-PUVA therapy and all lesions disappeared with no recurrence after 2 years.

Keratosis lichenoides chronica: treatment with bath-PUVA. Kunte C, Kerschenlohr K, Röcken M, et al. *Acta Derm Venereol* 2007; 87: 182–3.

A case report of a patient with typical features of KLC. Treatment with bath-PUVA therapy given as 75 sessions with a total dose of 285.8 J/cm² over 14 months led to partial regression of skin lesions and resolution of the severe itching.

Keratosis lichenoides chronica: marked response to PUVA in combination with acitretin. Demirci E, Boyvat A, Arica IE, et al. *Acta Derm Venereol* 2006; 85: 552–3.

A case report of a 52-year-old patient with KLC. Partial improvement was noted after 3 months of treatment with PUVA three times per week. Adding acitretin 35 mg daily to the PUVA regimen resulted in marked improvement and clearance of all lesions.

A mild case of adult-onset keratosis lichenoides chronica successfully treated with narrow-band UVB monotherapy. Nomura T, Toichi E, Miyachi Y, et al. *Case Rep Dermatol* 2012; 4: 238–41.

A case report of a 34-year-old female patient who failed to respond to topical corticosteroids and topical tacrolimus ointment but improved after 3 months of treatment with NB-UVB.

Keratosis lichenoides chronica: a diagnostic and therapeutic challenge. Wozniacka A, Schwartz RA, Omulecki A, et al. *Clin Exp Dermatol* 2006; 31: 48–50.

A case report of a patient with KLC. Topical treatment with tar, retinoic acid, and local steroids was tried without clinical improvement. Systemic steroids, antimalarials, and methotrexate were also unhelpful. The patient was subsequently treated with PUVA using 8-methoxypsoralen (0.4 mg/kg) taken 1 hour before

UVA. The patient had significant improvement after 50 sessions and cumulative dose of 148.8 J/cm².

Keratosis lichenoides chronica: report of a new case with partial response to PUVA therapy. Douri T, Shawaf AZ. *Dermatol Online J* 2005; 11: 28.

A case report of an adult female patient who developed KLC. Treatment with oral isotretinoin 25 mg/day was ineffective. Partial improvement was noted after treatment with 26 sessions of PUVA (86.5 J).

Vascular variant of keratosis lichenoides chronica associated with hypothyroidism and response to tacalcitol and acitretin. Nijsten T, Mentens G, Lambert J. *Acta Derm Venereol* 2002; 82: 128–30.

A case report of a patient with KLC and hypothyroidism who responded well to oral acitretin with tacalcitol.

Keratosis lichenoides chronica: case report. Martins LC, Horne M, Moreira Júnior DN, et al. *An Bras Dermatol* 2011; 86: S148–51.

A case of an adult male patient with KLC with genital ulcers. Treatment with oral dapsone 100 mg daily resulted in regression of genital lesions but only mild improvement of body skin lesions. Adding oral acitretin 25 mg daily resulted in significant improvement of the skin lesions. Duration of treatment and whether recurrence happened later was not mentioned.

Second-Line Therapy

- Topical calcipotriol

E

Keratosis lichenoides chronica: response to calcipotriol. Grunwald MH, Hallel-Halevy D, Amichai BJAAD 1997; 37: 263–4.

A case report of an adult patient with KLC who failed prolonged treatment with topical and systemic oral etretinate and griseofulvin. Treatment with topical calcipotriol once daily for 4 months resulted in marked clinical improvement.

Keratosis lichenoides chronica: marked response to calcipotriol ointment. Chang SE, Jung EC, et al. *J Dermatol* 2000; 27: 123–6.

A case report of a 35-year-old woman with KLC. She failed 6 months of 20 mg daily of oral etretinate but responded well to treatment with calcipotriol, with almost complete resolution after 3 months.

Third-Line Therapies

- Dapsone E
- Oral isotretinoin E
- Ciclosporin E
- Efalizumab E
- Topical tacrolimus 0.1% ointment E
- Electron beam E
- Etoposide E
- Photodynamic therapy E
- Isotretinoin in combination with oral methotrexate E

Response of keratosis lichenoides chronica to efalizumab therapy. Munoz-Santos C, Yebenes M, Romani J, et al. *Arch Dermatol* 2009; 145: 867–9.

A case report describes a 19-year-old patient with KLC. The patient failed multiple treatments including oral acitretin (dose ranging from 25–35 mg/day), RE-PUVA with acitretin 25 mg daily with oral PUVA (four times per week), and subcutaneous etanercept therapy (50 mg twice a week). Treatment with subcutaneous efalizumab at an initial dose of 0.7 mg/kg followed by 1 mg/kg per week resulted in significant improvement after 16 weeks.

Juvenile-onset keratosis lichenoides chronica treated successfully with topical tacrolimus: a safe and favourable outcome. Oyama N, Mitsuhashi Y, Yamamoto T. *Eur J Dermatol* 2011; 21: 595–6.

A case report from Japan described a young patient with long-standing refractory KLC who responded to topical 0.1% tacrolimus ointment.

Case of keratosis lichenoides chronica. Tsuboi H, Katsuoka K. *J Dermatol* 2007; 34: 801–3.

Treatment with systemic retinoid and topical corticosteroids for 4 months was ineffective. Systemic ciclosporin (dose was not mentioned) for 12 months was partially effective. Patient was then treated with electron beam therapy (total of 40 Gy), which resulted in partial improvement. The patient was subsequently treated with etoposide 100 mg daily, then every other day later, which also led to complete resolution.

Nekam's disease. Aruna C, Ramamurthy DV, Neelima T, et al. *Indian Dermatol Online J* 2016; 7: 520–2.

A 40-year-old man with KLC. The patient showed mild improvement after 8 weeks of treatment with oral steroids (prednisolone 30 mg daily) and dapsone 100 mg daily.

Keratosis lichenoides chronica. Konstantinov KN, Søndergaard J, Izuno G, et al. *Am Acad Dermatol* 1998; 38: 306–9.

A 26-year-old woman with KLC. Treatment with isotretinoin, 40 mg daily, for 3 months considerably improved and almost cleared the skin lesions. Six months after treatment, the improvement was maintained.

Keratosis lichenoides chronica: response to photodynamic therapy. Lopez-Navarro N, Alcaraz I, Bosch RJ, et al. *J Dermatolog Treat* 2008; 19: 124–5.

A case report of a 55-year-old female patient with KL. The patient failed multiple treatments including topical and systemic prednisolone (50 mg/day for 6 months), oral ciclosporin (at 3 mg/kg/day) for 3 months, acitretin (10 mg/day) for 6 months, and photochemotherapy with a cumulative light dose of 30 J/cm². Patient was then treated with photodynamic therapy using methyl 5-aminolaevulinic acid, 160 mg/g in cream, and red light at a wavelength of 630 nm (energy density of 37 J/cm²). The patient underwent serial treatment sessions 7 days apart. Marked improvement was noted after 3 months with no recurrence 12 months after the finishing the last session.

Keratosis lichenoides chronica successfully treated with isotretinoin and methotrexate. Li AW, Damsky W, King BA. *JAAD Case Rep* 2017; 3: 205–7.

A case report describing a patient with KLC whose cutaneous lesions responded to treatment with oral isotretinoin at 40 mg daily but with persistence of oral ulcers and blepharoconjunctivitis. Addition of methotrexate, 5 mg weekly, resulted in a marked improvement of both the oral and ocular lesions. The patient's disease remained in remission for 9 months on this regimen.

Keratosis pilaris and variants

Michael A. Bell, Anna L. Grossberg



Keratosis pilaris (KP) is a common inherited disorder characterized by tenacious keratin plugging of follicular orifices affecting characteristic body sites. It typically presents in childhood on the extensor aspects of the upper arms, anterior surfaces of the thighs, and lateral aspects of the cheeks. In more extensive cases, it may extend onto the distal extremities, shoulders, back, and buttocks. Perifollicular erythema is common, and a background of erythema on the cheeks may also be seen in keratosis pilaris rubra (KPR). Other variants of KP include erythromelanosis follicularis faciei et colli (EFFC) and keratosis pilaris atrophicans (KPA), which includes keratosis pilaris atrophicans faciei (ulerythema ophryogenes), keratosis follicularis spinulosa decalvans (KFSD), folliculitis spinulosa decalvans (FSD), and atrophoderma vermiculatum; these subtypes are also addressed in this chapter.

KP may be seen in conjunction with other skin disorders, such as atopic dermatitis; it may also arise or become exacerbated in states of androgen and insulin dysregulation, such as diabetes, obesity, and pregnancy, and may be seen in conjunction with malnutrition. Extensive disease has also been observed in patients with Down syndrome and with drugs.

MANAGEMENT STRATEGY

KP is commonly asymptomatic and often does not require treatment. Those with extensive or symptomatic involvement often

desire treatment, and even mild KP may cause patients cosmetic distress. It may become less prominent with age, even without directed therapy.

Initial treatments aim to decrease roughness and follicular accentuation. *Keratolytic agents*, such as glycolic acid, ammonium lactate, salicylic acid (SA), and urea-containing humectants, are the mainstays of treatment. Use of a compound of 2% SA in 20% urea cream or 6% SA in propylene glycol combines the properties of an emollient with a keratolytic agent. Twice-daily application of one of these agents for at least a 3-week trial is recommended. Vigorous scrubbing can lead to irritation and should be avoided. Once adequate improvement has been achieved, maintenance therapy of weekly or twice-weekly application of a topical keratolytic agent is recommended.

Topical retinoids may be utilized and should be gradually up-titrated to avoid irritation. Tazarotene 0.05% cream has been shown to decrease pruritus, erythema, and roughness in a placebo-controlled trial of KP. *Oral isotretinoin* has been helpful in some patients with ulerythema ophryogenes, atrophoderma vermiculatum, and KFSD.

If a significant inflammatory component is present, treatment with a *medium-potency topical corticosteroid* in an emollient base can be utilized. Once inflammation has abated, corticosteroids should be discontinued, and treatment should transition to keratolytics.

Cutaneous laser and light therapies have been utilized for several variants of KP (Table 125.1).

Specific Investigations

- Consider serum testosterone levels in obese females
- Ophthalmologic examination in cases of KPA

The prevalence of cutaneous manifestations in young patients with type 1 diabetes. Pavlović MD, Milenković T, Dinić M, et al. *Diabetes Care* 2007; 30: 1964–7.

KP affected 12% of diabetic patients compared with 1.5% of healthy sex and age-matched subjects.

Other conditions associated with KP include high body mass index, ichthyosis, atopy, pregnancy, cardiofaciocutaneous syndrome, and hyperandrogenism in obese females. KP-like lesions have been observed in patients treated with vemurafenib for metastatic melanoma.

Keratosis pilaris atrophicans. One heterogeneous disease or a symptom in different clinical entities. Oranje AP, van Osch LD, Oosterwijk JC. *Arch Dermatol* 1994; 130: 500–2.

Patients with KPA are reported to have increased incidence of ocular abnormalities, including photophobia, corneal deposits, and juvenile cataracts.

This review also clarifies the confusing nosology of KP variants.

Red face revisited: disorders of hair growth and the pilosebaceous unit. Ramos-e-Silva M, Pirmez R. *Clin Dermatol* 2014; 32: 784–99.

This review includes epidemiology, clinical presentation, pathogenesis, and therapy of the inflammatory follicular keratotic syndromes.

Keratosis pilaris and its subtypes: associations, new molecular and pharmacologic etiologies and therapeutic options. Wang JE, Orlov SJ. *Am J Clin Dermatol* 2018; 19: 733–57.

Table 125.1 Cutaneous laser and light therapies in the treatment of keratosis pilaris (KP) and variants

KP variant	Modality	Details
Keratosis pilaris spinulosa decalvans (KPSD)	Non-Q-switched, high-energy, pulsed ruby laser	Five treatments at fluences of 19–21 J/cm ² at 6-week intervals led to a significant reduction of inflammation in treated areas, at the expense of a persistent diminution of hair growth at 8-month follow-up in one patient with KPSD ^a
Keratosis follicularis spinulosa decalvans (KFSD)	800-nm diode laser	Case report of patient treated with five sessions at pulse width 30 ms, fluence 9 J/cm ² with smoothening of the skin and complete resolution of inflammation without recurrence after 2.5 years ^b
KP atrophicans (KPA)	585-nm PDL	12 patients received 2–8 treatments at fluences ranging from 6 J/cm ² to 7.5 J/cm ² , resulting in improvement in erythema but not texture ^c
Keratosis pilaris rubra (KPR)	532-nm potassium titanyl phosphate (KTP) laser	Fluences of 12–14 J/cm ² and pulse width of 510 ms were used, resulting in cosmetic clearance of keratotic papules and reduction in facial erythema ^d
KPR	PDL	Case report of seven treatments at fluence of 12 J/cm ² and pulse duration 3 ms, with marked improvement in erythema and follicular hyperkeratosis for 9 months ^e In a retrospective study, eight adolescent patients received between one and four PDL treatments. All patients reported improvement in erythema, with two lost to follow-up ^f
KPA	Intense pulsed light (IPL)	Four patients were treated with 5–9 sessions of IPL resulting in over 75% reduction in erythema, reduced roughness, and no recurrence after 10 months ^g
KPR or KPA	PDL	10 patients with either condition were treated with 2–7 sessions of PDL with fluence 5–9 J/cm ² and pulse duration 0.5–1.5 ms, resulting in >75% resolution of erythema, with one case of postinflammatory hyperpigmentation ^h
KP	Q-switched 1064-nm Nd:YAG laser	12 patients were treated with 10 sessions every 2 weeks, resulting in improvements in skin texture and dyspigmentation ⁱ
KP	Long-pulsed 1064-nm Nd:YAG laser	18 patients underwent three sessions with 30-msec pulse width and fluence 34 J/cm ² , with the contralateral arm serving as a control. Significant improvements in erythema and number of keratotic papules reported ^j
KP	FRAC3 1064-nm Nd:YAG laser	23 of 24 patients completed four treatments and experienced statistically significant improvement in skin roughness measured by Antera 3D and subjective improvement in roughness, erythema, and hyperpigmentation compared with controls at 16 weeks ^k
KP	Combination of PDL, long-pulsed 755-nm alexandrite laser, and microdermabrasion	26 patients were treated using combination laser therapy. Pretreatment and posttreatment photographs and patient satisfaction rates were compared 3 months after treatment. Significant improvements were noted in erythema, skin texture, and discoloration ^l
KP	810-nm diode laser	After three treatments, skin texture improved significantly, but baseline erythema was not improved in this blinded, randomized, split-body, placebo-controlled trial ^m
KP	Fractional CO ₂ laser	12 weeks following a single treatment, physicians' global assessment showed 30% of lesions on treated side had moderate-to-good improvement ⁿ Another prospective, single-blinded, split-body, placebo-controlled study of 60 patients demonstrated significant clinical and dermatoscopic improvement in KP lesions treated with two sessions of fractional CO ₂ laser therapy 4 weeks apart compared to control areas treated with 10% urea ^o
KP	IPL	Of 24 patients, there was a statistically significant reduction of skin roughness as measured by Antera 3D and subjective improvement in roughness, erythema, and hyperpigmentation compared to controls at 16 weeks ^p
KP	Combination of fractional CO ₂ laser and Q-switched Nd:YAG	Prospective, intraindividual study of 18 patients with comparison of baseline and postlaser clinical photographs. Blinded investigators did not agree upon the superior therapy, but patients reported the most satisfaction with combination therapy ^q

Table 125.1 Cutaneous laser and light therapies in the treatment of keratosis pilaris (KP) and variants—cont'd

KP variant	Modality	Details
Erythromelanosis follicularis faciei et colli (EFFC)	Dual 585-nm PDL and 1064-nm Nd:YAG laser	Split-face case report using dual PDL and Nd:YAG, with significant reduction in facial erythema after five sessions ^f

^aChui CT, Berger TG, Price VH, et al. Recalcitrant scarring follicular disorders treated by laser-assisted hair removal: a preliminary report. *Dermatol Surg* 1999; 25:34–7.

^bBhoyrul B, Sinclair R. Successful treatment of keratosis follicularis spinulosa decalvans with an 800-nm diode laser. *Dermatol Surg* 2020;46:849–50.

^cClark SM, Mills CM, Lanigan SW. Treatment of keratosis pilaris atrophicans with the pulsed tunable dye laser. *J Cutan Laser Ther* 2000;2:151–6.

^dDawn G, Urcelay M, Patel M, et al. Keratosis rubra pilaris responding to potassium titanyl phosphate laser. *Br J Dermatol* 2002;147:822–4.

^eKaune KM, Haas E, Emmet S, et al. Successful treatment of severe keratosis pilaris rubra with a 595-nm pulsed dye laser. *Dermatol Surg* 2009;35:1592–5.

^fSchoch JJ, Tollefson MM, Witman P, et al. Successful treatment of keratosis pilaris rubra with pulsed dye laser. *Pediatr Dermatol* 2016;33:443–6.

^gRodríguez-Lojo R, Pozo JD, Barja JM, et al. Keratosis pilaris atrophicans: treatment with intense pulsed light in four patients. *J Cosmet Laser Ther* 2010;12:188–90.

^hAlcántara González J, Boixeda P, Truchuelo Díez MT, et al. Keratosis pilaris rubra and keratosis pilaris atrophicans faciei treated with pulsed dye laser: report of 10 cases. *J Eur Acad Dermatol Venerol* 2011;25:710–4.

ⁱPark J, Kim BJ, Kim MN, et al. A pilot study of Q-switched 1064-nm Nd:YAG laser treatment in the keratosis pilaris. *Ann Dermatol* 2011;23:293–8.

^jSaelim P, Pongprutthipan M, Pootongkam S, et al. Long-pulsed 1064-nm Nd:YAG laser significantly improves keratosis pilaris: a randomized, evaluator-blind study. *J Dermatolog Treat* 2013;24:318–22.

^kMaitriwong P, Tangkijngamvong N, Asawanonda P. Innovative 1064-nm Nd:YAG laser significantly improves keratosis pilaris, a randomized, double-blind, sham-irradiation-controlled trial. *Lasers Surg Med* 2019 Nov 11 [Epub ahead of print].

^lLee SJ, Choi MJ, Zheng Z, et al. Combination of 595-nm pulsed dye laser, long-pulsed 755-nm alexandrite laser, and microdermabrasion treatment for keratosis pilaris: retrospective analysis of 26 Korean patients. *J Cosmet Laser Ther* 2013;15:150–4.

^mIbrahim O, Khan M, Bolotin D, et al. Treatment of keratosis pilaris with 810-nm diode laser: a randomized clinical trial. *JAMA Dermatol* 2015;151:187–91.

ⁿVachiramon V, Anusaksathien P, Kanokrunsee S, et al. Fractional carbon dioxide laser for keratosis pilaris: a single-blind, randomized, comparative study. *Biomed Res Int* 2016;2016:1928540. 2016 May 9 [Epub ahead of print].

^oIsmail S, Omar SS. Clinical and dermoscopic evaluation of fractional carbon dioxide laser in management of keratosis pilaris in Egyptian type skin. *J Cosmet Dermatol* 2020;19:1110–20.

^pMaitriwong P, Tangkijngamvong N, Asawanonda P. Intense pulsed-light therapy significantly improves keratosis pilaris: a randomized, double-blind, sham-irradiation-controlled trial. *J Clin Aesthet Dermatol* 2019;12:E53–E57.

^qSobhi RM, Adawy NAH, Zaky IS. Comparative study between the efficacy of fractional CO₂ laser, Q-switched Nd:YAG laser (1064nm), and both types in treatment of keratosis pilaris. *Lasers Med Sci* 2020 Jan 11 [Epub ahead of print].

^rLi YH, Zhu X, Chen JZS, et al. Treatment of erythromelanosis follicularis faciei et colli using a dual-wavelength laser system: a split-face treatment. *Dermatologic Surg* 2010;36:1344–47.

This review details clinical characteristics and pathophysiology of KP and its subtypes, and evaluates topical, systemic, and energy-based therapies.

First-Line Therapies

• 10% lactic acid cream	B
• 5% SA cream	B
• Sodium lactate and urea cream	B
• Polyester sponge	D
• SA in urea	D
• Topical corticosteroids	D

Epidermal permeability barrier in the treatment of keratosis pilaris. Kootiratrakarn T, Kampirapap K, Chunhasewee C. *Dermatol Res Pract* 2015; 205012: 1–5.

A blinded, prospective, randomized, split-side trial of 50 KP patients compared twice-daily 10% LA and 5% SA. Mean reduction of lesions from baseline was statistically significant for both LA and SA, with LA being statistically more effective after 3 months of use.

Evaluation of a sodium lactate and urea crème to ameliorate keratosis pilaris. Weber TM, Kowcz A, Rizer R. *J Am Acad Dermatol* 2004; 50(S1): 47.

A formulation containing sodium lactate and urea was tested on 32 subjects with KP, with statistically significant improvements in skin tone and roughness reported after 3–12 weeks.

Practical management of widespread, atypical keratosis pilaris. Novick NL. *J Am Acad Dermatol* 1984; 11: 305–6.

Thirty patients with widespread, atypical KP were treated with application of 2%–3% SA in 20% urea cream using a polyester sponge and use of topical corticosteroids for associated inflammation. Clearance was noted in 75%–100% of cases within 2–3 weeks.

Keratosis pilaris decalvans nonatrophicans. Drago F, Maietta G, Parodi A, et al. *Clin Exp Dermatol* 1993; 18: 45–6.

This is the first case report of a patient with an eruption of KP decalvans non-atrophicans with follicular keratotic papules on the limbs and trunk, and body hair loss. The patient was treated with emollients and multivitamins, with clearance of the eruption and hair regrowth after 3 months.

Traditional methods of KP treatment may be effective in treating cases of keratosis pilaris decalvans.

Second-Line Therapies

• Topical tazarotene	A
• Topical tretinoin	D
• Isotretinoin	E
• Topical tacrolimus	A
• Aquaphor	A
• Dermabrasion (atrophoderma vermiculatum)	E

A comparative trial comparing the efficacy of tacrolimus 0.1% ointment with Aquaphor ointment for the treatment of keratosis pilaris. Breithaupt AD, Alio A, Friedlander SF. *Pediatr Dermatol* 2011; 28: 459–60.

In this double-blinded comparative trial of 27 KP patients, topical tacrolimus was more likely than Aquaphor to lead to >75% improvement, though this failed to reach statistical significance.

Tazarotene 0.05% cream for the treatment of keratosis pilaris. Bogle MA, Ali A, Bartel H. *J Am Acad Dermatol* 2004; 50(S1): 39.

A randomized, placebo-controlled, double-blind, prospective study of tazarotene 0.05% cream for the treatment of posterior arm KP in 33 patients resulted in statistically significant improvement in pruritus, erythema, and roughness of KP lesions.

Natural history of keratosis pilaris. Poskitt L, Wilkinson JD. *Br J Dermatol* 1994; 130: 711–3.

This retrospective questionnaire of 49 patients with KP yielded 14 patients who had benefited from a variety of treatments. Of these patients, eight reported that therapy with topical tretinoin cream was helpful.

Two patients reported dramatic improvement with oral tetracyclines; however, the questionnaire did not exclude possible coincident acne.

Clinical findings, cutaneous pathology, and response to therapy in 21 patients with keratosis pilaris atrophicans. Baden HP, Byers HR. *Arch Dermatol* 1994; 130: 469–75.

Twenty-one patients with KPA were treated with various agents, including keratolytics, antibiotics, topical corticosteroids, and oral retinoids, all with limited response. Treatment of four patients with isotretinoin (1 mg/kg) resulted in little or no improvement in three and exacerbation in one.

A case of atrophoderma vermiculatum showing a good response to topical tretinoin. Lee YC, Son S-J, Han TY, et al. *Ann Dermatol* 2018; 30: 116–8.

In this case report of a 12-year-old girl with atrophic scarring, daily 0.01% topical tretinoin halted progression and slightly improved color and cosmetic appearance with no additional scarring at 12-month follow-up.

A case of atrophoderma vermiculatum responding to isotretinoin. Weightman W. *Clin Exp Dermatol* 1998; 23: 89–91.

Atrophoderma vermiculatum is a variant of KP resulting in honeycomb scarring of the face. In this case report, two 6-month courses of isotretinoin (0.50 mg/kg/day) halted progression of atrophy, and the patient remained free of new lesions after 1 year.

In severe cases of atrophoderma vermiculatum with significant scarring, a trial of isotretinoin therapy may be worthwhile to halt disease progression.

Atrophoderma vermiculatum. Case reports and review. Frosch PJ, Brumage MR, Schuster-Pavlovic C, et al. *J Am Acad Dermatol* 1988; 18: 538–42.

Dermabrasion may be used to reduce scarring in atrophoderma vermiculatum.

A case of ulerythema ophryogenes responding to isotretinoin. Layton AM, Cunliffe WJ. *Br J Dermatol* 1993; 129: 645–6.

Ulerythema ophryogenes presents in the eyebrows as horny, follicular-based papules that spread to the scalp, with resultant atrophy and alopecia. There is variable response to isotretinoin.

Keratosis follicularis spinulosa decalvans with associated mental retardation: response to isotretinoin. Sanke S, Mendiratta V, Singh A, et al. *Int J Trichology* 2017; 9: 138–9.

KFSD is an X-linked disorder beginning in infancy or early childhood, characterized by photophobia, corneal dystrophy,

widespread follicular hyperkeratosis, and scarring alopecia of the scalp, eyebrows, and eyelashes. This case report highlights improvement in KFSD in a patient started on daily isotretinoin (0.5 mg/kg) for 6 months, including significant hair growth by 3 months.

Keratosis follicularis spinulosa decalvans showing excellent response to isotretinoin. Gupta D, Kumari R, Bahunutula RK, et al. *Indian J Dermatol Venereol Leprol* 2015; 81: 646–8.

A case report of a patient with KFSD responding to isotretinoin (0.5 mg/kg) without relapse at 1-year follow-up.

Third-Line Therapies

• Tetracyclines	E
• Long-pulsed, non-Q-switched, ruby laser (KPSD)	E
• Dapsone (KFD)	E
• Pulsed tunable dye laser (KPA)	C
• Intense pulsed light (KP, KPA)	A, E
• Potassium titanyl phosphate laser (KPR)	E
• Pulsed-dye laser (KPR)	D
• Pulsed-dye laser (KP or KP atrophicans faciei)	C
• Q-switched 1064-nm neodymium-doped yttrium-aluminum-garnet laser	C
• Long-pulsed 1064-nm neodymium-doped yttrium-aluminum-garnet laser	C
• FRAC3 1064-nm neodymium-doped yttrium-aluminum-garnet laser	A
• 810-nm diode laser	C
• Fractional CO ₂ laser	B
• <i>Nitrosomonas eutropha</i> spray	B
• Chlorine dioxide complex cleanser	D

Keratosis pilaris rubra: a common but underrecognized condition. Marqueling AL, Gilliam AE, Prendiville J, et al. *Arch Dermatol* 2006; 142: 1611–6.

Treatments for KPR in 27 patients included emollients, urea, LA, SA, topical corticosteroids, or a combination; topical cholecalciferol; and topical or systemic retinoid agents. There was no substantial improvement with these treatments in most patients. One patient had excellent response with pulsed-dye laser (PDL).

Folliculitis spinulosa decalvans: successful therapy with dapsone. Kunte C, Loeser C, Wolff H. *J Am Acad Dermatol* 1998; 39: 891–3.

In this case report, a patient presented with FSD with keratotic follicular papules on the trunk and extremities, eyebrow alopecia, and erythema and follicular hyperkeratoses of the scalp. Isotretinoin and topical corticosteroids were ineffective. Dapsone (100 mg/day) led to the resolution of inflammation and pustulation of the scalp within 1 month.

Photopneumatic therapy for the treatment of keratosis pilaris. Ciliberto H, Farshidi A, Berk D, et al. *J Drugs Dermatol* 2013; 12: 804–6.

In this unblinded study of 10 KP patients, one treatment with photopneumatic therapy improved erythema for at least 1 month.

Dermal microflora restoration with ammonia-oxidizing bacteria *Nitrosomonas eutropha* in the treatment of keratosis

pilaris: a randomized clinical trial. Lee NY, Ibrahim O, Khetarpal S, et al. J Drugs Dermatol 2018; 17: 285-8.

After 4 weeks of twice-daily *Nitrosomonas eutropha* spray application, nine of 24 patients had complete clearance of KP compared to three of 24 control patients in this placebo-controlled, randomized, double-blinded trial.

Chlorine dioxide complex cleanser: a new agent with rapid efficacy for keratosis pilaris. Zirwas MJ, Fichtel J. J Drugs Dermatol 2018; 17: 554-6.

This case series reports a chlorine dioxide complex cleanser as an effective antimicrobial and keratolytic agent with beneficial effects on KP.

Langerhans cell histiocytosis

Claudia Lang, Reinhard Dummer



Langerhans cell histiocytosis (LCH) is a rare, proliferative neoplastic condition of inflammatory cells with clonal proliferation of a subtype of epidermal dendritic cells, the Langerhans cells. It affects children about five times more frequently than adults. The individual disease evolution may vary from self-healing to life-threatening disseminated disease.

The former classification of histiocytosis distinguished between Langerhans cell, non-Langerhans cell-related, or malignant histiocytosis. Considering clinical picture, pathological, and radiological findings, LCH is now part of the 'L' group according to the new classification of histiocytic neoplasms. The group is accompanied by Erdheim–Chester disease (ECD), indeterminate histiocytosis (IDH), and extracutaneous juvenile xanthogranuloma due to similar findings of clonal mutations involving genes of the MAPK pathway and similar clinical complications; 20% of patients with ECD also have LCH lesions.

The names histiocytosis X, eosinophilic granuloma, Hand–Schüller–Christian disease, Letterer–Siwe disease, congenital self-healing reticulohistiocytosis (Hashimoto–Pritzker), Langerhans cell granulomatosis, and non-lipid reticuloendotheliosis lost their importance due to impracticability. LCH is newly grouped into single-system disease, lung involvement, multisystem disease with/without risk organ involvement, and association with another myeloproliferative/myelodysplastic disorder.

MANAGEMENT STRATEGY

Due to the range of clinical outcomes, an extensive workup is important at the time of diagnosis. It includes a full clinical exam; blood-work; skin biopsy with immunohistochemistry, notably CD1a and CD207 denoting Birbeck granules; skeletal radiography; and wide

molecular testing, including the search for mutations in major signaling pathways (e.g., BRAF mutation).

Treatment strategies depend on the age of onset, organ involvement, and severity of disease. Most available data are from case reports, case series, or small studies up to 20 patients. Recommendations for children may not be directly applicable for adults and vice versa. According to careful clinical, serological, and radiological workup, disease extension can be staged into single-system (SS) disease with unifocal or multifocal involvement, lung involvement, multisystem (MS) disease with/without risk organ involvement. Risk organs include liver, spleen, and bone marrow. If involved, it results in poor prognosis. The most frequent organs affected in children are the bones (80% of cases), skin (33%), pituitary gland (25%), liver, spleen, hematopoietic system, or lungs (15% each), lymph nodes (5–10%), and central nervous system (2–4%, excluding pituitary gland). In adults, lung involvement is more frequent and typically associated with smoking. Therefore, smoking cessation should be the first therapeutic intervention in those cases.

As a topical option in SS disease with skin involvement, *surgical excision* could be a practical consideration in certain cases (localized disease). Other topical treatments include *topical nitrogen mustard* (20%), *topical tacrolimus*, *topical steroids*, and *phototherapy*. For extensive skin disease that does not respond to these measures, low-dose, weekly *methotrexate* (5–10 mg/week) or treatment with *azathioprine* (2 mg/kg/day) can lead to resolution.

In SS, LCH with localized bone involvement *radiotherapy* could be a topical treatment option with acceptable side effects for adult patients. In the presence of multifocal bone lesions, *hydroxyurea*, with or without *methotrexate* or *bisphosphonate*, might be effective.

For MS-LCH or SS-LCH with multifocal bone lesions, no clear standard treatments are yet available. In pediatric patients the first-line treatment recommendation is a combination of *vinblastine* and *prednisolone* therapy. Adult patients show a higher toxicity for that regimen, resulting in a poor overall response; hence, *cytarabine* or *cladribine* (2-Chlorodeoxyadenosine, 2CdA) might be preferred as the first-line option. In patients with central nervous system (CNS) lesions, 2CdA and *cytarabine* show a better efficacy due to higher blood–brain barrier penetration. Short-course chemotherapy with *methotrexate*, *doxorubicin*, *cyclophosphamide*, *vincristine*, *prednisone*, and *bleomycin* are reserved for aggressive LCH in adults and should be applied only in very severe cases. As a second-line option for aggressive cases, allogeneic hematopoietic stem cell transplantation has been documented successful in various cases.

Findings of BRAF V600E mutations and other genetic variants in the MAPK pathway within the last 10 years opened new treatment options. The BRAF inhibitor *vemurafenib*, the combination of the BRAF inhibitor *dabrafenib* and the MEK inhibitor *trametinib*, and monotherapy with the MEK inhibitor *trametinib* were used successfully in adult patients, although some experienced early relapse after discontinuation. Most patients suffered adverse side effects that led to dose reduction or discontinuation. Due to this toxicity, dose finding is still ongoing for children. A recent international observational study showed promising results for the use of *vemurafenib* in children. Regarding those developments, a change in treatment recommendation is developing and a targeted therapy regimen is expected to replace chemotherapy as first-line treatments. *Vemurafenib* is already FDA approved for the indication of Erdheim–Chester disease. The efficacy of *imatinib*, a tyrosine kinase inhibitor, has been shown in refractory MS-LCH cases, although unfavorable outcomes were reported also, so it is rarely recommended as a treatment option.

Specific Investigations

Routine investigations

- Biopsy of organ involved for H&E staining and immunohistochemistry for CD1a and CD207 (Birbeck granules)
- Full blood count with differential
- Coagulation studies: INR/PT (prothrombin time), APTT/PTT (activated partial thromboplastin time, partial thromboplastin time), fibrinogen/factor 1
- ESR (erythrocyte sedimentation rate)
- Blood chemistry: total protein, albumin, bilirubin, ALT (alanine transaminase), AST (aspartate transaminase), γ GT (gamma-glutamyl transferase), creatinine, electrolytes, C-reactive protein
- Abdominal ultrasound (size of liver and spleen, lymph nodes)
- Chest X-ray (CXR)
- Skeletal radiograph survey
- Positron emission tomography-CT (PET-CT) instead of ultrasound, CXR and bone CT

Indicated investigations

- Lung involvement: lung function tests, high-resolution CT chest, bronchoalveolar lavage for CD1a + cells, lung biopsy
- Polyuria or polydipsia: early morning urine specific gravity and osmolality, water deprivation test, MRI of the head
- *Cytopenia*: bone marrow aspiration, triglycerides, and ferritin (DD macrophage activation and hemophagocytic syndrome)
- Liver dysfunction: liver MRI, liver biopsy if there is significant clinical involvement
- Suspected craniofacial bone lesions: MRI of head or CT of head
- Aural discharge: formal hearing assessment, MRI of head, or HR-CT of temporal bone
- Vertebral lesions: MRI of spine
- Visual or neurological abnormalities: MRI of head, neurological assessment, neuropsychometric assessment
- Suspected other endocrine abnormality: endocrine assessment, MRI of head
- Chronic diarrhea: endoscopy, biopsy
- Enlarged lymph nodes: extirpation, PET-CT

Revised classification of histiocytosis and neoplasms of the macrophage-dendritic cell lineages. Emile JF, Abila O, Fraïtag S, et al. Blood 2016; 127: 2672–81.

Histiocytoses are thought to be rare, proliferative disorders deriving from dendritic cells or macrophages. Classification should regard clinical, radiographic, pathological, phenotypic, genetic, and molecular features. LCH belongs to the 'L' group, together with indeterminate histiocytosis and Erdheim–Chester disease. The 'C' group contains cutaneous and mucocutaneous histiocytoses, while the 'R' group stands for Rosai–Dorfman disease and miscellaneous non-cutaneous, non-Langerhans cell histiocytoses. The 'M' (malignant) group and 'H' (hemophagocytic lymphohistiocytosis and macrophage activation syndrome) group include more aggressive disease prolongation with worse outcomes.

Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. Haupt R, Minkov M, Astigarraga I, et al. Pediatr Blood Cancer 2013; 60: 175–84.

The wide clinical spectrum of LCH implies a broad differential according to different organ involvement. Diagnostic workup in children includes full blood count, prolonged blood chemistry, erythrocyte sedimentation reaction, coagulation studies and imaging studies with abdominal ultrasound, chest X-ray, and skeletal radiographic survey. Additional testing is recommended for specific clinical scenarios.

First-Line Therapies

Skin disease

• Surgical excision of solitary disease	E
• Topical steroids	E
• Topical tacrolimus	E
• Phototherapy (psoralen ultraviolet A [PUVA], narrowband UVB)	E
• Imiquimod (5%)	E
• Topical nitrogen mustard (20%)	C

Multisystem disease

• Vinblastine and prednisone (children)	B
• Cytarabine (adults)	B
• Cladribine (adults, risk organ involvement)	E
• Vemurafenib (adults)	C

Management of adult patients with Langerhans cell histiocytosis: Recommendations from an expert panel on behalf of Euro-Histio-Net. Michael G, Maurizio A, Diego C, et al. Orphanet J Rare Dis 2013; 8: 72.

Single-system disease, especially of the skin, can be treated first line with excision if solitary lesions or topical regimens such as nitrogen mustard or UV therapy. Second-line options are thalidomide (100 mg/day), azathioprine (2 mg/kg/day), or methotrexate (up to 20 mg once weekly). Radiotherapy is an effective treatment option for adult patients with localized disease (e.g., bone, lungs) in which lesions are unresectable. A general dose range of 10–20 Gy is recommended. There is no standard treatment defined for adults with SS multifocal disease or MS disease. Vinblastine/prednisolone as first line in children show higher toxicities in adults. Cytarabine 100 mg/m² d1–5 q4w intravenous showed superiority to cladribine 6 mg/m² d1–5 q4w subcutaneous/intravenous in a study with 58 patients with bone lesions. Experts recommend cladribine as a first option with risk organ involvement, but cytarabine is a good alternative. Follow-ups with restaging should take place every 2–3 months due to possible reactivation, development of chronic local symptoms, or organ dysfunction. Additionally, there is a rare association to malignant tumors.

Current therapy for Langerhans cell histiocytosis. Broadbents V, Gadner H. Hematology/Oncology Clinics of North America 1998; 12: 327–38.

Painful skin lesions may respond to intralesional steroids. Single-system skin disease, if mild, may respond to topical steroid application. For severe single-system skin disease, topical nitrogen mustard on lesional skin is recommended.

Langerhans cell histiocytosis in children: diagnosis, differential diagnosis, treatment, sequelae and standardized follow-up. Krooks J, Minkov M, Weatherall AG. J Am Acad Dermatol 2018; 8(6): 1047–56.

Isolated cutaneous disease can be treated with topical applications of nitrogen mustard, but use should be limited to severe, refractory disease due to oncogenic potential and high rate of contact sensitivity. Case reports show some good results with topical imiquimod, which could be reapplied in case of recurrence. For UV-treatment, narrowband UVB is a safer option than PUVA. For more extensive disease, systemic treatments with methotrexate, azathioprine, or vitamin A derivatives have been documented with good results in case reports.

Langerhans cell histiocytosis. Rodriguez-Galindo C, Allen CE. *Blood* 2020; 135(16): 1319–31.

Patients with SS disease with only a local site affected can be treated with local therapy or observation. Patients with more extensive disease with risk of organ involvement require systemic therapy. First-line treatment is vinblastine + prednisone for 1 year with the potential addition of mercaptopurine for high-risk LCH. For recurrent but low-risk disease, less toxic regimens including 6-mercaptopurine and methotrexate, indomethacin, bisphosphonates, and hydroxyurea may be considered. Treatment with MAPK pathway inhibitors shows great responses in adults with LCH and ECD, although rapid reactivations occur after treatment discontinuation. In those cases, retreatment with BRAF inhibitors is still effective.

Satisfactory remission achieved by PUVA therapy in Langerhans cell histiocytosis in an elderly patient. Sakai H, Ibe M, Takaahashi H, et al. *J Dermatol* 1996; 23: 42–6.

Case report of a 74-year-old man with cutaneous LCH and diabetes insipidus. Five weeks of PUVA therapy led to complete clearance of skin lesions. The endocrinopathy persisted.

Cutaneous Langerhans cell histiocytosis in an elderly man successfully treated with narrowband ultraviolet B. Imafuku S, Shibata S, Tashiro A, et al. *Br J Dermatol* 2007; 157: 1277–9.

Doses of 0.4–1.0 J/cm² were given incrementally (total irradiation of 9.3 J/cm²). Eleven sessions led to almost complete resolution in a Japanese man, which persisted at least 12 months after therapy was discontinued.

Long term follow up of topical mustine treatment for cutaneous Langerhans cell histiocytosis. Hoeger PH, Nanduri VR, Harper JL, et al. *Arch Dis Child* 2000; 82: 483–7.

Topical nitrogen mustard (0.02% mechlorethamine hydrochloride mustard) was found to be safe in cutaneous disease. Follow-up in this study was an average of 8.3 years.

Topical imiquimod for the treatment of childhood cutaneous Langerhans cell histiocytosis. Dodd E, Hook K. *Pediatr Dermatol* 2016; 33: e184–85.

Case report of a 16-month-old girl with isolated cutaneous LCH refractory to treatment with topical steroids and topical tacrolimus. Treatment was initiated with 5% topical imiquimod cream twice daily, 5 days a week. The rash completely resolved, and treatment was discontinued after 5 months and did not recur during a follow-up period of 2 years.

Therapy prolongation improves outcome in multisystem Langerhans cell histiocytosis. Gardner H, Minkov M, Grois N, et al. *Blood* 2013; 121: 5006–14.

More than 400 children were included, stratified in groups with risk organ involvement and low-risk organ. The risk organ involvement group was randomized in arm A, receiving vinblastine 6 mg/m² intravenous at days 1, 8, 15, 22, 29, and 36 + prednisone 40 mg/m²/daily orally, and arm B with vinblastine

6 mg/m² intravenous at days 1, 8, 15, 22, 29, and 36 + prednisone 40 mg/m²/daily orally + methotrexate 500 mg/m² every 2 weeks (+CA-folate rescue). Low-risk organ involvement patients received vinblastine + prednisone.

Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. Hyman DM, Puzanov I, Subbiah V, et al. *N Engl J Med* 2015; 373: 726–36.

In this study, 18 adults with BRAF V600E-positive LCH or ECD were treated with vemurafenib monotherapy and showed a response rate in 41%. Response rate was measured as Response Evaluation Criteria in Solid Tumors (RECIST). The dose regimen was 960 mg twice daily orally; the most common adverse events were rash, fatigue, and arthralgias. Side effects were comparable to previous data from studies in melanoma patients, but sample size is too small to allow a definite comparison.

Second-Line Therapies

• Radiotherapy (bone, lungs)	D
• Prednisolone	B
• Azathioprine	B
• Thalidomide	C
• Methotrexate	C
• Hydroxyurea	C
• Bisphosphonates	C
• Cladribine (risk organ involvement)	C
• Cytarabine	C
• MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin)	D

Vemurafenib for refractory multisystem Langerhans cell histiocytosis in children: an international observational study. Donadieu J, Larabi IA, Tardieu M, et al. *J Clin Oncol* 2019; 37: 2857–65.

In this study, 54 children (median age 1.8 years) from 12 different countries with MS-LCH and BRAF mutation were classified according to risk of organ involvement and treated with vemurafenib monotherapy 10 mg/kg twice a day orally for at least 8 weeks. After that time period, 38 CR and 16 PR were observed with skin rash as the most frequent side effect. Discontinuation of vemurafenib in 30 patients led to 24 LCH reactivations.

MACOP-B regimen in the treatment of adult Langerhans cell histiocytosis: experience on seven patients. Derenzini E, Fina MP, Stefoni V, et al. *Ann Oncol* 2010; 21: 1173–8.

Case series with seven adult patients, three MS-LCH and four SS-LCH, treated with the chemotherapy regimen methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B). Initial overall response rate was 100% (5 CR, 2 PR); 3 patients relapsed after 5, 8, and 62 months, respectively.

Third-Line Therapies

• Clofarabine	D
• Indomethacin	D
• Vemurafenib (children)	
• Dabrafenib (adults)	D
• Trametinib (adults)	D
• Bone marrow transplantation	D
• IVIG	D

Langerhans-cell histiocytosis. Allen CE, Merad M, McClain K. *N Engl J Med* 2018; 379: 856–68.

Vinblastine + prednisone remains the standard of care for children with multifocal LCH. Combination therapy with cytarabine and cladribine shows high rates of cure among high-risk patients but are associated with prolonged hospitalization and treatment-related deaths. Promising results were shown with monotherapy of cytarabine or clofarabine. Intravenous immunoglobulin G (IgG) can lead to symptom stabilization. Targeted therapy to BRAF and MEK inhibitors is becoming a treatment option for adults, but for children dose finding remains.

Clofarabine salvage therapy in refractory multifocal histiocytic disorders, including Langerhans cell histiocytosis, juvenile xanthogranuloma and Rosai–Dorfman disease. Simko SJ, Tran HD, Jones J, et al. *Pediatr Blood Cancer* 2014; 61: 479–87.

Case series of children with histiocytoses (11 LCH, four systemic juvenile xanthogranuloma, and three Rosai–Dorfman disease) treated with clofarabine as a third- or fourth-line option. Clofarabine was administered 25 mg/m²/day for 5 days; cycles were administered every 28 days for a median of six cycles. One patient died, the remaining 17 showed improvement with 11 CR and four PR, and two patients were still being treated at the time of publication. All patients showed neutropenia as a side effect.

Symptomatic bone Langerhans cell histiocytosis treated at diagnosis or after reactivation with indomethacin alone. Braier J, Rosso D, Pollono D, et al. *J Pediatr Hematol Oncol* 2014; 36: e280–4.

In this study, 22 patients with symptomatic bone LCH were treated with indomethacin 2 mg/kg/day orally for a median of 4 months. Of these, 18 showed criteria of non-active disease after initial treatment, three patients improved and showed non-reactive disease after adding steroids and radiotherapy, and one patient developed progressive bone disease and was treated with steroids and chemotherapy additionally.

Strategies for the prevention of central nervous system complications in patients with Langerhans cell histiocytosis: the problem of neurodegenerative syndrome. Imashuku S, Arceci RJ. *Hematol Oncol Clin North Am* 2015; 29: 875–93.

Intravenous immunoglobulins can stabilize symptoms of neurodegenerative LCH with CNS involvement.

Nationwide retrospective review of hematopoietic stem cell transplantation in children with refractory Langerhans cell histiocytosis. Kudo K, Maeda M, Suzuki N, et al. *Int J Hematol* 2020; 111: 137–48.

Retrospective analysis of 30 Japanese children with refractory LCH who underwent hematopoietic stem cell transplantation; 23 patients had risk of organ involvement. The patients received myeloablative conditioning (11) or reduced-intensity conditioning (19) as preparation before transplantation. At a median follow-up of 433 days, 17 children were alive. In eight out of 13 patients who died, death occurred within the first 3 months after transplantation. Disease state at the time of transplantation was the most important prognostic factor.

A Phase I and pharmacokinetic study of oral dabrafenib in children and adolescent patients with recurrent or refractory BRAF v600 mutation-positive solid tumors. Kieran MW, Georger B, Dunkel IJ, et al. *Clin Cancer Res* 2019; 25: 7294–302.

This study included two patients with refractory LCH of which one was treated with dabrafenib. One patient received 3.75 mg/kg/day. The second patient had refractory MS-LCH and received 4.5 mg/kg/day but had to discontinue treatment after 30 months due to development of Epstein–Barr virus-associated diffuse large B-cell lymphoma.

Real-world toxicity experience with BRAF/MEK inhibitors in patients with Erdheim–Chester disease. Saunders IM, Goodman AM, Kurzrock R. *Oncologist* 2020; 25: e386–90.

Review of 10 patients with Erdheim–Chester disease receiving 16 regimens of BRAF, MEK monotherapy or combined therapies. Different dosing regimens were used. Trametinib monotherapy was applied in three patients: two received an oral dose of 0.5 mg/day and one started with 1 mg/day but reduced to 0.5 mg/day due to toxicity. In spite of adverse reactions (rash, arthralgias, and uveitis; renal toxicity and congestive heart failure were seen in one patient each), eight of 10 patients (80%) achieved a partial remission on therapy.

Leg ulcers

Maximillian A. Weigelt, Robert S. Kirsner



Leg ulcers are common and pose a major threat to public health and the economy due to their high prevalence, recurrence rates, cost, and their impact on patients' quality of life. Often recalcitrant to therapy, the most common etiologies of leg ulcers are chronic venous insufficiency (CVI), arterial disease, neuropathy, or pressure. These causes make up 90% of chronic leg ulcers but metabolic conditions, cancer, infection, and autoimmune diseases, among others, may also cause leg ulcers. This chapter focuses on venous leg ulcers (VLUs) and arterial ulcers; the remainder are discussed elsewhere.

MANAGEMENT STRATEGY

The most important aspect of treating leg ulcers is appropriate recognition of the underlying etiology since each type of leg ulcer requires a unique treatment approach. There are a number of principles that are applied to all patients presenting with leg ulcers.

Smoking cessation, correction of anemia, glycemic control (in patients with diabetes mellitus), and nutritional optimization in malnourished patients are critical to optimize healing. Age, obesity, and medications, especially cytotoxic agents, hydroxycarbamide, and nicorandil, also impede wound healing.

All patients with leg ulcers should undergo *vascular assessment* to confirm if arterial perfusion is adequate for healing to occur. Up to 25% of VLUs may be complicated by peripheral arterial disease (PAD), which may be a contraindication for some forms of compression therapy (see Treatment Strategy later).

Subjective tests such as palpation of pedal pulses, and objective measures such as ankle-brachial index (ABI) measurements, should be performed. An ABI less than 1 is abnormal; lower ABIs are associated with PAD and a lower likelihood of healing. However, in a subset of patients such as those with diabetes mellitus or the elderly, ABI may be falsely elevated (>1.3) due to incompressible calcified vessels. Transcutaneous oxygen measurement (TCO₂), toe-brachial pressure index (TBPI), or pulse-volume recordings (PVRs) are alternative methods for assessing vascular flow.

Quantitative monitoring of wound size allows for assessment of treatment response. Capturing serial clinical photos in the electronic medical record facilitates qualitative comparison to previous time points. Guidelines vary for determining healing status of leg ulcers. For VLUs of less than 10 cm², typically a size reduction of 40% in 4 weeks is used. Wounds that fail to demonstrate an appropriate healing response are considered refractory and may require adjunctive treatment. Additionally, advanced testing with histology and tissue culture obtained via biopsy may help discern an atypical cause of an ulcer. Other reasons to obtain a wound biopsy include wounds with an atypical appearance, an atypical location, and unusual symptoms. These will help diagnose other causes such as cancer or autoimmune diseases.

Wound bed preparation is a systematic approach to addressing factors that inhibit wound healing and is best represented by the "TIME" concept: Tissue (removal of necrotic tissue, exudate, bio-film); Infection/Inflammation; Moisture balance; and Epithelial Edge advancement. Debridement is generally considered to be a necessary component of this process, which is instrumental for effective wound healing. *Debridement* can be performed by various means, including surgical, mechanical, autolytic, enzymatic, and biologic. Surgical debridement is contraindicated if arterial blood flow is compromised or in certain wounds such as inadequately treated pyoderma gangrenosum.

Dressings act as physical barriers to protect the wound and facilitate healing by various mechanisms including regulating moisture balance, allowing growth factors and matrix materials to remain intact in the wound bed, and facilitating the normal electrical gradient needed for healing. Dressings are often chosen based on wound exudate. Highly exudative wounds are best managed with absorptive dressings (e.g., foams, alginates, or gelling fibers). Dry wounds would benefit from dressings that either donate water (e.g., hydrogels) or preserve/bind water (e.g., hydrocolloids, films). Other factors influencing dressing choice include wound etiology, odor, pain, and microbiology (e.g., silver-based dressings for critically colonized or infected wounds).

Routine infection testing is not recommended for leg ulcers due to the high rate of false positives from wound colonization. Wound culturing and empiric antibiotic therapy should be carried out based on clinical index of suspicion for wound infection, and the culture results should guide antibiotic therapy if the initial empiric therapy fails. Clinical signs of infection (erythema, warmth, increased pain/drainage from baseline) used to guide care have limited sensitivity and specificity, and may be diminished by coexisting neuropathy, vasculopathy, venous insufficiency, and diabetes.

CVI may develop from venous obstruction, valvular reflux (commonly due to postthrombotic obliteration of valves), calf muscle dysfunction, or a combination. VLUs are classically geographic, shallow ulcers with flat to slightly raised borders and a granulating or fibrinous wound bed on the medial aspect of the lower third of the leg. *Duplex ultrasound* may be useful to confirm the presence of reflux and/or to determine the extent and location of involvement when planning venous intervention.

High-level evidence supports *leg compression* as the gold standard for treating VLUs. Multilayered compression therapy is superior to single-layer systems. Once healed, patients should wear compression stockings indefinitely. Compression must be used with caution in patients with congestive heart failure or PAD.

Elevation of the legs above the heart for 30 min TID is also recommended. There is evidence that *exercise* improves healing by engaging the calf muscle pump to promote venous outflow. Oral *pentoxifylline* 400 mg–800 mg three times daily has been found to improve healing. It may work by increasing erythrocyte

deformability and inhibiting leukocyte function. Other medical treatments to speed VLU healing include oral agents such as *aspirin, statins, and flavonoids*. Venous intervention also speeds healing. Laser or radiofrequency are used for *endovenous ablation*. *Cell- and tissue-based products* (CTPs) (i.e., cellular, acellular, and amniotic membranes, among others) also are effective in healing refractory VLUs.

Chronic ischemia from PAD may lead to skin ulceration or may delay or prevent healing due to other causes. Arterial ulcers are classically punched-out lesions on the distal extremities (e.g., tips of the toes) but may also present elsewhere on the leg. Patients with hemodynamically significant arterial insufficiency require medical, surgical, and/or behavioral intervention, such as *angioplasty, stenting, and anti-platelet and/or lipid-lowering agents*.

Up to 25% of VLUs may be complicated by arterial disease. Low compression (25–35 mmHg) improves both venous and arterial flow in patients with ABI 0.6–0.8. Compression should be used very cautiously, if at all, in patients with ABI less than 0.5. ABI readings of >1.3 are likely unreliable due to calcification; therefore, alternative vascular assessment should be undertaken before compression is applied.

Investigations

- Blood count, chemistry profile, and nutritional testing
- ABI + arterial pulses exam
- TBPI/TCO₂/PVR if necessary
- Venous duplex ultrasound to assess reflux
- Non-healing wounds may require a wound biopsy for histology and tissue culture

First-Line Therapies

- Compression (VLU) **A**
- Revascularization (arterial/mixed) **A**
- Debridement (VLU) **B**
- Exercise **B**

Compression therapy for venous leg ulcers. Nair, B. *Indian Dermatol Online J* 2014; 5; 378–82.

Review on the use of compression to treat VLUs. Compression is better than no compression and high compression (25–35 mmHg) is better than low compression. Multilayer systems are more effective than single-layer systems. In patients with ABI 0.6–0.8, inelastic compression may increase both arterial and venous flow.

Debridement for venous leg ulcers. Gethin G, Cowman S, Kolbach DN. *Cochrane Database Syst Rev* 2015; 9.

Systematic review of debridement for VLUs. The authors identified 10 small randomized controlled trials (RCTs), most of which compared different methods of autolytic debridement. One looked at enzymatic debridement. No RCTs tested sharp, surgical, or mechanical methods and none compared debridement to no debridement. The overall quality of evidence is low. Nonetheless, debridement continues to be recommended based on expert consensus opinion.

Prescribed exercise with compression vs compression alone in treating patients with venous leg ulcers: a systematic review and meta-analysis. Jull A, Slark J, Parsons J. *JAMA Dermatol* 2018; 11; 1304–11.

This systematic review of six RCTs with meta-analysis of five found exercise to be associated with increased VLU healing at 12 weeks. The effect was imprecise. Increasing exercise is an easy recommendation to make for most patients.

Second-Line Therapies

- Venous interventions (VLU) (e.g., endovenous ablation, foam sclerotherapy) **B**
- CTPs **B**
- Pentoxifylline (400 mg thrice daily) **A**
- Micronized purified flavonoid fraction **B**
- Sulodexide **B**
- Mesoglycan **C**
- Aspirin (300 mg daily) **B**
- Oral statins (e.g., simvastatin 40 mg daily) **B**

A systematic review of the efficacy and limitations of venous intervention in stasis ulceration. Montminy ML, Jayaraj A, Raju S. *J Vasc Surg Venous Lymphat Disord* 2018; 6; 376–98. e1.

A review of 45 RCTs evaluating the efficacy of venous ablation in achieving ulcer healing and preventing recurrence. The quality of evidence ranged from very low to moderate for various techniques. The authors concluded that these minimally invasive techniques achieve good healing rates in most patients with VLUs.

Skin substitutes for treating chronic wounds [Internet]. Snyder D, Sullivan N, Margolis D, et al. Agency for Healthcare Research and Quality (US); 2020 Feb 2. <https://ncbi.nlm.nih.gov/books/NBK554220>.

Aggregation of systemic reviews and RCTs evaluating the efficacy of CTPs for VLUs. Two RCTs report that acellular dermal substitutes improved time to heal compared with standard of care. One RCT found cellular dermal substitutes plus compression achieved significantly higher rates of healing versus compression alone.

Pharmacologic treatment to improve venous leg ulcer healing. Raffeto JD, Eberhardt RT, Dean SM, et al. *J Vasc Surg Venous Lymphat Disord* 2016; 3; 371–4.

Evidence-based review assessing the effectiveness of various pharmacologic agents to improve healing in patients with VLUs. The following agents have RCT-level evidence for this: micronized purified flavonoid fraction, pentoxifylline, sulodexide, and mesoglycan.

Simvastatin as a novel therapeutic agent for venous ulcers: a randomized, double-blind, placebo controlled trial. Evangelista MTP, Casintahan MFA, Villafuerte LL. *BJD* 2014; 170; 1151–7.

RCT of 66 patients with VLUs wherein treatment with simvastatin 40 mg PO daily resulted in greater proportion of healed ulcers; faster healing time; and improved quality of life index, in combination with standard wound care and compression, when compared with placebo.

Leiomyoma

Donna Cummins, Nick Collier, Ian H. Coulson



Cutaneous leiomyomas are rare, benign neoplasms originating from smooth muscle. Three types exist: (1) piloleiomyoma, the most common type, arising from the arrectores pilorum muscle; (2) dartoid myoma, or genital leiomyoma, arising from the scrotal/labial dartos muscle or smooth muscle of the nipple; and (3) angioleiomyoma, arising from the vascular wall muscle. Piloleiomyomas frequently occur as multiple lesions (80%). Multiple leiomyomas can be inherited in an autosomal dominant fashion in association with uterine leiomyomata [MCUL1; OMIM 150800]. Familial multiple leiomyomata can rarely be associated with renal cell cancer (hereditary leiomyomatosis and renal cell cancer [HLRCC; OMIM 105800]). Both familial forms are caused by mutations in the fumarate hydratase gene (coding for an enzyme in the tricarboxylic acid cycle) on 1q42.1, which is hypothesized to act as a tumor suppressor gene through an unknown mechanism. Cutaneous leiomyomas present as flesh-colored or brownish-red dermal papules or nodules up to 2 cm in diameter, typically distributed on the trunk and extensor surfaces of extremities. They often appear from the second to fourth decade and gradually increase in number and size. Paroxysmal pain, described as stabbing, burning, or pinching, may be triggered by cold or mechanical stimulation and is possibly due to muscle contraction or compression of entrapped nerves. Angioleiomyomas are less frequently symptomatic, whereas genital leiomyomas are asymptomatic.

MANAGEMENT STRATEGY

Symptomatic solitary lesions are best *excised*. Symptomatic multiple leiomyomas are therapeutically challenging because they involve a large area and recur after excision in 50% of cases. Selective excision of larger painful lesions may be considered, provided patients are warned of the relatively high chance of recurrence. CO_2 laser ablation of symptomatic lesions may be successful. Other therapeutic methods aim to inhibit smooth muscle contraction, and thus pain, by interfering with local tissue

mediators (e.g., norepinephrine, epinephrine, and acetylcholine). There are reports of success with oral *doxazosin* (a selective α_1 -blocker) 1–4 mg daily, oral *nifedipine* (calcium channel blocker) 10 mg three times daily, *amlodipine* (calcium channel blocker) 5 mg twice daily, *phenoxybenzamine* (non-selective α -blocker) 10 mg twice daily, topical 9% *hyoscine hydrobromide* (anticholinergic), and oral *glyceryl trinitrate* (nitroglycerin) 0.8–1.6 mg as needed. Analgesics that target neuropathic pain (e.g., oral *gabapentin* 300 mg three times daily and *duloxetine*) have been beneficial. Potential triggers should be avoided. Intraleisional injection of *botulinum toxin A* (5 units per cm^2), cryotherapy, and lidocaine patches have shown some benefit.

Women, particularly those with a family history, should undergo gynecologic review to exclude possible uterine involvement ('fibroids'). Menorrhagia may necessitate hysterectomy, and leiomyosarcoma, although rare, should be excluded. Potential familial forms require referral to a clinical geneticist with informed consent for mutational analysis of the fumarate hydratase gene. Individuals considered to have HLRCC will require renal ultrasound surveillance to detect the development of renal tumors.

Specific Investigations

- Biopsy
- Biochemical assay of fumarate hydratase – for low/absent activity
- Genetic analysis – for fumarate hydratase gene mutations

Cutaneous smooth muscle neoplasms: clinical features, histologic findings and treatment options. Holst VA, Junkins-Hopkins JM, Elenitas R. *J Am Acad Dermatol* 2002; 46: 477–90.

A well-referenced review covering leiomyoma and angioleiomyoma. On histologic examination, leiomyomas stained with Masson trichrome reveal brick-red smooth muscle fibers. Immunohistochemical techniques demonstrating desmin, smooth muscle actin, or muscle-specific actin confirm tumor origin.

Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Tomlinson IP, Alam NA, Rowan AJ, et al. Multiple Leiomyoma Consortium. *Nature Genet* 2002; 30: 406–10.

The authors demonstrate that the gene predisposing to uterine fibroids, cutaneous leiomyoma, and renal cell carcinoma encodes fumarate hydratase.

Hereditary leiomyomatosis and renal cell cancer syndrome: an update and review. Patel VM, Handler MZ, Schwartz RA, et al. *J Am Acad Dermatol* 2017; 77: 149–58.

An overview of HLRCC and the sensitivity of immunohistochemistry markers, including 2SC in confirming the diagnosis.

First-Line Therapy

- Surgical excision

D

Leiomyomas of the skin. Fisher WC, Helwig EB. *Arch Dermatol* 1963; 88: 510–20.

The clinical findings and natural course of 54 cutaneous leiomyomas from 38 patients are described. Surgically excised leiomyomas had a high recurrence rate of 50%.

Second-Line Therapies

• Doxazosin	E
• Phenoxybenzamine	E
• Topical hyoscine hydrobromide	E
• Nifedipine	E
• Amlodipine	E
• Oral glyceryl trinitrate	E
• Cryotherapy	E
• Gabapentin	E
• Duloxetine	E
• Botulinum toxin A	E
• CO ₂ laser	E
• 5% lidocaine patch	E

The rarity of the condition means that most publications on therapy are case reports. The therapeutic agents are not consistently effective.

Successful treatment of pain in two patients with cutaneous leiomyomata with the oral alpha-1 adrenoceptor antagonist, doxazosin. Batchelor RJ, Lyon CC, Highet AS. *Br J Dermatol* 2004; 150: 775–6.

Two women with symptomatic cutaneous leiomyoma were treated with oral doxazosin 1 to 4 mg daily. Patients experienced 'dramatic improvement', sustained for 6 months in one patient.

Pharmacologic modulation of cold-induced pain in cutaneous leiomyomata. Archer CB, Whittaker S, Greaves MW. *Br J Dermatol* 1988; 118: 255–60.

Two cases of cutaneous leiomyoma. One patient responded only to phenoxybenzamine 10 mg twice daily, and the other responded to hyoscine hydrobromide (the response lasted only 6 hours). The latter patient also improved with cryotherapy.

Therapy for painful cutaneous leiomyomas. Thompson JA. *J Am Acad Dermatol* 1985; 13: 865–7.

A 24-year-old man with multiple painful leiomyomas treated successfully with nifedipine 10 mg three times daily for 8 months. The dosage was increased to 10 mg four times daily after the onset of cool weather and increased pain.

Leiomyomatosis cutis et uteri. Engelke H, Christophers E. *Acta Derm Venereol* 1979; 59: 51–4.

A woman with cutaneous leiomyoma who responded to oral glyceryl trinitrate 0.8–1.6 mg for acute attacks, with maintenance nifedipine 20 mg and phenoxybenzamine 60 mg administered during 2 years of follow-up.

Disseminated cutaneous leiomyomatosis treated with oral amlodipine. Aggarwal S, De D, Kanwar AJ, et al. *Indian J Dermatol Venereol Leprol* 2013; 79: 136.

A 32-year-old male with multiple painful cutaneous leiomyomas, intolerant of nifedipine due to headaches, experienced significant pain reduction and reduced side effects using amlodipine.

Gabapentin treatment of multiple piloleiomyoma-related pain. Alam M, Rabinowitz AD, Engler DE. *J Am Acad Dermatol* 2002; 46: S27–9.

A 54-year-old woman with numerous cutaneous leiomyomas experienced near-complete pain relief with gabapentin 300 mg three times daily.

Successful pain relief of cutaneous leiomyomata due to Reed syndrome with the combination treatment of pregabalin and duloxetine. Kostopanagiotou G, Arvaniti C, Kitsiou MC, et al. *Pain Symptom Manage* 2009; 38: e3–5.

Pregabalin 600 mg daily and duloxetine 60 mg daily successfully treated a 34-year-old woman with multiple leiomyomas. This produced complete pain relief maintained over a 12-month follow-up period.

Efficacy of intralesional botulinum toxin A for treatment of painful cutaneous leiomyomas: a randomized clinical trial. Naik HB, Steinberg SM, Middleton LA, et al. *JAMA Dermatol* 2015; 151: 1096–102.

Eighteen participants received placebo or five units per cm² of botulinum toxin A. There was a 4-point fall in the skin-related Dermatology Life Quality Index (DLQI). There was a reduction in resting leiomyoma-related pain but not after ice provocation.

Treatment of multiple cutaneous leiomyomas with CO₂ laser ablation. Christenson LJ, Smith K, Arpey CJ. *Dermatol Surg* 2000; 26: 319–22.

A 73-year-old woman not eligible for pharmacologic therapy who had multiple cutaneous leiomyomas. CO₂ laser ablation of six symptomatic cutaneous leiomyomas induced complete pain relief sustained during 9 months of follow-up.

Successful treatment of multiple cutaneous leiomyomas with carbon dioxide laser ablation. Michajłowski I, Błażewicz I, Karpinsky G, et al. *Postepy Dermatol Alergol* 2015; 32: 480–511.

Leiomyomas over the deltoid were treated with CO₂ laser ablation, with each lesion being treated on four occasions at monthly intervals. The cosmetic result was suboptimal, but pain was greatly diminished.

Treatment of cutaneous leiomyomas with 5% lidocaine patches in a patient with hereditary leiomyomatosis and renal cell cancer (Reed syndrome). Hsu T, Cornelius LA, Rosman IS. *JAAD Case Rep.* 2017; 3: 407–9.

A 37-year-old woman with HLRCC and multiple painful leiomyomas cut 5% lidocaine patches to size. After using the patches for several months, the patient's pain frequency significantly decreased from a patch application of 1–3 times per week to once every 1–2 months.

Leishmaniasis

Suhail M. Hadi, Ali S. Hadi



Leishmaniasis is a flagellate protozoan disease caused by many species of the genus *Leishmania*. It can be classified into three clinical forms: visceral (kala azar), which is the most severe form; mucocutaneous, which may lead to extensive destruction of the mucous membranes; and cutaneous (Old and New World), which affects mainly exposed parts of the body, causing ulcers and eventually scarring.

Generalized and mucosal leishmaniasis may be seen in patients with human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS). Subclinical forms of the disease do exist. Leishmaniasis is transmitted mainly by the bite of the infected female phlebotomine sandfly. However, other possible routes of transmission exist, including transfusion, needle sharing, and congenital, sexual, and person-to-person contact. Only the management of cutaneous leishmaniasis (CL) will be addressed here.

Many faces of cutaneous leishmaniasis. Bari AU, Rahman SB. Indian J Dermatol Venereol Leprol 2008; 74: 23–7.

A total of 718 patients with CL were analyzed; 5.7% had unusual presentations. The most common of these presentations was lupoid leishmaniasis.

Cutaneous leishmaniasis mimicking inflammatory and neoplastic processes: a clinical, histopathological and molecular study of 57 cases. Saab J, Fedda F, Khattab R, et al. J Cutan Pathol 2012; 39: 251–62.

Skin biopsies from 145 patients were studied; 125 were confirmed as CL by polymerase chain reaction (PCR). Eighteen cases presented with a prebiopsy clinical diagnosis that ranged from dermatitis to neoplasm. Of the 125 cases, 57 showed a histopathologic pattern other than CL.

MANAGEMENT STRATEGY

CL presents with a typical lesion and a history of exposure. A skin scraping for microscopic analysis is the simplest test. Cultures from an exudate or scraping show good results. PCR offers a rapid, highly sensitive, and specific modality of diagnosis. Serologic tests can be used and include the indirect immunofluorescent antibody test, direct agglutination test, fast agglutination screening test, and enzyme-linked immunosorbent assay (ELISA).

A new vaccine has been recently studied for its protection against CL. Results showed durable protective immunity. It has the advantages of being inexpensive and administered by a non-invasive nasal route. However, no vaccines are yet approved for immunization against CL.

Pentavalent antimonials are the first-line therapy. *Meglumine antimoniate* is the drug of choice. It can be given intralesionally with local anesthetic (particularly in children, because of pain) or systemically 10 mg/kg daily for 2 weeks. *Leishmania recidivans* requires higher doses for longer periods. *Sodium stibogluconate* can be infiltrated into individual lesions 1–2 mL/week. In widespread severe cases it can be given intramuscularly or intravenously in a dose of 10 mg/kg/day for 2 weeks.

Pentavalent antimoniate use is complicated by a high rate of side effects, including arthralgia; fatigue; gastrointestinal (GI) upset; elevation of amylase, lipase, and liver enzyme levels; leukopenia; anemia; and electrocardiogram (ECG) abnormalities. Side effects appear to be dose related and are more common in patients with renal and liver impairment and those with cardiac arrhythmias. *Amphotericin B* has been used in antimony-resistant cases.

Pentamidine isethionate (aromatic diamidine) is effective for diffuse CL. Side effects of pentamidine include hypoglycemia, diabetes mellitus, hypotension (if administered too rapidly), GI upset, and headache.

Allopurinol has antileishmanial activity, and other oral drugs such as *miltefosine*, *zinc sulfate*, *rifampin*, *doxycycline*, and *azoles* are also beneficial. *Interferon-γ* was shown to be effective as monotherapy treatment. Topical preparations such as *paromomycin* ointment and 5% *imiquimod* show considerable therapeutic potential.

Good cure rates have been achieved with both thermotherapy and cryotherapy. Lasers have been used, but further studies are needed to support their benefit.

Specific Investigations

- Skin biopsy
- Fine needle aspiration
- Slit-skin smear, press imprint smear
- Culture
- Leishmanin (Montenegro) skin test
- Serology
- Polymerase chain reaction (PCR) for leishmanial deoxyribonucleic acid (DNA)

The margin of the lesion contains amastigotes, whereas the center has dead skin and debris. Accordingly, the margin is preferred when performing a slit-skin smear. The aspirate can then be sent for culture or histology, which shows Leishman–Donovan bodies inside macrophages using Giemsa stain.

The gold-standard medium for culture is Novy–MacNeal–Nicolle, with positive results in 1–3 weeks, or Schneider *Drosophila* medium, which gives positive results in 1 week.

Microculture is a new culture medium that has higher carbon dioxide concentrations and lower oxygen and pH, which encourages more rapid amastigote to promastigote differentiation. Culture is not a reliable method in older lesions, as the organisms become scarce and difficult to isolate.

Serologic tests aim to detect the presence of antibodies against *Leishmania*. They are particularly valuable in visceral and mucocutaneous leishmaniasis.

PCR is a sensitive and powerful method of diagnosis of CL. Recently it was found that important genes involved in the innate immune response to *Leishmania* are downregulated in natural killer (NK) cells from patients with diffuse CL, particularly toll-like receptors (TLRs) and Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathways.

Comparison of molecular, microscopic, and culture methods for diagnosis of cutaneous leishmaniasis. Rasti S, Ghorbani-zadeh B, Kheirandish F, et al. J Clin Lab Anal 2016; 30: 610–5.

In total, 130 patients were tested, and 66.9%, 56.2%, 75.4%, 73.8%, and 76.2% were positive for microscopic culture, PCR, nested PCR, and combined PCR and microscopy (proposed method), respectively. Sensitivity, specificity, and positive and negative predictive values of PCR were 99%, 100%, 100%, and 96.9%, respectively; for microscopy 87.9%, 100%, 100%, and 72.1%; for culture 72.7%, 100%, 100%, and 53.4%; and 97%, 100%, 100%, and 91.2% for nested PCR. kDNA-PCR was the most sensitive method for diagnosis of CL.

Molecular detection of *Leishmania* spp. isolated from cutaneous lesions of patients referred to Herat Regional Hospital, Afghanistan. Mosawi SH, Dalimi A. East Mediterr Health J 2016; 21: 878–84.

Light microscopy examination was positive in 58%, whereas PCR was positive in 78% of cases.

Press imprint smear: a rapid, simple, and cheap method for the diagnosis of cutaneous leishmaniasis caused by *Leishmania (Viannia) braziliensis*. Sousa AQ, Pompeu MM, Frutuoso MS, et al. Am J Trop Med Hyg 2014; 91: 905–7.

Amastigotes were seen in 92% of 75 patients. The press imprint smear was positive in 85.3%, and histopathology was positive in 44%. It is a rapid and relatively sensitive method for the diagnosis of CL.

Performance of an ELISA and indirect immunofluorescence assay in serologic diagnosis of zoonotic cutaneous leishmaniasis in Iran. Sarkari B, Ashrafmansori M, Hatam G, et al. Interdiscip Perspect Infect Dis 2014; 505: 134.

Sixty-one sera from parasitologically confirmed CL patients and 50 sera from healthy controls, along with 50 sera from non-CL patients, were studied. Indirect fluorescent antibody (IFA) was used to detect anti-*Leishmania* IgG; ELISA was used to detect anti-*Leishmania* IgM, total IgG, or IgG1 and IgG4. Sensitivity and specificity of IFA were 91.6% and 81%, respectively. ELISA showed reasonable sensitivity and specificity. Serologic tests can be used for proper diagnosis of CL.

Down-regulation of TLR and JAK/STAT pathway genes is associated with diffuse cutaneous leishmaniasis: a gene expression analysis in NK cells from patients infected with *Leishmania mexicana*. Fernández-Figueroa EA, Imaz-Rosshandler I,

Castillo-Fernández JE, et al. PLoS Negl Trop Dis 2016; 10: e0004570.

First-Line Therapies

Pentavalent antimonials

- Meglumine antimoniate **B**
- Sodium stibogluconate antimony **B**

Clinical features, epidemiology, and efficacy and safety of intralesional antimony treatment of cutaneous leishmaniasis: recent experience in Turkey. Uzun S, Durdu M, Culha G, et al. J Parasitol 2004; 90: 853–9.

Intralesional meglumine antimoniate was given as first-line therapy for 890 patients with CL. A weekly dose of 0.2–1 mL was given for up to 20 weeks or until complete cure. It was found to have an efficacy of 97.2%, with a low relapse rate (3.9%) and no serious side effects.

Clinical efficacy of intramuscular meglumine antimoniate alone and in combination with intralesional meglumine antimoniate in the treatment of Old World cutaneous leishmaniasis. Munir A, Janjua SA, Hussain I. Acta Dermatovenereol Croat 2008; 16: 60–4.

Sixty patients were studied. A combination of intramuscular meglumine antimoniate 20 mg/kg/day plus intralesional meglumine antimoniate 0.5 mL daily for 21 days was superior to intralesional treatment alone, with 75% complete cure for the former.

Intralesional antimony for single lesions of Bolivian cutaneous leishmaniasis. Soto J, Rojas E, Guzman M, et al. Clin Infect Dis 2013; 56: 1255–60.

A randomized, open-label trial of 80 patients in Bolivia divided patients into three groups, each receiving either intralesional antimony, cryotherapy, or placebo. At 6 months the cure rate was 70% for the antimony group, 20% for the cryotherapy group, and 17% for placebo.

Second-Line Therapies

- Pentamidine isethionate **B**
- Rifampin **A**
- Azoles **B, A**
- Cryotherapy **A, B**
- Thermotherapy **B**
- Hypertonic sodium chloride **A**

Recurrent American cutaneous leishmaniasis. Gangneux JP, Sauzet S, Donnard S, et al. Emerg Infect Dis 2007; 13: 1436–8.

Twenty-one patients with recurrent CL were enrolled. Intravenous or intramuscular pentamidine isethionate (4 mg/kg) on alternate days cured the lesions within 1–3 months.

The role of rifampicin in the management of cutaneous leishmaniasis. Kochar DK, Aseri S, Sharma BV, et al. Q J Med 2000; 93: 733–7.

In this study of 46 patients, 23 received rifampin 600 mg twice daily for 4 weeks, and 23 received placebo. Of the rifampin group, 73.9% had complete healing of their lesions, compared with 4.3% of the placebo group. Rifampin is suitable for multiple lesions and is well tolerated.

Fluconazole for the treatment of cutaneous leishmaniasis caused by *Leishmania major*. Alrajhi AA, Ibrahim EA, De Vol EB. *N Engl J Med* 2002; 346: 891–5.

Patients ($n=106$) received fluconazole 200 mg daily, and 103 received placebo for 6 weeks. Healing was complete in 79% of the fluconazole group and 34% of the placebo group at 3 months' follow-up.

Comparison of oral itraconazole and intramuscular meglumine antimoniate in the treatment of cutaneous leishmaniasis. Saleem K, Rahman A. *J Coll Phys Surg Pak* 2007; 17: 713–6.

This study included 200 patients with wet and dry CL. Itraconazole (100 mg twice daily for 6–8 weeks) was superior to meglumine antimoniate in achieving complete clinical and parasitologic cure (75% compared with 65%), with fewer side effects.

Intralesional sodium stibogluconate alone or its combination with either intramuscular sodium stibogluconate or oral ketoconazole in the treatment of localized cutaneous leishmaniasis: a comparative study. El-Sayed M, Anwar AE. *J Eur Acad Dermatol Venereol* 2010; 24: 335–40.

In group 1, 10 patients were treated with intralesional sodium stibogluconate (SSG) alone. In group 2, 10 patients were treated with the combination intralesional SSG + intramuscular SSG. Group 3 comprised 10 patients treated with the combination intralesional SSG + oral ketoconazole. Treatment period was 12 weeks. Cure rate was 58.3% in group 1, 93.3% in group 2, and 92.3% in group 3. Combination of oral ketoconazole with intralesional SSG was more effective than intralesional SSG alone.

Efficacy of a weekly cryotherapy regimen to treat *Leishmania major* cutaneous leishmaniasis. Mosleh IM, Geith E, Natsheh L, et al. *J Am Acad Dermatol* 2008; 58: 617–24.

Patients ($n=120$) were treated with cryotherapy once weekly over one to seven sessions; 84% of lesions were cured after one to four sessions. The side effects were minimal.

Evaluation of thermotherapy for the treatment of cutaneous leishmaniasis in Kabul, Afghanistan: a randomized controlled trial. Case AJ, Safi N, Davis GD, et al. *Mil Med* 2012; 177: 345–51.

Patients ($n=382$) with CL were randomly assigned to two treatment groups and followed for 6 months. The cure rate for the thermotherapy group was 82.5%, compared with 74% in the glucantime group. A single localized treatment with thermotherapy was more effective than 5 days of intralesional glucantime. Also, thermotherapy was cost effective, with fewer side effects, and with better patient compliance than intralesional glucantime.

Thermotherapy effective and safer than miltefosine in the treatment of cutaneous leishmaniasis in Colombia. López L, Cruz C, Godoy G, et al. *Rev Inst Med Trop Sao Paulo* 2013; 55: 197–204.

In an open-label trial, one group received oral miltefosine 50 mg daily for 28 days, and the other group received thermotherapy of 50°C on the lesion and perilesional area. There was no statistically significant difference in efficacy between the two groups, but the miltefosine group experienced GI discomfort.

Randomized, double-blind, controlled, comparative study on intralesional 10% and 15% hypertonic saline versus intralesional sodium stibogluconate in *Leishmania donovani* cutaneous leishmaniasis. Ranawaka RR, Weerakoon HS, de Silva SH. *Int J Dermatol* 2015; 54: 555–63.

This was a randomized, double-blind, controlled study of 10% and 15% hypertonic saline injections compared with that of sodium stibogluconate. Four hundred forty-four patients were studied and followed for 18 months. All three groups had cure rates above 90%. The 15% hypertonic saline group showed cutaneous necrosis in 30.6% of lesions, compared with 3.1% of lesions in the 10% hypertonic group. Ten percent hypertonic saline can be considered an alternative to SSG.

Third-Line Therapies

• Miltefosine (hexadecylphosphocholine)	A, B
• Imiquimod 5%	D
• Paromomycin ointment	B
• Photodynamic therapy	B
• Direct current electrotherapy	D
• CO ₂ laser	B
• Intralesional zinc sulfate	A
• Pentoxifylline	B
• Amphotericin	B
• Trichloroacetic acid	B
• Radiofrequency heat therapy	B
• Topical <i>Juniperus excelsa</i> with cryotherapy	C
• Immunization	A
• Pulsed-dye laser	C
• Erbium glass laser	C
• Nd:YAG laser	C

Safety and efficacy of miltefosine in cutaneous leishmaniasis: an open label, non-comparative study from Balochistan. Tahir M, Bashir U, Hafeez J, et al. *Pak J Med Sci*. 2019; 35: 495–9.

Forty-two patients were enrolled; all received miltefosine 2.5 mg/kg orally. Average duration of treatment was 23.47 days. Complete clinical response was observed in 39 (92.9%) patients.

Miltefosine in the treatment of cutaneous leishmaniasis caused by *Leishmania braziliensis* in Brazil: a randomized and controlled trial. Machado PR, Ampuero J, Guimarães LH, et al. *PLoS Negl Trop Dis* 2010; 21: e912.

In this study of 90 patients, 60 received miltefosine orally and 30 received pentavalent antimony. Six months later, the cure rate was 53.3% in the pentavalent antimony group and 75% in the miltefosine group. Apoptosis-like death of *Leishmania donovani* may be a possible explanation of the mode of action of miltefosine.

Role of imiquimod and parenteral meglumine antimoniate in the initial treatment of cutaneous leishmaniasis. Arevalo I, Tulliano G, Quispe A, et al. *Clin Infect Dis* 2007; 44: 1549–54.

Combination treatment with imiquimod and meglumine antimoniate gave superior results, with rapid healing and better cosmetic outcome. Imiquimod kills the intracellular *Leishmania amastigotes* in vitro by activating macrophages to release nitric oxide.

Topical paromomycin with or without gentamicin for cutaneous leishmaniasis. Ben Salah A, Ben Messaoud N, Guedri E, et al. *N Engl J Med* 2013; 368: 524–32.

A randomized, controlled study of 375 patients using topical paromomycin with and without gentamicin for ulcerative CL. Three groups received 15% topical paromomycin and 0.5% gentamicin, paromomycin alone, or control. Treatment continued for 20 days; cure rates were 81%, 82%, and 58% for the

paromomycin–gentamicin, paromomycin, and control groups, respectively.

Comparison between the efficacy of photodynamic therapy and topical paromomycin in the treatment of Old World cutaneous leishmaniasis: a placebo-controlled, randomized clinical trial. Asilian A, Davami M. Clin Exp Dermatol 2006; 31: 634–7.

This study compared the parasitologic and clinical efficacy of photodynamic therapy (PDT) and topical paromomycin in 60 patients. Topical PDT was given weekly for 4 weeks. Complete improvement was seen in 93.5% of patients treated with topical PDT versus 41.2% in the topical paromomycin group.

The parasitocidal effect of electricity on *Leishmania major*, both in vitro and in vivo. Hejazi H, Eslami G, Dalimi A. Ann Trop Med Parasitol 2004; 98: 37–42.

Exposure to direct current of 3, 6, 9, and 12 V (at 0.2–10.7 mA) killed all promastigotes (in culture) within 10–15 min. Three weeks of electrotherapy at 3 V for 10 min twice weekly appeared to cure all the lesions in mice.

Efficacy of CO₂ laser for treatment of anthroponotic cutaneous leishmaniasis, compared with combination of cryotherapy and intralesional meglumine antimoniate. Shamsi Meymandi S, Zandi S, Aghaie H, et al. J Eur Acad Dermatol Venerol 2011; 25: 587–91.

A single treatment session of CO₂ laser was more effective in treating dry-type CL than combined cryotherapy and intralesional glucantime with a shorter healing time (6 weeks vs. 12 weeks).

Comparison of intralesionally injected zinc sulfate with meglumine antimoniate in the treatment of acute cutaneous leishmaniasis. Iraj F, Vali A, Asilian A. Dermatology 2004; 209: 46–9.

A total of 104 patients with acute cutaneous leishmaniasis (ACL) were studied. The duration of treatment was 6 weeks. Thirty-five patients received meglumine antimoniate, and 31 received intralesional zinc sulfate. Cure rates were 60% for meglumine antimoniate and 83.8% for zinc sulfate. Intralesional injection of 2% zinc sulfate is a good alternative for the treatment of ACL.

Clinical and immunologic outcome in cutaneous leishmaniasis patients treated with pentoxifylline. Brito G, Dourado M, Polari L, et al. Am J Trop Med Hyg 2014; 90: 617–20.

Thirty-six patients with CL were studied. One group received intralesional antimony along with pentoxifylline, and the other received antimony with placebo. The pentoxifylline group showed a decrease in tumor necrosis factor- α (TNF- α) and interferon- γ levels compared with the placebo group. Cure rate was higher in the pentoxifylline group, but not statistically significant. Pentoxifylline has an antiinflammatory effect.

Comparison of efficacy of two different concentrations of intralesional amphotericin B in the treatment of cutaneous leishmaniasis; a randomized controlled trial. Goswami P, Ghiya BC, Kumar V, et al. Indian Dermatol Online J 2019; 10: 627–31.

In this trial of 50 patients, 25 were treated with intralesional injection of amphotericin B at a concentration of 2.5 mg/mL weekly for 8 weeks, while the other 25 patients received a

concentration of 5.0 mg/mL weekly for 8 weeks. There was no statistically significant difference in treatment response between the two groups, with both groups showing clinical improvement.

Liposomal amphotericin B treatment of cutaneous leishmaniasis due to *Leishmania tropica*. Solomon M, Pavlotsky F, Leshem E, et al. J Eur Acad Dermatol Venerol 2011; 25: 973–7.

A group of 13 patients received liposomal amphotericin B (5 consecutive days of 3 mg/kg, followed by a sixth dose on day 10); 85% had facial lesions. Of the 13 patients, 11 (84%) achieved complete clinical cure within 2 months. There were no reported relapses after 11 months, and the side effects were mild.

Salvage therapy with *Sodium chlorosum* (formerly DAC N-055) for cases of refractory lupoid cutaneous leishmaniasis: results from a compassionate use study with 0.09% *Sodium chlorosum* in amphiphilic basic cream. Molkara S, Poursoltani E, Stahl KW, et al. BMC Infect Dis 2019; 19: 1005.

In this study, 20 patients with lupoid cutaneous leishmaniasis were enrolled. They were treated with sodium chlorosum cream twice daily for at least 6 weeks, continuing up to 12 weeks in patients who showed a clinical response in the first 6 weeks. A complete response was seen in nine (45%) patients. Erythema and itching were reported side effects.

The efficacy of 5% trichloroacetic acid cream in the treatment of cutaneous leishmaniasis lesions. Ali NM, Fariba J, Elaheh H, et al. J Dermatolog Treat 2012; 23: 136–9.

Sixteen patients with CL were treated with 5% trichloroacetic acid cream twice daily for 8 weeks. Mean area of the lesions was 38.81 + 81.9 mm². After 6 months, it was 3.6 + 9.1 mm². All patients were cured by week 8. No side effects.

Long-term efficacy of single-dose radiofrequency-induced heat therapy vs. intralesional antimonials for cutaneous leishmaniasis in India: RFHT for cutaneous leishmaniasis. Bumb RA, Prasad N, Khandelwal K, et al. Br J Dermatol 2013; 168: 1114–9.

In total, 100 patients with CL were studied; 50 patients received one treatment of radiofrequency-induced heat therapy (RFHT) while the other 50 received intralesional SSG injections. Follow-up was for 18 months. After 6 months, the cure rate was 98% in the RFHT group and 95% in the SSG group. No relapse in any patient.

Cluster randomised trial to evaluate the effectiveness of a vaccine against cutaneous leishmaniasis in the Caratinga microregion, south-east Brazil. Mayrink W, Mendonca-Mendes A, de Paula JC, et al. Trans R Soc Trop Med Hyg 2013; 107: 212–9.

A randomized trial of 8734 patients in a Brazilian area with a high frequency of CL were given a killed vaccine from 2002 to 2011. They showed a significantly lower number of individuals infected with CL in the vaccine group compared with the placebo group.

Efficacy of cryotherapy plus topical *Juniperus excelsa* M. Bieb cream versus cryotherapy plus placebo in the treatment of Old World cutaneous leishmaniasis: a triple-blind randomized controlled clinical trial. Parvizi MM, Handjani F, Moein M, et al. PLoS Negl Trop Dis 2017; 11: e0005957.

In this trial, 72 patients were enrolled. Both groups received cryotherapy as baseline standard treatment. One group received

topical formulation of leaf of *Juniperus excelsa*, while the other group received placebo; 82% of patients in the treatment group experienced complete cure, while 34% of the placebo group had complete cure.

The pulsed dye laser is more effective and rapidly acting than intralesional meglumine antimoniate therapy for cutaneous leishmaniasis. Radmanesh M, Omidian E. J Dermatolog Treat. 2017; 28(5): 422–5.

Seventeen patients with CL were studied. A total of 81 lesions were treated. 42 lesions were treated with pulsed dye laser, while 39 were treated with intralesional meglumine antimoniate. Over 90% of laser treated lesions cleared after two treatments.

Efficacy of erbium glass laser in the treatment of Old World cutaneous leishmaniasis: A case series. Mashayekhi Goyonlo V, Karrabi M, Kiafar B. Australas J Dermatol. 2019; 60(1): e29–32.

Fourteen patients with CL were enrolled in this study. The device was a 1540-nm non-ablative fractional Erbium glass laser. Nine patients with twelve CL lesions completed the study. 11 lesions had complete clearance 12 weeks after all treatments were completed. The mean number of sessions required for clearance for lesions treated with meglumine antimoniate was 4.6.

The effect of Nd:YAG laser therapy on cutaneous leishmaniasis compared to intralesional meglumine antimoniate. Omidian M, Jadbabaei M, Omidian E, Omidian Z. Postepy Dermatol Alergol. 2019; 36(2): 227–31.

Sixteen patients with CL were studied. In each patient, one CL lesion was treated with intralesional meglumine antimoniate while another lesion was treated with 1064 nm Nd:YAG laser. All lesions eventually cleared. The mean number of laser sessions required was 2.6 ± 0.9 .

Lentigo maligna

Graham H. Litchman, Aaron S. Farberg, Darrell S. Rigel



Lentigo maligna (LM) is a subtype of preinvasive intraepidermal melanoma (viewed by some as melanoma in situ) that classically presents as widespread pigmented patches of atypical melanocytes in the background of longstanding sun damage. The lifetime risk of LM progressing to invasive lentigo maligna melanoma (LMM) varies from 2.2%–4.7%, depending on patient age at diagnosis. LMM represents 4%–15% of all melanomas, and its incidence is increasing at a greater rate than any other melanoma subtype. LM has traditionally been challenging to diagnose because it is difficult to distinguish non-malignant atypical melanocytic hyperplasia from melanoma in situ (MIS) in chronically sun-damaged skin. Treatment of LM remains complex, with recurrence rates that remain high (2%–50%) due to subclinical extension.

MANAGEMENT STRATEGY

Successful management of LM depends on early diagnosis and definitive removal. Confirmatory biopsy is necessary before definitive treatment. The use of a Wood lamp and dermoscopy may help to determine the perimeter of the lesion. Excisional biopsy of the entire lesion is ideal in order to ascertain its maximum depth. However, the lesion tends to be large (>1 cm) due to its propensity for extensive radial growth before vertical growth into the dermis. Treatment is primarily surgical, although eradication by other methods may be considered. Patients with a history of LM should have periodic full-body skin examinations to determine recurrence as well as new skin malignancies, and they need sun avoidance advice.

Specific Investigation

- Skin biopsy and patient evaluation

Diagnosis and treatment of early melanoma. NIH Consensus Statement. 1992; 10: 1–26.

Biopsy of sufficient depth is critical for diagnosis and management of pigmented lesions. Punch, saucerization, excision, or incisional biopsy may be acceptable. On microscopic examination, LM is characterized by increased numbers of atypical melanocytes at the epidermal–dermal junction, which may be solitary or arranged in nests but do not invade the dermis. Evaluation should include a personal and family history, complete skin examination, and palpation of regional lymph nodes. Blood tests or imaging studies are not indicated.

From the Academy Guidelines of care for the management of primary cutaneous melanoma. Swetter SM, Tsao H, Bichakjian CK, et al. J Amer Acad Dermatol 2019; 80: 208–50.

Management guidelines for these lesions were recently updated by the Academy in the 2019 JAAD article referenced above.

First-Line Therapies

• Excision	A
• Mohs micrographic surgery	D
• Modified Mohs surgery	D
• Staged excision	D

Diagnosis and treatment of early melanoma. NIH Consensus Statement. 1992; 10: 1–26.

Current recommendations are based on the National Institutes of Health (NIH) consensus for MIS, which suggests excision of the lesion or biopsy site with a margin of 0.5 cm of clinically normal skin and layer of subcutaneous tissue. In general, margins of 0.5–1.0 cm are suggested for LM where feasible. A Wood lamp may be useful in defining subclinical extension. Reflectance confocal microscopy (RCM) may also improve diagnostic accuracy of LM by identifying optimal biopsy sites. RCM may assist in presurgical mapping, intraoperative margin assessment, assessing response to non-surgical therapies, and monitoring for recurrence. Accurate determination of margins is key because LM is likely to recur after inadequate excision.

Usefulness of the staged excision for lentigo maligna and lentigo maligna melanoma: the “square” procedure. Johnson TM, Headington JT, Baker SR, et al. J Am Acad Dermatol 1997; 37: 758–64.

With this technique, a margin of 0.5–1.0 cm is outlined with angled corners to facilitate processing. A peripheral strip of tissue 2–4 cm wide is excised and processed for evaluation of permanent sections. The residual tumor is subsequently excised in a directed fashion based on mapping. There were no recurrences in 35 patients at 2 years.

Ten years’ experience using the Johnson square procedure for lentigo maligna. Smith H, Olabi B, Lam M, et al. Brit J Dermatol 2019; 181: 602–4.

In the UK, between July 2007 and July 2017, 44 biopsy-confirmed, ill-defined head and neck LM/LMM from 43 patients (median age 75 years [range 49–92]; male-to-female ratio 27:16) underwent the Johnson square procedure. Of these lesions, 25

were cleared with one stage, 15 with two stages, one with three stages, and three with four stages (1 lesion extended beyond the mucosal surface of the left inner canthus making margin control impossible). Therefore, 73% (32 lesions) required more than a standard 5-mm margin to clear. Clearance rate reported as 97.7%. No patients with completely excised lesions were rereferred during the 10-year study period.

Mohs micrographic surgery is accurate 95.1% of the time for melanoma in situ: a prospective study of 167 cases. Bene NI, Healy C, Coldiron BM. *Dermatol Surg* 2008; 34: 660–4.

Patients ($n = 116$) with MIS in sun-exposed skin of LMM type were treated by Mohs micrographic surgery (MMS) with subsequent evaluation of the final margin with paraffin-embedded sections that were cut en face over a period of 12 years (mean follow-up, 50 months; median 48 months; 594.5 patient-years). The clearance rate by MMS technique using frozen sections was 94.1% for the MIS LM type. The cure rate was 99.0% for the MIS LM type.

MMS is a viable option for treatment of MIS that may increase cure rate and reduce the size of the defect, especially in cosmetically and functionally sensitive areas.

Conventional surgery compared with slow Mohs micrographic surgery in the treatment of lentigo maligna: a retrospective study of 62 cases. Hilari H, Llorca D, Traves V, et al. *Actas Dermosifiliogr* 2012; 103: 614–23.

A review of the clinical records of patients with LM of the head treated definitively with conventional surgical excision or slow MMS. Surgical margins larger than 0.5 cm were required in 69.2% of recurrent LM and in 26.5% of primary LM. Factors associated with the need for wider margins were prior treatment that might have interfered with the clinical delineation of the border, lesions in the center of the face, and skin phototypes III–V. Surgical margins of 0.5 cm are inadequate for the treatment of a considerable number of LM lesions located on the head, particularly if these are recurrent. Slow MMS using paraffin-embedded sections appears to be the treatment of choice in such cases, particularly for recurrent lesions or lesions with poorly defined borders or possible subclinical extension.

A potential disadvantage of relying on 'slow Mohs' is the amount of time added to each procedure. In addition, the technique depends on off-site tissue processing and interpretation, thereby magnifying the possibility of error.

Upstaging of melanoma in situ and lentigo maligna [on sun-damaged skin] treated with Mohs micrographic surgery rarely results in additional surgical management. Levoska MA, Schmults CD, Waldman AH. *Arch Dermatol Res* 2020; doi: 10.1007/s00403-020-02034-9.

A retrospective chart review of 117 MIS/LM lesions treated with MMS at Brigham and Women's Hospital revealed a low rate of tumor upstaging (8.5% or 10/117) and only 1.7% (2/117) required wide local incision and sentinel lymph node.

Five-year outcomes of wide excision and Mohs micrographic surgery for primary lentigo maligna in an academic practice cohort. Hou JL, Reed KB, Knudson RM, et al. *Dermatol Surg* 2015; 41: 211–8.

In total, 423 LM lesions were treated with either wide excision (269) or Mohs (154). Recurrence rates were 1.9% for the Mohs-treated group and 5.9% for the wide excision group. The study concluded that Mohs surgery may offer increased cure rates and avoid the need for repeat surgery and thus may be the preferred treatment for LM.

Geometric staged excision for the treatment of lentigo maligna and lentigo maligna melanoma: a long-term experience with literature review. Abdelmalek M, Loosemore MP, Hurt MA, et al. *Arch Dermatol* 2012; 148: 599–604.

Patients with a diagnosis of LM and LMM treated by staged excision from 1999 to 2007 were included in this retrospective review. The rate of recurrence after geometric staged excision was 1.7% (4 of 239), with a mean of 32.3 months of follow-up. The mean margin to clearance after excision was 6.6 mm for LM and 8.2 mm for LMM. A total of 11.7% of LMM was initially diagnosed as LM on biopsy, with the invasive component discovered during the excision.

Intraoperative real-time reflectance confocal microscopy for guiding surgical margins of lentigo maligna melanoma. Hibler BP, Cordova M, Wong RJ, et al. *Dermatol Surg* 2015; 41: 980–3.

This case study demonstrates the utility of RCM in augmenting the management of LM. It may be used to guide surgical management to verify surgical margins to decrease patient morbidity. Initial cost and the associated learning curve are limitations to widespread use of the technology.

Videodermoscopy-assisted Mohs micrographic surgery vs other treatments for lentigo maligna in 54 patients with a long-term follow-up. Dika E, Fanti PA, Christman H, et al. *J Eur Acad Dermatol Venereol* 2016; 30: 1440–1.

Patients were divided into three groups: standard excision, MMS, and videodermoscopy-assisted MMS. Videodermoscopy-assisted MMS was used to evaluate all margins, and additional excision was performed where positive for frozen sections. Videodermoscopy-assisted MMS reduced the number of steps and overall timing of the surgical procedure. Recurrence was 24% for standard excision, 5% of MMS, and 0% in the videodermoscopy-assisted MMS group.

AAD/ACMS/ASDSA/ASMS 2012 appropriate use criteria for Mohs micrographic surgery: a report of the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery. Connolly SM, Baker DR, Coldiron BM, et al. *J Am Acad Dermatol* 2012; 67: 531–50.

Of all the clinical scenarios for LM as determined by this consortium, five were deemed appropriate for Mohs surgery, one uncertain, and zero inappropriate with consensus reached for all scenarios. MMS was deemed appropriate for primary LM in areas H and M (face, genitalia, hands, feet, nails, pretibial surface, ankles, areolae) for healthy and immunocompromised patients. Locally recurrent LM was rated appropriate for MMS in all body locations for both healthy and immunocompromised patients. The use of MMS for primary LM in healthy or immunocompromised patients was determined to be uncertain when located on area L (trunk and extremities excluding pretibial, hands, feet, nails, ankles).

Mohs micrographic surgery for melanoma: a prospective multicenter study. Ellison PM, Zitelli JA, Brodland DG. *J Amer Acad Dermatol* 2019; 81: 767–74.

A prospective, multicenter, cohort study of 562 melanomas treated with MMS with melanoma antigen recognized by T cells 1 (MART-1) immunostaining. The authors found that primary melanomas, both invasive and non-invasive, located on trunk and extremities achieved histologically negative margins in 97% of tumors with 10-mm margins. In the case of head and neck melanomas, 12-mm margins were needed to achieve histologically

negative margins in 97% of tumors. MMS paired with MART-1 staining is well suited to achieve histologically negative margins, especially when treating cosmetically or functionally demanding areas, e.g. head, neck, hands, feet, and genitalia. It is well documented that melanoma may grow with clinically invisible, amelanotic extensions, thereby necessitating comprehensive margin evaluation. Ultimately, they concluded that MMS with melanoma with MART-1 staining safely and cost-effectively provides tissue conservation and same-day reconstruction of histologically proven tumor-free margins.

Second-Line Therapies

- Radiation therapy **D**
- Cryotherapy **D**

Radiotherapy for lentigo maligna: a literature review and recommendations for treatment. Fogarty GB, Scolyer RA, Lin E, et al. *Br J Dermatol* 2013; 170: 52–8.

Nine studies described 537 patients with LM treated with definitive primary radiotherapy. There was a 5% recurrence rate of 349 assessable patients. Salvage was successful in most recurrent cases. Progression to LMM occurred in five patients. Marginal and in-field recurrence rates were 4% and 5%, respectively. Median study follow-up was 3 years.

Experience with treating lentigo maligna with definitive radiotherapy. Fogarty GB, Hong A, Economides A, et al. *Dermatol Res and Pract* 2018; 2018: 1–11.

This review covers how to properly plan and manage side effects of radiotherapy (RT). The article comprises sections that highlight the necessary decisions if contemplating radiotherapy as a definitive treatment of LM: whether or not the patient is a good surgical candidate; other patient/treatment factors (performance/fitness, ability to tolerate course, life expectancy, immune system health, previous therapies, e.g., radiation or surgery); tumor factors (size, location, proximity to radiation-sensitive structures); treatment-planning considerations (depth of penetration as 5 mm is needed for treatment, proximity to vital structures, department limitations, ability to abide by the 'inverse square law' of radiotherapy); optimal modalities (avoiding grenz rays and using external beam radiotherapy [EBRT] or superficial radiotherapy [SXRT] to achieve the appropriate penetration); proper dose and fractionation (avoiding excessive tissue fibrosis); simulation to optimize treatment outcomes (oral exam by dentist, following computed tomogram protocol scanning, which is typically 10 cm above and below clinical target volume except for specific locations and types of RT); treatment schedule (RT delivered 5 days a week with no more than 4 days' break during treatments, with a minimum of three fractions per week for LM; reviewing treatments weekly, measure bodyweight weekly, ensure adequate nutrition); optimizing skin care (using moisturizer at the beginning of treatment to delay onset of acute normal skin effects, e.g., erythema, desquamation, etc., avoiding antibiotics for presumed cellulitis, replacing moisturizer with moist barrier cream, e.g., benzoyl peroxide, nasal packing + intranasal shields to avoid damage to nasal mucosa, application of vitamin E in an oil-based cream, Vaseline to prevent bleeding of nasal mucosa); appropriate follow-up (determine LM clearance at 6 months).

Grenz ray treatment of lentigo maligna and early lentigo maligna melanoma. Hedblad MA, Mallbris L. *J Am Acad Dermatol* 2012; 67: 60–8.

In total, 593 patients were treated with grenz rays (GR) (primary therapy, $n=350$; partial excision followed by GR, $n=71$; radical excision followed by GR as recurrence-prophylactic treatment, $n=172$) at Karolinska University Hospital, Stockholm, Sweden between 1990 and 2009. The treatment was given twice a week over three consecutive weeks in total doses of 100–160 Gy. Dosage depended on the stage of LM and the depth of perianal atypical melanocytic extension in histologically examined materials before treatment. Follow-up occurred for at least 2 years in 425 patients and, of these, 241 were followed-up for 5 years. Overall, 520 of 593 patients (88%) showed complete clearance after one fractionated treatment. Residual lesions were seen in 15 patients, and 58 patients relapsed, 53 of whom (72%) within 2 years.

One of the advantages of this soft X-ray or Miescher technique is exclusion of underlying bone and minimization of risk of bony necrosis. The potential disadvantage is inadequate depth of penetration.

Cryosurgery for lentigo maligna. Kuflik E, Gage A. *J Am Acad Dermatol* 1994; 31: 75–8.

Thirty white patients were treated with cryosurgery. The lesions ranged from 1.3–4.5 cm in diameter. Treatment consisted of freezing with liquid nitrogen delivered by open spray. Lesions recurred in two patients, yielding a recurrence rate of 6.6% during the average follow-up period of 3 years. The two recurrent lesions were successfully re-treated with cryosurgery. Eleven patients observed for more than 5 years showed no recurrence.

Third-Line Therapies

- Q-switched ruby laser **E**
- Q-switched neodymium-doped yttrium-aluminum-garnet laser **D**
- CO₂ laser **D**
- Interferon- α **D, E**
- Imiquimod **D**
- Tazarotene **E**
- Photodynamic therapy **D**
- Combination therapy **D**

Q-switched neodymium:yttrium-aluminum-garnet laser treatment of lentigo maligna. Orten SS, Waner M, Dinehart SM, et al. *Otolaryngol Head Neck Surg* 1999; 120: 296–302.

Eight patients with LM were treated with the neodymium-doped yttrium-aluminum-garnet laser. Three patients were treated with both 532 and 1064 nm. Two of these had complete eradication without recurrence at 3.5 years. The other showed a partial response but died of unrelated causes before completion of therapy.

The Nd:YAG laser emits energy at 532 nm and 1064 nm, which may be especially suited to LM. Melanin has greater absorption at 532 nm, whereas the longer wavelength, 1064 nm, may provide deeper penetration.

Lentigo maligna – outcomes of treatment with Q-switched Nd:YAG and alexandrite lasers. Madan V, August PJ. *Dermatol Surg* 2009; 35: 607–11.

This study evaluated the use of the aforementioned lasers for treatment of LM in patients unsuitable for surgical management. Complete clinical response was seen in 12 patients after 1–4 treatments and a follow-up of 2–5 years after last treatment. This treatment yielded long-term clearance in only 12 of the 22 patients, but presented a modality that is both simple and quick

and that provides excellent cosmesis. The authors conclude that this treatment is also especially suited for elderly people, large lesions, or in patients who refuse surgical treatment.

Carbon dioxide laser treatment for lentigo maligna: a retrospective review comparing 3 different treatment modalities. Lee H, Sowerby LJ, Temple CL, et al. *Arch Facial Plast Surg* 2011; 13: 398–403.

This study included 73 patients aged 39–93 years (mean age, 64.8 years). Of these, 27 patients were treated with surgical excision, 31 patients with radiation therapy, and 15 patients with CO₂ laser ablation. The median follow-up times were 16.6 months for surgical excision, 46.3 months for radiation therapy, and 77.8 months for CO₂ laser ablation ($p < 0.001$). Recurrence rates by treatment modality were 4.2% (1 of 27) for surgical excision, 29.0% (9 of 31) for radiation therapy, and 6.7% (1 of 15) for CO₂ laser ablation. A trend toward lower recurrence rates with surgical excision and CO₂ laser ablation was identified, but the results were not statistically significant.

CO₂ laser ablation may have a role as an alternative treatment for lentigo maligna among patients in whom standard treatments, such as surgical excision and radiation therapy, are declined or carry significant morbidity.

Intralesional interferon treatment of lentigo maligna. Cornejo P, Vanaclocha F, Polimon I, et al. *Arch Dermatol* 2000; 136: 428–30.

Interferon- α effects both immunomodulation and direct antiproliferative effects. Successful treatment of 11 LM lesions in 10 patients at doses of 3×10^6 to 6×10^6 IU administered three times weekly is reported, with clearance in all patients after 12–29 doses.

A quantitative systematic review of the efficacy of imiquimod monotherapy for lentigo maligna and an analysis of factors that affect tumor clearance. Mora AN, Karia PS, Nguyen BM. *J Am Acad Dermatol* 2015; 73: 205–12.

This systematic review based on 347 tumors from 45 studies revealed histologic and clinical clearance rates to be 76.2% and 78.3%, respectively. The incidence of clinical recurrence was 2.3% with a mean follow-up of 34 months. Treatment with more than 60 total applications or more than five applications per week was associated with a higher likelihood of clearance.

Imiquimod 5% cream as primary or adjuvant therapy for melanoma in situ, lentigo maligna type. Swetter SM, Chen FW, Kim DD, et al. *J Am Acad Dermatol* 2015; 72: 1047–53.

Fifty-eight cases analyzed for local recurrence after topical imiquimod 5% treatment for either primary therapy or adjuvant after narrow-margin excision. In this study 86.2% demonstrated clinical clearance at mean follow-up of 42.1 months; 72.7% primary and 94.4% adjuvant. Imiquimod cream appears to be a viable option for primary or adjuvant treatment of LM in patients who are poor surgical candidates.

Rate of recurrence of lentigo maligna treated with off-label neoadjuvant topical imiquimod, 5%, cream prior to conservatively staged excision. Donigan JM, Hyde MA, Goldgar DE, et al. *JAMA Dermatol* 2018; 154: 885–9.

This retrospective review of 334 patients (345 biopsy-confirmed LM tumors) who were pretreated with imiquimod prior to staged excisions (starting at 2 mm) from 2004 to 2012 set out to

examine the rate of recurrence of LM under the aforementioned treatment conditions. Patients were treated with 5% imiquimod cream 5 nights per week for 2–3 months. Those found to have an inadequate inflammatory response were given tazarotene 0.1% gel two times a week to supplement the response. There was a 3.9% ($n = 12$) rate of recurrence, a mean time to recurrence of 4.3 years, and a mean length of follow-up of 5.5 years. The authors concluded that neoadjuvant topical imiquimod therapy allowed for negative histologic margins (median final margin of 2 mm) and similar rate of recurrence to that of standard staged excision, e.g., Mohs.

Treatment of lentigo maligna with tazarotene 0.1% gel. Chimenti S, Carrozzo AM, Citarella L, et al. *J Am Acad Dermatol* 2004; 50: 101–3.

In this series, two elderly patients with facial LM were treated with daily application of tazarotene gel 0.1% for 6–8 months. No recurrence in either patient was observed after follow-up periods of 18 and 30 months, respectively. These results should be interpreted with caution, considering the relatively short follow-up.

A randomized trial of the off-label use of imiquimod, 5%, cream with vs without tazarotene, 0.1%, gel for the treatment of lentigo maligna, followed by conservative staged excisions. Hyde MA, Hadley ML, Tristani-Firouzi P, et al. *Arch Dermatol* 2012; 148: 592–6.

This prospective, randomized study assessed response rates of LM patients who received imiquimod alone vs. imiquimod + topical tazarotene. A group of 90 patients (91 LMs) were randomized into two groups. All patients underwent staged excisions and frozen section analysis with Melan-A immunostaining to confirm negative margins. Sixty-four percent ($n = 27$) of the monotherapy group achieved a complete response, whereas 78% ($n = 37$) of the combination therapy achieved a complete response. Despite this difference not being statistically significant ($p = 0.17$), there have been no recurrences withing a 42-month follow-up period. The authors concluded that combination treatment may confer a modest benefit and would likely not be harmful to the patient. However, total reliance on topical imiquimod treatment as an alternative to surgery is not wholeheartedly recommended and may place the patient at an increased risk of total recurrence.

Pretreating LM with imiquimod 5% cream may decrease surgical defect sizes; however, total reliance on topical imiquimod as an alternative to surgery may put the patient at increased risk of a local recurrence.

A two-staged treatment of lentigo maligna using ablative laser therapy followed by imiquimod: excellent cosmesis, but frequent recurrences on the nose. Greveling K, de Vries K, van Doorn MB, et al. *Br J Dermatol* 2016; 174: 1134–6.

Retrospective study of ablative laser therapy followed by 6 weeks of topical imiquimod 5% cream (5 days/week). Thirty-five patients were treated with median follow-up of 42 and 14 months for different cohorts. A strong inflammatory response was found in 100% of the subjects in contrast to imiquimod monotherapy where there were non-responders. After 2 and 3 years of follow-up, cumulative incidence of recurrence was 23.5%, with five of six being on the nose. Patient self-rated cosmetic outcome was 8.5/10.

The use of photodynamic therapy in the treatment of lentigo maligna. Karam A, Simon M, Lemasson G, et al. *Pigment Cell Melanoma Res* 2013; 26: 275–7.

This study included 15 cases from a retrospective, single-center review of patients with LM on the face. Patients underwent aminolevulinate treatment before red light therapy (40–90J/cm²) from three to nine sessions at 3-week intervals. Initial clinical evaluation occurred after three sessions, and three immediate failures were observed. Clinical and histologic healing was observed in the other patients with a 10- to 29-month follow-up.

Immunocryosurgery as monotherapy for lentigo maligna or combined with surgical excision for lentigo maligna melanoma. Matas-Nadal C, Soria X, Garcia-De-La-Fuente MR, et al. *J Dermatol* 2018; 45: 564–70.

This prospective case series looks at three patients who undergo immunocryosurgery, rather than complete surgical excision,

because they were poor (standard surgery) surgical candidates. The authors note that the rationale for this limited surgical resection is based on the fact that tumor cryoablation releases tumor antigens that trigger the systemic antitumor immune response, which, in turn, is enhanced by the TLR-7 agonist imiquimod (Redondo, et al. *JID* 2007). The three patients successfully underwent their respective procedures and were found to be disease free at 48 months (84-year-old female with suborbital LM), 42 months (66-year-old female with forehead LM), and 41 months (87-year-old female with malar LM). The authors consider immunocryosurgery as a suitable treatment alternative for LM, or even LMM, in that it provides good therapeutic, functional, and cosmetic results in candidates who cannot undergo standard surgical treatment.

Leprosy (including reactions)

Anne E. Burdick, Ivan D. Camacho



Leprosy, or Hansen disease (HD), is an infection caused by *Mycobacterium leprae*, affecting the skin, respiratory mucosa, peripheral nerves, and other organs. The cardinal features are anesthetic skin lesions, enlarged peripheral nerves, and peripheral neuropathy with acid-fast bacilli (AFB) in tissue biopsies or skin slit smears. Paucibacillary (PB) cases include tuberculoid (TT), borderline tuberculoid (BT) (see figure), and indeterminate (I); multibacillary (MB) cases include midborderline (BB), borderline lepromatous (BL), and lepromatous (LL). A patient's cell-mediated immunity against *M. leprae* determines the presentation of leprosy. A patient with TT leprosy has high cell-mediated immunity to *M. leprae* and 1–5 well-demarcated lesions located on cooler parts of the body. A patient with LL leprosy has low cell-mediated immunity to *M. leprae* and numerous disseminated infiltrated erythematous papules, plaques, and nodules, often presenting with peripheral neuropathy. BB leprosy patients have multiple annular plaques. On biopsy, TT lesions reveal rare and sometimes absence of AFB; polymerase chain reaction (PCR) may be positive for *M. leprae* or *M. lepromatosis*. LL lesions have innumerable AFB. Indeterminate (I) leprosy presents as a single or a few hypopigmented patches that tend to resolve spontaneously but may progress to leprosy anywhere on the spectrum. Pure neural leprosy is limited to peripheral nerve involvement without skin lesions.

Leprosy reactions occur in 25–50% of patients before, during, or after treatment. BT, BB, and BL patients may develop a delayed hypersensitivity reaction, a type 1 'reversal' reaction, with the reappearance of red edematous lesions and an acute peripheral neuritis. Patients on etanercept, infliximab, and adalimumab may manifest leprosy and a type 1 reversal reaction if they have concomitant subclinical leprosy. HIV patients may develop BT lesions and a type 1 reversal reaction as an immune reconstitution inflammatory syndrome within 6 months of starting highly active antiretroviral therapy if they also have a subclinical leprosy infection.

Erythema nodosum leprosum, a type 2 reaction, is an immune complex reaction that develops in BL and LL cases. In a type 2 reaction, crops of new red, indurated, tender papules, plaques, or nodules develop, usually with fever and occasionally with iritis or

orchitis. Lucio phenomenon, a rare vasculitic reaction, presents as tender purpuric and necrotic lesions in BL and LL cases.

MANAGEMENT STRATEGY

Since 2018, the World Health Organization (WHO) recommends **multidrug therapy** (MDT) with *rifampicin* 600 mg monthly, *dapsone* 100 mg daily, and *clofazimine* 300 mg monthly and 50 mg daily for all forms of leprosy to avoid undertreating multibacillary patients misclassified as having paucibacillary disease. This uniform regimen varies in duration depending on the type of leprosy: 6 months for paucibacillary HD and 12 months for multibacillary HD.

The US National Hansen's Disease Program (NHDP) recommends *rifampin* 600 mg daily and *dapsone* 100 mg daily for 12 months for paucibacillary HD and *rifampin* 600 mg daily, *dapsone* 100 mg daily, and *clofazimine* 50 mg daily for 24 months for multibacillary HD. In the US, clofazimine is available only through the NHDP as an investigational drug.

If clofazimine is not available or declined due to skin hyperpigmentation, or if a patient cannot take rifampicin or dapsone, alternative antibiotics are *minocycline* 100 mg, *ofloxacin* 400 mg, *levofloxacin* 500 mg, *clarithromycin* 500 mg, or *moxifloxacin* 400 mg, all in daily doses. Rifampicin is often prescribed monthly for patients on prednisone, warfarin, oral contraceptives, and other drugs with metabolism affected by rifampicin. If multidrug therapy is interrupted for any reason, it should be resumed when possible for the remaining months required to complete the recommended duration of multidrug therapy.

Multidrug therapy should be continued during reactions. Mild type 1 reversal reactions and type 2 reactions are treated with *non-steroidal antiinflammatory drugs*. For a severe type 1 reversal reaction with acute neuritis, particularly involving the face, aggressive therapy with systemic steroids is started to prevent potentially irreversible nerve damage. *Prednisone* 0.5–1 mg/kg daily should be started and a steroid-sparing immunosuppressive drug such as methotrexate (10–20 mg weekly) should be added promptly since high doses of steroids are required to control a type 1 reversal reaction. Immunosuppressant therapy is needed for 3–6 months or longer depending on the patient's response.

A severe type 2 reaction also responds to prednisone 0.5–1 mg/kg daily and often requires a slower taper of 6 months or longer. *Thalidomide*, a known teratogen, is the drug of choice for men and for women who are postmenopausal, surgically sterile, or using appropriate contraceptives. The initial *thalidomide* dose ranges from 100–200 mg nightly depending on the type 2 reaction severity. The dose is decreased slowly over several months to a maintenance dose of 50–100 mg nightly to prevent recurrences. Other drugs for type 2 reaction include *methotrexate*, *azathioprine*, *infliximab*, and *etanercept*. Lucio phenomenon is treated with prednisone, low-dose aspirin, and wound care.

Leprosy clinics are usually free and at WHO clinics compliance is monitored by attendance to witness the intake of monthly medications. After completion of MDT, PB cases are screened once and MB cases annually for 5 years. Household contacts, who lived with a leprosy patient during the 3 years before HD therapy, should have one screening examination and if negative no follow-up exam is needed. WHO advises that a single 600 mg dose of *rifampicin* may be used as leprosy preventive treatment for contacts of leprosy patients (adults and children aged 2 years and above) after excluding leprosy and tuberculosis disease, and in the absence of other contraindications.

For leprosy neuropathy and neuritis, *gabapentin*, *pregabalin*, or *amitriptyline* alleviate the pain.

Specific Investigations

- Skin biopsy from periphery of lesion for diagnosis
- Slit skin smears (WHO recommendation)
- PCR (if available)
- Neurosensory testing
- Chemistry panel, complete blood count
- Glucose-6-phosphate dehydrogenase level before dapsone
- Urinalysis (during a type 2 reaction)
- Purified protein derivative (PPD) or QuantiFERON Gold before immunosuppressant drugs added

First-Line Therapies

- Rifampicin, dapsone, clofazimine (paucibacillary and multibacillary) **B**
- Clofazimine (in high doses, for type 2 reaction) **B**
- Methotrexate (type 1 reversal reaction and type 2 reaction) **B**
- Non-steroidal antiinflammatory drugs (type 1 reversal reaction and type 2 reaction) **D**
- Prednisone (type 1 reversal reaction and type 2 reaction) **D**
- Thalidomide (type 2 reaction) **D**

Management guidelines from the US NHDP and WHO. Health Resources & Services Administration. 2020. NHDP Guide to the Management of Hansen's Disease. <https://www.hrsa.gov/sites/default/files/hrsa/hansens-disease/pdfs/hd-guide-management.pdf>.

Guidelines for the diagnosis, treatment and prevention of leprosy. World Health Organization. Regional Office South-East Asia. 2018. <https://apps.who.int/iris/handle/10665/274127>.

Leprosy: forgotten, but not gone (yet). Dinubile MJ, Keystone JS. *Int J Dermatol* 2011; 50: 1024–6.

Comparison of type 1 reversal reaction and type 2 reaction features.

Human immunodeficiency virus and leprosy: an update. Lockwood DN, Lambert SM. *Dermatol Clin* 2011; 29: 125–8.

The role of thalidomide in the management of erythema nodosum leprosum. Walker SL, Waters ME, Lockwood DN. *Lepr Rev* 2007; 78: 197–215.

Secondary leprosy infection in a patient with psoriasis during treatment with infliximab. Teixeira FM, Vasconcelos LM, Rola Cde A, et al. *J Clin Rheumatol* 2011; 17: 269–71.

A psoriatic man on infliximab for 2 years developed BL lesions and neuropathy.

Leprosy reaction manifesting after discontinuation of adalimumab therapy. Camacho ID, Valencia I, Rivas MP, et al. *Arch Dermatol* 2009; 145: 349–51.

An undiagnosed BT patient presented with a type 1 reversal reaction after discontinuing adalimumab 5 weeks prior for presumed seronegative arthritis.

Second-Line Therapies

- Minocycline, levofloxacin, ofloxacin, clarithromycin, moxifloxacin **B**
- Cyclosporin (type 1 reversal reaction) **D**
- Azathioprine (type 2 reaction) **D**
- Infliximab (type 2 reaction) **D**
- Etanercept (type 2 reaction) **D**
- Gabapentin or pregabalin (neuropathy and neuritis) **D**
- Amitriptyline (neuropathy and neuritis) **D**

Response to cyclosporine treatment in Ethiopian and Nepali patients with severe leprosy type 1 reactions. Marlowe SN, Leekassa R, Bizuneh E, et al. *Trans R Soc Trop Med Hyg* 2007; 101: 1004–12.

Forty-one patients with type 1 reversal reaction treated with cyclosporin 5–7.5 mg/kg/day for 12 weeks had 67–100% improvement after 24 weeks. Neuritis recurred when discontinued.

Using methotrexate to treat patients with ENL unresponsive to steroids and clofazimine: a report on 9 patients. Hossain D. *Lepr Rev* 2013; 82: 105–12.

Nine patients with type 2 erythema nodosum leprosum (ENL) resistant to prednisone and clofazimine responded well to prednisolone (30–40 mg/day for 3–6 months, then dose was halved and tapered slowly over 2.5–3 years) with methotrexate (7.5 mg weekly for 24–36 months). Patients remained relapse free for 2.5 years.

Methotrexate treatment for type 1 (reversal) leprosy reactions. Biosca G, Casallo S, López-Vélez R. *Clin Infect Dis* 2007; 45: e7–9.

A BL patient with type 1 reversal reaction and poor tolerance to corticosteroids responded to methotrexate 7.5 mg weekly. Prednisone was stopped in 2 months, and lesions resolved in 6 months.

Methotrexate in resistant ENL. Kar BR, Babu R. *Int J Lepr Other Mycobact Dis* 2004; 72: 480–2.

A patient with a type 2 reaction unresponsive to prednisolone 50 mg daily improved with methotrexate 15 mg weekly for 2 weeks. Prednisolone was tapered to 20 mg daily with continued improvement on methotrexate 7.5 mg weekly.

Azathioprine as a steroid sparing agent in leprosy type 2 reactions: report of nine cases. Duraes SM, Salles SA, Leite VR, et al. *Lepr Rev* 2011; 82: 304–9.

Review of nine reports of type 2 reaction cases refractory to prednisone and clofazimine responding to azathioprine 2–3 mg/kg/day. The prednisone dose was decreased in 4 weeks and halved after 12 weeks with fewer type 2 reactions.

Clinical outcomes in a randomized controlled study comparing azathioprine and prednisolone versus prednisolone alone in the treatment of severe leprosy type 1 reactions in Nepal. Marlowe SN, Hawksworth RA, Butlin CR, et al. *Trans R Soc Trop Med Hyg* 2004; 98: 602–9.

Forty patients with type 1 reversal reaction randomized to prednisolone 40 mg daily vs. prednisolone 40 mg daily with azathioprine 3 mg/kg daily for 12 weeks had no difference in outcome.

Biologics in leprosy: a systematic review and case report. Cogen AL, Lebas E, De Barros B, et al. Am J Trop Med Hyg 2020; 102(5): 1131–6.

TNF- α inhibitors may be a risk factor for developing leprosy or reactivating subclinical infections. *Infliximab* and *etanercept* have demonstrated effectiveness in treating ENL.

Severe refractory erythema nodosum leprosum successfully treated with the tumor necrosis factor inhibitor etanercept. Ramien ML, Wong A, Keystone JS. Clin Infect Dis 2011; 52: e133–5.

An LL patient who had type 2 reactions for 6 years despite daily thalidomide 100 mg and multiple courses of 40–60 mg/day of prednisone improved on etanercept 50 mg subcutaneously weekly for 6 weeks. Prednisone and thalidomide were stopped in 6 months.

Treatment of recurrent erythema nodosum leprosum with infliximab. Faber WR, Jensema AJ, Goldschmidt WF. N Engl J Med 2006; 355: 739.

A BL patient with type 2 reaction multidrug therapy refractory to daily prednisolone 40 mg and thalidomide 300 mg responded promptly to three doses of infliximab 5 mg/kg every other week with no recurrence for 1 year after the last dose.

Apremilast in chronic recalcitrant erythema nodosum leprosum: a report of two cases. Narang T, Kaushik A, Dogra S. Br J Dermatol 2019 Jun 19.

Two patients with severe ENL responded to the phosphodiesterase-4 inhibitor apremilast after failing steroids and clofazimine. Thalidomide was contraindicated.

Leukocytoclastic vasculitis (cutaneous small vessel vasculitis)

Nicole Fett, Jeffrey P. Callen



Leukocytoclastic vasculitis (LCV) is a histological term that denotes vasculitis of small vessels (capillaries and postcapillary venules). LCV is the histological presentation of cryoglobulinemic vasculitis, IgA vasculitis, normocomplementemic and hypocomplementemic urticarial vasculitis, vasculitis that may be associated with systemic disease (systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, inflammatory bowel disease, etc.), vasculitis associated with a probable etiology (drugs, infections), IgM/IgG vasculitis, nodular vasculitis, erythema elevatum diutinum, hypergammaglobulinemic macular vasculitis, and sometimes with ANCA-associated vasculitides (AAV) including microscopic polyangiitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis. Clinically, LCV may present as palpable purpura, urticarial papules or plaques, nodules, hemorrhagic bullae, or superficial ulceration. Given the broad range of diagnoses that present with LCV, careful evaluation for systemic involvement is necessary. Although histopathologically patients with AAV most commonly present with LCV, the management of AAV is beyond the scope of this chapter.

Nomenclature of cutaneous: dermatologic addendum to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Sunderkotter CH, Zegler B, Chen KR, et al. *Arthritis Rheumatol* 2018; 70(2): 171–84.

MANAGEMENT STRATEGY

Management of LCV requires evaluation for systemic involvement, removal of potential causative agents or treatment directed at associated diseases, management of symptoms in those patients with self-limiting disease, and targeted or empiric therapy for patients with recurrent or recalcitrant disease. Patients with systemic vasculitis, particularly when involving the kidneys, lungs, or central nervous system, require immediate referral to rheumatology, nephrology, or other specialists and frequently require hospitalization for treatment with systemic corticosteroids and immunosuppressive/immunomodulatory agents.

Patients with LCV in whom there is an identifiable cause, such as a drug, are treated symptomatically in addition to removing the presumed causative agent. Symptomatic measures include rest, elevation, gradient support stockings, and antihistamines.

The challenge is to treat the patient who has chronic LCV without a defined etiology and without systemic involvement. In patients with asymptomatic disease who are not bothered by the appearance of their vasculitic lesions, no treatment may be needed. For those patients who develop pain, ulcerations, or psychological distress, the risks and benefits of therapy should be discussed. Treatment recommendations for LCV are largely based on case reports, case series, and expert opinion. If systemic therapy is considered for disease 'confined to the skin', colchicine and dapsone are first-line agents, given their relative safety. Immunosuppressive/immunomodulatory agents including methotrexate and azathioprine have been used in patients who are refractory to colchicine and dapsone. Systemic corticosteroids should be avoided when possible due to the narrow window between therapeutic effect and toxicity.

Specific Investigations

For all patients

- Careful history for drugs, preceding illness, and signs of systemic involvement
- Serologic tests for infectious diseases (hepatitis C, hepatitis B)
- Complete blood count
- Comprehensive blood biochemistry
- Urinalysis

For patients with chronic or recurrent disease

- Skin biopsy of new lesions for routine histopathology and direct immunofluorescence
- Antineutrophil cytoplasmic antibodies (ANCA)
- Antinuclear antibody (ANA), rheumatoid factor, anti-Ro/SS-A, etc.
- Complement levels
- Cryoglobulins
- Immunofixation electrophoresis and serum free light chains

For selected patients

- Urine toxicology screen for cocaine/levamisole
- Chest radiograph
- HIV testing
- Echocardiography
- Visceral angiography
- Malignancy screening tests

The purpose of evaluating the patient with cutaneous vasculitis is to identify a cause of the process and assess for the presence of systemic involvement. The evaluation begins with a careful history and physical examination, followed by selected testing based on the acuteness of the process and the findings from the history and physical examination. Direct immunofluorescence (DIF) is required to differentiate IgA vasculitis, which might be associated with a higher risk of renal involvement, from other causes of LCV.

Cutaneous vasculitis in children and adults: associated diseases and etiologic factors in 303 patients. Blanco R, Martinez-Taboada VM, Rodriguez-Valverde V, et al. *Medicine* 1998; 77: 403–18.

Diagnoses and associated diseases of 172 adults and 131 children who presented to a medical center over a 19-year period. Of the 131 children, only one had a secondary vasculitis. In contrast, approximately 30% of the adults had systemic involvement or secondary vasculitis. The authors therefore recommend less intensive investigations in children than in adults.

A practical approach to the diagnosis, evaluation, and management of cutaneous small-vessel vasculitis. Goeser MR, Lianos V, Wetter DA. *Am J Clin Dermatol* 2014; 15: 299–306.

An approach to the patient with small vessel vasculitis and a very useful algorithm for evaluation and treatment.

Single-organ cutaneous small-vessel vasculitis according to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides: a study of 60 patients from a series of 766 cutaneous vasculitis cases. Loricera J, Blanco R, Ortiz-Sanjuán F, et al. *Rheumatology* 2015; 54: 77–82.

This retrospective review spanning 35 years assessed 766 patients with a diagnosis of cutaneous vasculitis. Of these patients, 60 (7.8%) met the 2012 CHCC definition of single-organ cutaneous small vessel vasculitis (SoCSVV). The etiology of the SoCSVV was medication-related in 52% and infection-related in 34%. Approximately a quarter of patients with SoCSVV were treated with systemic corticosteroids or non-steroidal antiinflammatory drugs (NSAIDs). Complete recovery was noted in all patients within 4 months; however, 8% of them developed recurrence.

First-Line Therapies

• Observation	C
• Removal or withdrawal of the causative agent (e.g., drug)	C
• Treatment of underlying disease process (e.g., systemic lupus erythematosus [SLE], RA, inflammatory bowel disease, infection)	C
• Colchicine	C
• Dapsone	C
• NSAIDs	C

Colchicine in the treatment of cutaneous leukocytoclastic vasculitis: results of a prospective, randomized controlled trial. Sais G, Vidaller A, Jucgla A, et al. *Arch Dermatol* 1995; 131: 1399–402.

Forty subjects with cutaneous small-vessel vasculitis (CSVV) were randomized to receive colchicine or topical emollients. The study was powered to detect a 40% difference between groups. The study failed to detect a statistically significant difference between groups; however, the colchicine-treated group included

all patients who had failed to respond to dapsone and a disproportionate number of subjects who had failed other therapies. Thus, the colchicine arm included patients with more recalcitrant disease, and this may have contributed to the negative result. It was also noted that the subjects' disease flared with withdrawal of the colchicine.

Colchicine is effective in controlling chronic cutaneous leukocytoclastic vasculitis. Callen JP. *J Am Acad Dermatol* 1985; 13: 193–200.

This open-label study involved 13 patients. This is the largest case series of colchicine use in CSVV.

Colchicine use in CSVV is supported by several case reports and case series. An inadvertently imbalanced randomized controlled trial (RCT) of colchicine in CSVV failed to show statistically significant improvement.

Sulfone therapy in the treatment of leukocytoclastic vasculitis. Report of three cases. Fredenberg MF, Malkinson FD. *J Am Acad Dermatol* 1987; 16: 772–8.

Three adult patients with CSVV were successfully treated with moderate doses of dapsone (100–150 mg daily).

Dapsone in Henoch-Schönlein purpura. Sarma PS. *Postgrad Med J* 1994; 70: 464–5.

Case series of six adults with IgA vasculitis treated with dapsone 100 mg daily. Four of six had clearance of arthritis and purpura within 1 week.

Indications and efficiency of dapsone in IgA vasculitis (Henoch-Schönlein purpura): case series and a review of the literature. Roman C, Dima B, Muyschont L, et al. *Eur J Pediatr* 2019; 178(8): 1275–81.

Case series including two children of IgA vasculitis and literature review to include 15 additional cases. All 17 children with refractory cutaneous IgA vasculitis responded to 1 to 2 mg/kg/day of dapsone for 7 days. One patient developed methemoglobinemia. No improvements were noted in systemic manifestations of IgA vasculitis.

The therapeutic response of urticarial vasculitis to indomethacin. Millns JL, Randle HW, Solley GO, et al. *J Am Acad Dermatol* 1980; 3: 349–55.

Open-label trial of 10 patients with urticarial vasculitis (UV) treated with indomethacin 25 mg three times daily to 50 mg four times daily. Six cleared within 17 days. Three had partial improvement.

Two case series report success with indomethacin use.

Second-Line Therapies

• Systemic corticosteroids	A
• Azathioprine	C
• Methotrexate	C
• Cyclosporin	C
• Mycophenolate mofetil	C
• Rituximab (for cryoglobulinemic and hypocomplementemic urticarial vasculitis)	A

Characteristics and management of IgA vasculitis (Henoch-Schönlein) in adults: data from 260 patients included in a French multicenter retrospective survey. Audemard-Verger A, Terrier B, Dechartres A, et al. *Arthritis Rheumatol* 2017; 69(9): 1862–70.

In total, 260 adult patients with IgA vasculitis were treated with combinations of corticosteroids, cyclophosphamide, and colchicine. Patients treated with corticosteroids alone had the highest response rate at 80%. Statistical modeling did not show clear support for the addition of cyclophosphamide to corticosteroids.

Early prednisone therapy in Henoch-Schönlein purpura: a randomized, double-blind, placebo-controlled trial. Ronkainen J, Koskimies O, Ala-Houhala M, et al. *J Pediatr* 2006; 149: 241–7.

A total of 171 children with Henoch-Schönlein purpura (HSP) were randomized to receive 1 mg/kg/day of prednisone for 2 weeks and 2 additional weeks of tapered prednisone versus placebo. The prednisone group had a statistically significant decrease in abdominal and joint pain and renal dysfunction. Prednisone did not prevent the development of renal symptoms. The authors conclude that prednisone may be used in children with HSP to treat abdominal pain, arthritis, and renal involvement.

The clinical and histopathologic spectrums of urticarial vasculitis: study of forty cases. Sanchez NP, Winkelmann RK, Schroeter AL, et al. *J Am Acad Dermatol* 1982; 7: 599–605. Case series of 40 patients with UV. Thirteen of 17 patients treated with prednisone 40 mg daily or greater had complete remission or decreased severity in clinical urticaria.

Chronic urticaria-like lesions in systemic lupus erythematosus. A review of 12 cases. O'Loughlin S, Schroeter AL, Jordon RE. *Arch Dermatol* 1978; 114: 879–83.

Twelve patients with SLE and UV. Ten of 12 treated with prednisone and improved. Doses ranged from 10 mg to 50 mg daily.

Prednisone is essentially uniformly effective in treating all forms of vasculitis; however, its associated morbidity should limit its use to those patients with systemic involvement, severe pain, or cutaneous necrosis.

The clinical spectrum and therapeutic management of hypocomplementemic urticarial vasculitis: data from a French nationwide study of fifty-seven patients. Jachiet M, Flageul B, Deroux A, et al. *Arthritis Rheumatol* 2015; 67: 527–34.

Patients were treated with many different agents, and the study is limited by the lack of untreated controls. Approximate complete response rates were 25% hydroxychloroquine, 18% colchicine, 18% dapsone, 20% corticosteroids, 45% azathioprine, 0% methotrexate, 55% mycophenolate mofetil, 80% ciclosporin, and 70% rituximab.

Azathioprine. An effective, corticosteroid-sparing therapy for patients with recalcitrant cutaneous lupus erythematosus or with recalcitrant cutaneous leukocytoclastic vasculitis. Callen JP, Spencer LV, Burruss JB, et al. *Arch Dermatol* 1991; 127: 515–22.

An open-label trial involving six patients who had failed to respond to 'less toxic' therapies.

Azathioprine therapy for steroid-resistant Henoch-Schönlein purpura: a report of 6 cases. Fotis L, Tuttle PV 4th, Baszis KW, et al. *Pediatr Rheumatol Online J*. 2016; 14(1): 37. doi: 10.1186/s12969-016-0100-x.

Six children with relapsing HSP without significant renal involvement were treated with azathioprine. All patients had relapsing symptoms despite corticosteroid use. They were successfully treated with azathioprine and were tapered off of corticosteroids. The duration of azathioprine therapy ranged from 7–21 months and no adverse events were reported.

Prednisone plus azathioprine treatment in patients with rheumatoid arthritis complicated by vasculitis. Heurkens AH, Westedt ML, Breedveld FC. *Arch Intern Med* 1991; 151: 2249–54.

Twenty-eight patients with rheumatoid arthritis-associated vasculitis were studied. Nine patients with severe systemic vasculitis improved with 60 mg of prednisone and 2 mg/kg/body weight of azathioprine daily. The remaining 19 patients with cutaneous vasculitis were randomized to prednisone plus azathioprine treatment versus continuation of a previous regimen. Although measures of both vasculitis and arthritis activity improved to a greater degree in the patients treated with prednisone plus azathioprine in the first 3 months of therapy, and this therapy was associated with a low incidence of relapse of vasculitis, there was not a statistically significant difference between the two treatment protocols at the end of the follow-up period.

Case reports and series, totaling 21 patients, have been published supporting the use of azathioprine. A randomized alternative-therapy-controlled trial of 19 patients with rheumatoid vasculitis failed to detect a statistically significant difference in number of vasculitic lesions.

Methotrexate in patients with moderate systemic lupus erythematosus (exclusion of renal and central nervous system disease). Gansauge S, Breitbart A, Rinaldi N, et al. *Ann Rheum Dis* 1997; 56: 382–5.

Open-label trial of methotrexate involving 22 patients with SLE. Nine of the 22 patients had vasculitis. Six of nine had resolution of their vasculitis with methotrexate.

Methotrexate use has been reported in 13 patients with CSVV in case reports and series.

Cyclosporin A in the treatment of cutaneous vasculitis. Clinical and cellular effects. Tosca A, Ioannidou DJ, Katsantonis JC, et al. *J EADV* 1996; 6: 135–41.

Twelve patients received 5 mg/kg/day for 2 months and then 2 months of prednisone ranging from 10 mg to 40 mg/day. Five had complete clearance and no relapses over a follow-up time of 4–12 months. Six responded but then relapsed during a follow-up range of 4–20 months.

Treatment of complicated Henoch-Schönlein purpura with mycophenolate mofetil: a retrospective case series report. Nikibakhsh AA, Mahmoodzadeh H, Karamyyar M, et al. *Int J Rheumatol* 2010; 2010: 5. Article ID: 254316.

Six children with steroid-resistant HSP were treated with mycophenolate mofetil 30 mg/kg/day. Five had improvement in their cutaneous symptoms or were reported to have 'all manifestations resolved'.

Mycophenolate mofetil is effective for maintenance therapy of hypocomplementaemic urticarial vasculitis. Worm M, Sterry W, Kolde G. *Br J Dermatol* 2000; 143: 1324.

Two women were initially treated with cyclophosphamide-dexamethasone and then transitioned to mycophenolate mofetil, 2 g daily. No vasculitis flares occurred during 15 months of maintenance therapy.

Efficacy of mycophenolate is supported by one open-label trial, case reports, and series.

A randomized controlled trial of rituximab following failure of antiviral therapy for hepatitis C-associated cryoglobulinemic vasculitis. Sneller M, Hu Z, Langford CA. *Arthritis Rheum* 2012; 64: 835–42.

Twenty-four patients who failed to improve with antiviral therapy were randomized to rituximab versus standard immunosuppression. Ten patients in the rituximab group (83%) were in remission at study month 6, compared with one patient in the control group (8%) ($p < 0.001$).

A randomized, controlled trial of rituximab for treatment of severe cryoglobulinemic vasculitis. De Vita S, Quartuccio L, Isola M, et al. *Arthritis Rheum* 2012; 64: 843–53.

Fifty-nine patients with CV and related skin ulcers, active glomerulonephritis, or refractory peripheral neuropathy who failed or were not candidates for antiviral therapy were randomized to receive rituximab or conventional treatment (glucocorticoids, cyclophosphamide or azathioprine, and plasma exchange). Rituximab showed statistically significant improvement over conventional treatment in all outcomes.

Retreatment regimen of rituximab monotherapy given at the relapse of severe HCV-related cryoglobulinemic vasculitis: long-term follow up data of a randomized controlled multicenter study. Quartuccio L, Zuliani F, Corazza L, et al. *J Autoimmun* 2015; 63: 88–93.

Retrospective evaluation of the 30 patients randomized to receive rituximab in the 2012 trial. Patients received this as monotherapy for vasculitis flares. After their initial treatment, 43.3% were in complete remission and did not require additional rituximab; 56.7% required at least one retreatment with rituximab. Of those who were retreated, 66% responded to retreatment.

Management of noninfectious mixed cryoglobulinemia vasculitis: data from 242 cases included in the CryoVas survey. Terrier B, Krastinova E, Marie I, et al. *Blood* 2012; 119: 5996–6004.

Retrospective analysis of patients who did not have hepatitis C. Thirty percent had a connective tissue disease, 22% had B-cell lymphoma, and 48% were essential (idiopathic). These authors compared outcomes of patients treated with rituximab plus corticosteroids, those with corticosteroids alone, and those with corticosteroids and immunosuppressive therapies. They found that those treated with rituximab were more likely to achieve complete clinical, serologic, and renal responses and were more likely to be on doses of prednisone below 10 mg/day than those treated with other regimens. However, rituximab-treated patients had more infectious complications (perhaps related to combination with high-dose corticosteroids). The mortality in the groups was identical.

Successful use of rituximab for cutaneous vasculitis. Chung L, Funke AA, Chakravarty EF, et al. *Arch Dermatol* 2006; 142: 1407–10.

Two women with recalcitrant CSVV, one of whom with a history of non-Hodgkin lymphoma, responded to infusions of rituximab.

Rituximab has become standard of care for cryoglobulinemic vasculitis refractory to antiviral therapy based on RCTs. However, with the approval of new antiviral therapies that cure hepatitis C infection in 96–98% of patients, additional therapies for hepatitis C-associated vasculitides may not be needed in the future. Rituximab use in CSVV, including in refractory urticarial vasculitis and IgA vasculitis, is supported by case series.

Third-Line Therapies

• Antihistamines	C
• Pentoxifylline	C
• Plasma exchange	C
• Intravenous immunoglobulin (IVIg)	C
• Infliximab	C
• Tacrolimus	C
• Omalizumab	C
• Anakinra	C

Synergistic effects of pentoxifylline and dapsone in leukocytoclastic vasculitis. Nurnberg W, Grabbe J, Czarnetzki BM. *Lancet* 1994; 343: 491.

Three cases of CSVV that resolved with pentoxifylline (1200 mg/day) and dapsone (100 mg/day).

Chronic leukocytoclastic vasculitis associated with polycythemia vera: effective control with pentoxifylline. Wahba-Yahav AV. *J Am Acad Dermatol* 1992; 26: 1006–7.

A single case improved with pentoxifylline 400 mg three times daily.

Plasma exchange in refractory cutaneous vasculitis. Turner AN, Whittaker S, Banks I, et al. *Br J Dermatol* 1990; 122: 411–5.

Eight patients with intractable CSVV were treated with plasma-exchange therapy. Seven improved.

Case report: steroid sparing effect of intravenous gamma globulin in a child with necrotizing vasculitis. Gedalia A, Correa H, Kaiser M, et al. *Am J Med Sci* 1995; 309: 226–8.

A boy aged 2.5 years with fever, arthritis, and necrotizing CSVV was able to taper off of prednisone after intravenous γ -globulin administration.

Successful treatment of chronic leukocytoclastic vasculitis and persistent ulceration with intravenous immunoglobulin. Ong CS, Benson EM. *Br J Dermatol* 2000; 143: 447–9.

A 24-year-old woman with chronic ulcerating CSVV refractory to multiple immunosuppressants cleared with IVIG.

Therapy for severe necrotizing vasculitis with infliximab. Mang R, Ruzicka T, Stege H. *J Am Acad Dermatol* 2004; 51: 321–2.

A 62-year-old female with chronic ulcerating CSVV refractory to prednisone, IVIG, and topical tacrolimus healed with two infusions of infliximab. Unfortunately, recurrent infections limited further use. It must also be noted that tumor necrosis factor- α therapies have also been reported to cause CSVV.

Response of deep cutaneous vasculitis to infliximab. Uthman IW, Touma Z, Sayyad J, et al. *J Am Acad Dermatol* 2005; 53: 353–4.

A 15-year-old female cleared with infliximab.

Treatment of severe and difficult cases of systemic lupus erythematosus with tacrolimus. A report of three cases. Duddridge M, Powell RJ. *Ann Rheum Dis* 1997; 56: 690–2.

Two of the three had clearing of CSVV.

Treatment of urticarial vasculitis: a systematic review. Kolkhir P, Grakhova M, Bonnekoh H, et al. *J Allergy Clin Immunol* 2019; 143(2): 458–66.

Systematic review of 789 patients with UV. Patients were treated with corticosteroids, dapsone, antihistamines,

hydroxychloroquine, NSAIDs, colchicine, cyclophosphamide, azathioprine, omalizumab, IL-1 blockers, mycophenolate mofetil, methotrexate, rituximab, IVIG, plasmapheresis, ciclosporin, anti-TNF α , tocilizumab, pentoxifylline, and thalidomide, all with varying success.

Lichen myxedematosus

Joslyn S. Kirby, Timothy Makkar



Lichen myxedematosus (LM) is a rare, chronic disease characterized by infiltration of the skin with mucin-producing fibroblasts. Typical examination findings include firm, indurated, shiny, skin-colored to erythematous papules that can coalesce into nodules and plaques. The face, trunk, and/or extremities may be affected. Extensive disease can cause widespread firm, thickened skin, including leonine facies. Typical histopathologic features include diffuse dermal mucin deposition and fibroblast proliferation. LM, typically scleromyxedema, can be associated with systemic sequelae including dysphagia due to esophageal dysmotility, proximal muscle weakness, arthralgia, arthritis, joint contractures, obstructive or restrictive lung disease, cardiac ischemia and cardiomyopathy, macular edema, peripheral neuropathy and dermatoneuro syndrome with encephalopathy, convulsions, coma, and/or psychosis. Thus, it is crucial to evaluate patients for systemic manifestations to distinguish those with a pure cutaneous form of LM from those with a severe form with systemic involvement. Localized forms typically do not have these associations and include acral persistent papular mucinosis, self-healing papular mucinosis, discrete LM, nodular LM, and cutaneous mucinosis of infancy.

MANAGEMENT STRATEGY

The treatment of LM remains a challenge. The absence of controlled studies makes comparison of different drugs or drug regimens difficult.

Localized forms may be observed or treated with topical medications (*topical corticosteroids or calcineurin inhibitors*) or destructive therapies such as *cryotherapy, dermabrasion, or hyaluronidase*.

The systemic form, scleromyxedema, is treated more aggressively and typically requires systemic treatment. *Intravenous immunoglobulin (IVIG)* is the first treatment of choice for patients with scleromyxedema, especially if there is rapid spread of skin disease or deterioration in systemic organ function. The standard dose is 2 g/kg divided, for 4 or 5 days. This is administered every 4 weeks, and once stability is achieved the frequency can be increased to 6 weeks. If there is no improvement after 6 months, then IVIG should be discontinued and an alternate treatment initiated. Given the association between scleromyxedema and monoclonal gammopathy, some therapies for systemic LM parallel the treatment of multiple myeloma. *Melphalan* has shown beneficial results when used alone or in combination with other therapies, including *systemic corticosteroids*, or *autologous stem cell transplant*. Melphalan use is severely limited by adverse effects, including malignancy, sepsis, and death.

Specific Investigations

- Review of systems
- Serum protein electrophoresis
- Thyroid function testing
- Assess risk factors and consider testing for viral hepatitis and/or HIV infection

Lichen myxedematosus: diagnostic criteria, classification, and severity grading. Nofal A, Amer H, Alakad R, et al. *Int J Dermatol* 2017; 56: 284–90.

This group suggests an alternative approach to categorizing LM based on extent of symptoms and cutaneous signs of disease: (1) mild, which has limited or localized cutaneous lesions without systemic symptoms; (2) moderate, which has generalized cutaneous lesions without systemic symptoms; and (3) severe, which includes people with localized or generalized cutaneous lesions and the presence of systemic symptoms. This helps to account for reported cases with localized skin changes and the presence of systemic symptoms as well as extensive skin involvement and the absence of systemic symptoms.

Scleromyxedema. Hummers LK. *Curr Opin Rheumatol* 2014; 26: 658–62.

An abnormal paraprotein is found in most patients (>80%) with scleromyxedema. The monoclonal gammopathy is usually IgG with a predominance of lambda light chains over kappa light chains, while IgM-kappa, IgA-kappa, or IgA-lambda are less frequent. Esophageal dysmotility can affect about 50% and myopathy about 10%–50%. The cause of the disease is unknown, and it must be distinguished from thyroid-related mucinosis. Associations with HIV and hepatitis C virus infections are rare.

Scleromyxedema secondary to hepatitis C virus and successfully treated with antiviral therapy. Smith JA, Kalimullah FA, Erickson CP, et al. *Dermatol Online J* 2015; 21: 9.

Small studies have associated scleromyxedema with hepatitis C infection. This appears more common in Japanese patients. A handful of cases outside Japan have been reported, including this patient who improved with ribavirin and interferon- α_{2b} .

Scleromyxedema and lichen myxedematosus: is it associated with viral hepatitis? Chen K, Tzeng I, Lee Y, et al. *J Dermatology* 2019; 46: 879–85.

A retrospective review of patients with scleromyxedema and LM that analyzed 28 patients. The analysis showed the rate of hepatitis B to be similar among patients and the general population, whereas for hepatitis C the rate was found to be increased 6.5-times relative to the general population.

Scleromyxedema or LM with Systemic Manifestations

First-Line Therapies

• Intravenous immunoglobulin (IVIG)	C
• Thalidomide, lenalidomide	D
• Systemic corticosteroids	D

Clinical and molecular phenotyping in scleromyxedema pre- and post-treatment with intravenous immunoglobulin. Mecoli CA, Talbot CC Jr, Fava A, et al. *Arthritis Care Res* 2019 Apr 22. doi:10.1002/acr.23908.

Fifteen patients with scleromyxedema were treated with IVIG 2 g/kg over a 2–5 day period every 4 weeks. The infusion interval is increased to every 6–12 weeks once improvement in skin flexibility and softening plateaus. Tc17 cells were elevated in the skin and correlated with extent of skin involvement and decreased with IVIG treatment.

High-dose intravenous immunoglobulin therapy for scleromyxedema: a prospective open-label clinical trial using an objective score of clinical evaluation system. Guarneri A, Coin M, Rongioletti F. *J Eur Acad Dermatol Venereol* 2017; 7: 1157–60.

In this trial, eight patients received IVIG 2 g/kg over 4–5 days and repeated monthly for at least 6 months. Patients were followed for 15–87 months. Skin changes improved by approximately 80%. Systemic symptoms improved in all instances, though paraproteinemia was unchanged. *Numerous other case reports and series, including several reports of patients with dermatoneuro syndrome, also demonstrated skin and systemic symptom improvement with IVIG. IVIG has also been shown to be beneficial in combination with several therapies, including systemic corticosteroids, melphalan, and thalidomide.*

Treatment of recalcitrant scleromyxedema with thalidomide in 3 patients. Sansbury J, Cocuroccia B, Jorizzo J, et al. *J Am Acad Dermatol* 2004; 51: 126–31.

Thalidomide is thought to inhibit proinflammatory and profibrotic cytokines. Thalidomide is started at 50–100 mg/day and slowly increased based on clinical response and tolerance to up to 150–400 mg/day. The lowest daily dose to maintain improvement should be used since teratogenicity and irreversible peripheral neuropathy are side effects. Patients should be monitored for peripheral neuropathy. Other potential adverse effects include drowsiness, constipation, thrombosis, and leukopenia. Three patients had marked improvement of cutaneous lesions, joint mobility, and reduction of paraprotein levels. Thalidomide can be used in combination with other therapies such as IVIG, dexamethasone, and chemotherapeutic agents.

Combination of intravenous immunoglobulins and lenalidomide in the treatment of scleromyxedema. Brunet-Possenti

F, Hermine O, Marinho E, et al. *J Am Acad Dermatol* 2013; 69: 319–20.

A few case reports have documented the use of lenalidomide, a thalidomide derivative with a more favorable safety profile. Lenalidomide 25 mg/day for 3 weeks per month appeared beneficial when used in combination with IVIG.

Scleromyxedema: an experience using treatment with systemic corticosteroid and review of the published work. Lin YC, Wang HC, Shen JL. *J Dermatol* 2006; 33: 207–10.

A case report of successful treatment with prednisolone 0.3 mg/kg/day divided four times daily for 1 week then tapered for 3 more weeks. Other studies have successfully used prednisone 60 mg four times daily for 4–6 weeks with gradual taper or pulse dexamethasone. However, other reports demonstrate a mixed success rate with steroids alone. Several case reports show a benefit of combining dexamethasone with bortezomib and/or thalidomide.

Second-Line Therapies

• Melphalan	C
• Autologous stem cell transplantation	D
• Bortezomib (± systemic corticosteroids)	D

Scleromyxedema. Dinneen AM, Dicken CH. *J Am Acad Dermatol* 1995; 33: 37–43.

If first-line therapies are not effective, then treatments aimed at the associated plasma cell dyscrasia can be utilized. In this review of 17 patients treated with melphalan, 12 patients revealed improvement in their cutaneous symptoms. However, eight patients had only temporary improvement; 10 of the treated patients died from complications of the disease or treatment.

Scleromyxedema: role of high-dose melphalan with autologous stem cell transplantation. Donato ML, Feasel AM, Weber DM, et al. *Blood* 2006; 107: 463–6.

All seven patients survived, five had a complete remission of the skin, and visceral disease greatly improved. However, there is a report of a patient with scleromyxedema who developed dermatoneuro syndrome after autologous stem cell transplantation.

Response to bortezomib of a patient with scleromyxedema refractory to other therapies. Migkou M, Gkatzamanidou M, Terpos E, et al. *Leuk Res* 2011; 35: e209–11.

A case report of a patient with a history of numerous unsuccessful treatments treated with 21-day cycles of bortezomib 1.3 mg/m² on days 1, 4, 8, and 11 and dexamethasone 40 mg on days 1–4. The patient experienced sensory peripheral neuropathy after the second cycle, so the bortezomib dose was reduced to 1 mg/m². Eight cycles of bortezomib with dexamethasone were completed with near resolution at 24 months.

The combination of bortezomib and dexamethasone is an efficient therapy for relapsed/refractory scleromyxedema: a rare disease with new clinical insights. Cañueto J, Labrador J, Román C, et al. *Eur J Haematol* 2012; 88: 450–4.

A case report of a patient with relapsed scleromyxedema following autologous stem cell transplant, who responded to bortezomib and dexamethasone. The patient had complete resolution of skin lesions and the monoclonal peak.

Third-Line Therapies

- Plasmapheresis **E**
- Total skin electron beam radiation* **E**

*Reported to improve skin findings, but do not treat systemic disease or paraproteinemia.

Scleromyxedema with monoclonal gammopathy and neurological involvement: recovery from coma after plasmapheresis. do Prado AD, Schmoeller D, Bisi MC, et al. *Int J Dermatol* 2012; 51: 1013–5.

A man with severe cutaneous and central nervous system disease (dermatoneuro syndrome) underwent three consecutive courses of plasmapheresis with remarkable neurologic improvement. There was mixed success in other case reports.

Scleromyxedema: treatment of widespread cutaneous involvement by total skin electron-beam therapy. Rampino M, Garibaldi E, Ragona R, Ricardi U. *Int J Dermatol* 2007; 46: 864–7.

The report of one patient successfully treated with radiation therapy and a review of previous reports.

Localized LM, without Systemic Manifestations

First-Line Therapies

- Topical or intralesional corticosteroids **E**
- Topical calcineurin inhibitors **E**
- Procedural modalities: dermabrasion, surgical excision, laser **E**

Nodular-type lichen myxedematosus: a case report. Ogita A, Higashi N, Hosone M, et al. *Case Rep Dermatol* 2010; 2: 195–200.

A case report of a complete response to intralesional triamcinolone acetonide for nodular-type LM. Other case reports showed mixed results with topical or intralesional steroids.

Treatment of localized lichen myxedematosus of discrete type with tacrolimus ointment. Rongioletti F, Zaccaria E, Cozzani E, et al. *J Am Acad Dermatol* 2008; 58: 530–52.

Two patients with near-complete resolution of lichen myxedematosus with twice-daily application for 8 weeks. One patient did not respond to topical steroids.

Plaque-like sclerodermiform localized mucinosis rapidly responsive to topical tacrolimus. Schmaltz R, Vogt T, Müller CS. *Case Rep Dermatol* 2010; 2: 165–8.

Case report of localized LM on the neck and shoulder that was not responsive to potent topical corticosteroid therapy. However, he had complete resolution after 3 weeks of treatment with tacrolimus 0.03% ointment used twice daily.

Surgical treatment of facial disfigurement due to lichen myxedematosus. Acikel C, Karagoz H, Kucukodaci Z. *Dermatol Surg* 2009 May; 35: 875–7.

A case report of a 44-year-old man with residual changes on his face after successful treatment of his systemic LM with IVIG. Excisions of thickened skin on his glabella and forehead were performed, then dermabrasion was performed on his nose, forehead, and medial cheeks. There was no reported relapse after 6 months.

Treatment of acral persistent papular mucinosis with electrocoagulation. André Jorge F, Mimura Cortez T, Guadalini Mendes F, et al. *J Cutan Med Surg* 2011; 15(4): 227–9.

A case report of a 51-year-old female with acral persistent papular mucinosis who did not respond to treatment with topical or intralesional corticosteroids. Intralesional corticosteroids caused atrophy, while ‘gentle’ electrocoagulation did well as rated by the physician and patient.

Treatment of acral persistent papular mucinosis using an Erbium-YAG laser. Graves M, Lloyd A, Ross E. *Lasers Surg Med* 2015; 47(6): 467–8.

A case report of an adult female patient with acral persistent papular mucinosis who was successfully treated with a 2940 nm erbium:YAG laser with a 1 mm spot size defocused to 2–3 mm, fluence of 200–300 mJ and multiple passes were made until the lesions were flush with the skin. There was slight scarring, though the patient was reportedly happy with the results.

Lichen nitidus

Jennifer Sharif, Andrew L. Wright



Lichen nitidus is an uncommon, idiopathic condition presenting with 1- to 2-mm diameter flat-topped or domed papules. They usually remain discrete but may be grouped. They can occur on any part of the body but mainly affect the forearms, penis, abdomen, chest, and buttocks. Palmar lesions may be hemorrhagic.

MANAGEMENT STRATEGY

Lichen nitidus persists for long periods but is generally asymptomatic, and *treatment may not be necessary*. No large controlled clinical trials have been reported; most treatments are based on anecdotal reports.

In patients with localized disease, *potent topical corticosteroids* and *topical tacrolimus* can be successful in clearing lesions. For more extensive disease, *phototherapy* (psoralen plus ultraviolet A [PUVA] and ultraviolet B [UVB]) has been reported to be successful. *Antihistamines*, including *astemizole* and *cetirizine*, are reported to have cleared lesions. Generalized lesions have cleared with *PUVA*, *UVB*, and *acitretin*.

Specific Investigation

- Biopsy

First-Line Therapies

- Topical corticosteroids
- UVB

E
D

Successful treatment of lichen nitidus. Wright S. Arch Dermatol 1984; 120: 155–6.

A 24-year-old woman with a 12-year history of extensive lesions cleared with 1 month's treatment using 0.05% fluocinonide cream twice daily. No recurrence was noted at 12-month follow-up.

Treatment of generalized lichen nitidus with narrow band ultraviolet light. Park JH, Choi YL, Kim WS, et al. J Am Acad Dermatol 2006; 54: 545–6.

A 33-year-old man with a 3-year history of generalized disease was reported as almost clear after 28 treatments and remained clear 11 months after cessation of therapy. A 10-year-old with generalized disease was reported as completely clear after 41 treatments and was clear at the 6-month follow-up.

Two cases of generalized lichen nitidus treated successfully with narrow band UVB phototherapy. Kim YC, Shim SD. Int J Dermatol 2006; 45: 615–7.

A 7-year-old girl and a 10-year-old boy, both with generalized lichen nitidus, were treated with narrowband UVB phototherapy, receiving between 17 and 30 treatments with maximum 9.5 J/cm². Both were reported as almost clear at the end of treatment and remained clear for at least 11 months.

A case of generalized lichen nitidus successfully treated with narrow-band ultraviolet B treatment. Bilgili SG, Karadag AS, Calka O, et al. Photodermatol Photoimmunol Photomed 2013; 29: 215–7.

A 15-year-old girl with generalized lichen nitidus was treated with 25 sessions of UVB over a 2-month period with complete clearance.

A case of generalized lichen nitidus successfully treatment with natural daylight therapy. Berman H, Truong A, Cheng C. Paediatr Dermatol 2019; 36: 690–2.

A 6-year-old boy with generalized lichen nitidus had complete resolution after 3 months of daily exposure in peak sun for 30 minutes in combination with once-daily application of topical tacrolimus 0.03% to the face and fluticasone acetate 0.01% to the body.

Second-Line Therapies

• Topical tacrolimus	E
• Antihistamines	D
• PUVA	E
• Oral retinoids	E
• Ciclosporin	E
• Topical pimecrolimus	E

Lichen nitidus treated with topical tacrolimus. Dobbs CR, Murphy SJ. J Drugs Dermatol 2004; 3: 683–4.

A 32-year-old man with lichen nitidus confined to the penis was treated with twice-daily tacrolimus 0.1%. The lesion was reported to be clear after 4 weeks' treatment and had not relapsed after 4 months.

Generalized lichen nitidus: a report of two cases treated with astemizole. Ocampo J, Torne R. Int J Dermatol 1989; 28: 49–51.

Two patients treated with astemizole, a 65-year-old man with a 3-month history and a 48-year-old woman with a 4-month history, were either cleared or dramatically improved with 6–12 days of astemizole 10 mg daily.

Lichen nitidus treated with astemizole. Thio HB. Br J Dermatol 1993; 129: 342.

A 20-year-old woman with widespread disease responded to astemizole 10 mg daily after relapsing after a successful course of PUVA. There was no recurrence of lesions at 2-year follow-up.

It should be noted that astemizole has been discontinued because of cardiotoxicity noted with certain drug interactions. It is presumed that safer antihistamines might also be valuable.

Treatment of generalized lichen nitidus with PUVA. Randle HW, Sander HM. *Int J Dermatol* 1986; 25: 330–1.

A 29-year-old woman with an 8-month history of a generalized eruption was treated with PUVA three times weekly. Lesions cleared after 46 treatments (290J) and remained clear 5 years later.

Association of lichen planus and lichen nitidus – treatment with etretinate. Aram H. *Int J Dermatol* 1988; 27: 117.

A 35-year-old woman with a 4-month history cleared with 8 weeks of etretinate 25 mg/50 mg on alternate days. Treatment was stopped 1 month later. There was no recurrence 5 months after completing the treatment.

Treatment of palmoplantar lichen nitidus with acitretin. Lucker GPH, Koopman RJJ, Steijlen PM, et al. *Br J Dermatol* 1994; 130: 791–3.

A 23-year-old man had a 14-month history of hand and foot involvement that failed to clear with acitretin 50 mg daily but was reported to have improved significantly on 75 mg daily.

Generalized lichen nitidus: a case report and review of the literature. Letter to the editor. Synakiewicz J, Adriana Polańska A, Bowszyc-Dmochowska M, et al. *Adv Dermatol Allergol* 2016; 33: 488–90.

A 34-year-old woman had a 2-year history of generalized lichen nitidus. Acitretin was given at an initial dose of 50 mg/day and reduction of the skin lesions within 3–4 months was observed. The response was maintained at a dose of 10 mg/day with lesions only persisting on the palms.

Acitretin would not usually be used in women of childbearing age without careful counseling due to its prolonged teratogenicity.

A case of generalized lichen nitidus treated with low dose cyclosporine. Lee YK, Choi KW, Lee CW, et al. *Korean J Dermatol* 2007; 45: 1311–4.

A 16-year-old female with generalized lichen nitidus was significantly improved with 8 weeks of ciclosporin 2 mg/kg/day.

Generalized lichen nitidus successfully treated with pimecrolimus 1% cream. Farshi S, Mansouri P. *Dermatol Online J* 2011; 17: 11.

Lesions were reduced and flattened after treatment twice daily for 8 weeks.

Generalized lichen nitidus: successful treatment with systemic isotretinoin. Topal IO, Gokdemir G, Sahin IM. *Indian J Dermatol Venereol Leprol* 2013; 79: 554.

A 15-year-old female patient cleared completely with 4 months of isotretinoin 40 mg daily.

Third-Line Therapies

• Itraconazole	E
• Dinitrochlorobenzene	E
• Cetirizine dihydrochloride and levamisole	E
• Isoniazid	E

Treatment of lichen planus and lichen nitidus with itraconazole: reports of six cases. Libow LF, Coots NV. *Cutis* 1998; 62: 247–8.

A report of two cases showing partial clearance of lichen nitidus after 2 weeks of itraconazole 200 mg twice daily.

Improvement of lichen nitidus after topical dinitrochlorobenzene application. Kano Y, Otake Y, Shiohara T. *J Am Acad Dermatol* 1998; 39: 305–8.

This paper reports a patient treated with 0.1% dinitrochlorobenzene (DNCB) applied at 2-weekly intervals after sensitization with 1% DNCB. The lesions were said to have cleared after 7 months of treatment, compared with a control area. Six months after cessation of treatment, lesions were said to be recurring in the treated area.

Generalized lichen nitidus in a child: response to cetirizine dihydrochloride/levamisole. Sehgal VN, Jain S, Kumar S, Bhat-tacharya SN, et al. *Australas J Dermatol* 1998; 39: 60.

A 6-year-old boy with a 6-month history of generalized involvement showed complete regression/healing of lesions over a 4-week period of treatment with cetirizine dihydrochloride 5 mg daily and levamisole 50 mg on alternate days for 4 weeks.

Generalized lichen nitidus is successfully treated with an antituberculous agent. Kubota Y, Kirya H, Nakayama J. *Br J Dermatol* 2002; 146: 1081–3.

A 10-year-old Japanese girl with a 2-year history of lichen nitidus showed almost complete clearance after a 6-month course of oral isoniazid.

Facial actinic lichen nitidus successfully treated with hydroxychloroquine: a case report. Bouras M, Benchikhi H, Ouakkadi A, et al. *Dermatol Online J* 2013; 19: 20406.

Treatment with a combination of topical steroids and hydroxychloroquine produced complete clearance in 4 weeks in a 23-year-old female with facial lichen nitidus.

Lichen planopilaris

Anwar Al Hammadi, Khadija Aljefri



Lichen planopilaris (LPP), also known as *follicular lichen planus*, is a clinical syndrome consisting of lichen planus (LP) associated with cicatricial scalp alopecia. The condition is more common in women and presents with perifollicular erythema and keratotic plugs at the margins of the expanding alopecia. The follicular involvement is limited to the infundibulum and the isthmus, both demonstrating lichenoid inflammation. The main complications of follicular LP are atrophy and scarring, with permanent hair loss. Three forms of LPP are recognized: classic LPP; Graham–Little syndrome, characterized by the triad of multifocal scalp cicatricial alopecia, non-scarring alopecia of the axilla and/or groin, and keratotic follicular papules; and frontal fibrosing alopecia that affects mainly postmenopausal women and appears as cicatricial alopecia of the frontoparietal hairline and is associated with non-scarring alopecia of the eyebrows.

MANAGEMENT STRATEGY

Therapeutic management for LPP is challenging. However, if the associated inflammation can be controlled in its early stages, follicular units could be preserved, and hair regrowth may be possible. A good therapeutic response aims to halt disease activity and would include a reduction in associated symptoms along with stabilization of the disease and some regrowth of hair in the active perimeter of the alopecic patch. Treatment recommendations vary and tend to be multifaceted due to the lack of high-quality data on therapies. *High-potency topical corticosteroids* are used to control the inflammation in early lesions. *Intralesional injections of 3–5 mg/mL of triamcinolone acetonide* are effective in

well-developed lesions and especially at the edge of the patches. Systemic therapy includes short courses of *oral corticosteroid* for active and progressive disease. *Hydroxychloroquine* and *tetracycline antibiotics* may be efficacious and are commonly considered as second-line therapy. Other agents such as *ciclosporin* and *mycophenolate mofetil* are reported to be useful in refractory cases; attention must be paid to monitoring for side effects and relapse posttreatment is also prevalent. More recently, antiandrogens (*5 α -reductase inhibitors*) were found to be effective. There is some rationale for trying biologic agents such as *tumor necrosis factor (TNF)-blocking agents* for this condition. Finally, *cosmetic measures* can be helpful in camouflaging hair loss on the scalp or eyebrows. These include wigs, hairpieces, microfiber powder, cosmetic makeup, semipermanent makeup, and tattoos. A cosmetic camouflage expert is a useful resource.

Specific Investigations

- Skin biopsy
- Immunofluorescence studies
- Dermoscopy

A histologic review of 27 patients with lichen planopilaris.

Tandon YK, Somani N, Bergfeld WF. *J Am Acad Dermatol* 2008; 59: 91–8.

Characteristic features of LPP include the absence of arrector pili muscles and sebaceous glands, a perivascular and perifollicular lymphocytic infiltrate, mucinous perifollicular fibroplasia with absence of interfollicular mucin, and superficial perifollicular wedge-shaped scarring.

Dermoscopy guided scalp biopsy in cicatricial alopecia.

Miteva M, Tosti A. *J Eur Acad Dermatol Venereol* 2013; 27(10): 1299–303.

Obtaining the biopsy from the correct site is essential for accurate pathologic interpretation in scarring alopecia, as the disease may be focal and difficult to appreciate with the naked eye. In this study of 80 patients, 95% of the dermoscopic-guided biopsies yielded correct pathologic diagnosis. Dermoscopic features of reduced follicular ostia, perifollicular scale, and white dots are suggestive of LPP.

Immunofluorescence abnormalities in lichen planopilaris.

Ioannides D, Bystryk JC. *Arch Dermatol* 1992; 128: 214–6.

Direct immunofluorescence studies were performed on biopsied lesions of patients with LPP and LP. All of the LPP studies demonstrated abnormal linear deposits of immunoglobulin, consisting of IgG or IgA restricted to the basement membrane. The biopsies from those with LP demonstrated fibrillar deposits.

These different appearances suggest different disease processes for LPP and LP.

Dermoscopy: alternative uses in daily clinical practice.

Micali G, Lacarrubba F, Massimino D, et al. *J Am Acad Dermatol* 2011; 64: 1135–46.

Video dermoscopy is performed with a video camera equipped with lenses providing magnification ranging from $\times 10$ to $\times 1000$ and shows the reduction to total absence of orifices, hyperkeratotic perifollicular scales, and erythema. In addition, perifollicular arborizing vessels, pigmented networks, and white pale or blue–gray dots in dark-skinned individuals, corresponding to focal decrease in melanin content.

The use of anti-keratin 903 antibodies to visualize colloid bodies and diagnose lichen planopilaris. Lanoue J, Yanofsky VR, Mercer SE, et al. *Am J Dermatopathol* 2016; 38: 353–8.

CK-903 is a useful adjunctive tool that will allow for a quicker, less costly, and more accurate diagnosis of LPP given its ability to identify colloid bodies even in the setting of significant inflammation and fibrosis and its advantages over direct immunofluorescence of low cost, short preparation time, and lack of need for a specialized fluorescent microscope.

First-Line Therapies

• High-potency corticosteroids	D
• Intralesional corticosteroids	C

Lichen planopilaris: report of 30 cases and review of the literature. Chieragato C, Zini A, Barba A, et al. *Int J Dermatol* 2003; 42: 342–5.

This retrospective case series of 30 patients with LPP reports good therapeutic benefit from early treatment with high-potency topical steroids. Only four patients did not respond to the therapy and needed other treatments.

A case-series of 29 patients with lichen planopilaris: the Cleveland Clinic Foundation experience on evaluation, diagnosis, and treatment. Cevasco NC, Bergfeld WF, Remzi BK, et al. *J Am Acad Dermatol* 2007; 57(1): 47.

In this retrospective case series, 20 patients were treated with intralesional corticosteroid injections. A good response was documented in 40% of patients; 50% of patients stabilized and 10% worsened. This study also commented on the benefit of using tetracyclines (1 g/day), contrary to what was thought before.

Second-Line Therapies

• Oral corticosteroids	C
• Antimalarials	C
• Antiandrogens	C
• Tetracycline	D

Treatment of frontal fibrosing alopecia and lichen planopilaris: a systematic review. Rácz E, Gho C, Moorman PW, et al. *J Eur Acad Dermatol Venereol* 2013; 27(12): 1461.

In this systematic review, the treatment of 114 patients is described. They received 10 different regimens. Hydroxychloroquine (400 mg/day or 6.5 mg/kg/day, the duration varied between 3 and 12 months) resulted in good clinical response in 23% and partial response in 30% of the 71 patients treated for LLP; 5 α -reductase inhibitors (oral finasteride 2.5 mg daily for 12–18 months or dutasteride 0.5 mg daily for 12 months) resulted in good clinical response in 45% of the 38 patients treated for frontal fibrosing alopecia (FFA). The oral treatments were often combined with topical treatments such as corticosteroids, topical minoxidil, and intralesional steroid injections. Topical corticosteroids were found to be ineffective in FFA.

Postmenopausal frontal fibrosing alopecia: a frontal variant of lichen planopilaris. Kossard S, Lee MS, Wilkinson B. *J Am Acad Dermatol* 1997; 36: 59–66.

Oral corticosteroids and antimalarials were found to slow the course of LPP.

Lichen planopilaris: clinical and pathologic study of forty-five patients. Mehregan DA, Van Hale HM, Muller SA. *J Am Acad Dermatol* 1992; 27: 935–42.

This study of 45 patients involved multiple different therapeutic modalities. High-potency topical steroids and oral steroids (30–40 mg daily) for 3 months demonstrated high success rates. Good response was documented in 9 of 11 patients treated with oral corticosteroids.

Hydroxychloroquine and lichen planopilaris: efficacy and introduction of Lichen Planopilaris Activity Index scoring system. Chiang C, Sah D, Cho BK, et al. *J Am Acad Dermatol* 2010; 62: 387–92.

This retrospective study of 40 adult patients showed significant efficacy of hydroxychloroquine in the treatment of LPP. After 6 months, 69% of patients (26 of 38) were full or partial responders. After 12 months, 83% of patients (33 of 40) were full or partial responders. Of the nine responders at 12 months, six were able to discontinue hydroxychloroquine and had a sustained remission with no systemic medication for at least 1 year.

Frontal fibrosing alopecia: a multicenter review of 355 patients. Vañó-Galván S, Molina-Ruiz AM, Serrano-Falcón C, et al. *J Am Acad Dermatol* 2014; 70(4): 670–8.

This large, retrospective, multicenter study included 355 patients, 343 females and 12 males. It reported that oral antiandrogens, such as finasteride and dutasteride, were the most useful treatments. Of the 111 patients who received antiandrogens, 52 (47%) showed improvement and 59 (53%) showed stabilization in the disease.

Third-Line Therapies

• Mycophenolate mofetil	D
• Ciclosporin	D
• Tacrolimus	E
• Retinoids	C
• Thalidomide	E
• TNF-blocking drugs	E
• Low-dose excimer 308-nm laser	D
• Pioglitazone	D
• Naltrexone	D
• Tofacitinib	D
• Oral minoxidil	D

Efficacy and safety of mycophenolate mofetil for lichen planopilaris. Cho BK, Sah D, Chwalek J, et al. *J Am Acad Dermatol* 2010; 62: 393–7.

In this retrospective study of 16 adult patients, mycophenolate mofetil was effective at reducing the signs and symptoms of active LPP in 83% of patients (10 of 12 completers) who had failed multiple prior treatments after at least 6 months of treatment. Patients received 0.5 g twice daily orally for 4 weeks, increased to 1 g twice daily orally for at least 22 weeks. Five of 12 patients were complete responders, five of 12 patients were partial responders, and two of 12 patients were treatment failures. Four patients withdrew from the trial because of adverse events.

Mycophenolate mofetil has a safer side-effect profile and patients with refractory disease could remain on the treatment for longer periods when compared to ciclosporin.

Short course of oral cyclosporine in lichen planopilaris. Mirmirani P, Willey A, Price V. *J Am Acad Dermatol* 2003; 49: 667–71.

The authors present three patients with recalcitrant LPP unresponsive to hydroxychloroquine, high-potency topical steroids, and intralesional steroids, who were treated with ciclosporin 300 mg/day. The duration of treatment ranged from 3 to 5 months, with resolution of symptoms, no progression of hair loss, and no evidence of disease activity. One of the patients had a mild recurrence, which resolved with topical 0.1% tacrolimus in Cetaphil lotion.

Lichen planopilaris: update on diagnosis and treatment. Assouly P, Reygagne P. *Semin Cutan Med Surg* 2009; 28: 3–10.

The authors treated 13 patients with ciclosporin and reported success rate of 77% based on clinical assessment and hair count. The optimal dose was 4–5 mg/kg/day. Relapse remained an issue; 60% relapsed at 6 months and 80% at 12 months posttreatment.

Efficacy of oral retinoids in treatment-resistant lichen planopilaris. Spano F, Donovan JC. *J Am Acad Dermatol*. 2014; 71(5): 1016–8.

This data series of 21 patients with treatment-resistant LPP represents the largest to date, evaluating the benefit of oral retinoids (acitretin 25–50 mg/day and isotretinoin 1 mg/kg/day) in LPP. Only five of the 21 patients (25%) had benefited from adjuvant therapy with oral retinoids. Three received acitretin and two isotretinoin. The responders remained on treatment and under follow-up for 8–18 months. Notably four of five responders had LP in other body parts.

Thalidomide-induced remission of lichen planopilaris. Boyd AS, King LE Jr. *J Am Acad Dermatol* 2002; 47: 967–8.

The authors describe the case of a patient who was diagnosed with LPP and treated with hydroxychloroquine, azathioprine, isotretinoin, cyclophosphamide, dapsone, ciclosporin, levamisole, chloroquine, acitretin, methotrexate, clofazimine, and enoxaparin, all without any benefit. The patient was then started on thalidomide 50 mg orally twice a day, with resolution of the symptoms. Side effects limited the ability to continue the medication. Initially, the patient only complained of fatigue and constipation; however, at 4 months, mild numbness and tingling of the fingers and toes developed, and the patient experienced significant depression, necessitating discontinuation of the medication.

Thalidomide's mechanism of action in this disorder may involve TNF inhibition, suggesting that medications such as adalimumab, etanercept, or infliximab may be beneficial. There has, however, been a case report of LPP developing in a patient treated with etanercept.

Low-dose excimer 308-nm laser for treatment of lichen planopilaris. Navarini AA, Kolios AG, Prinz-Vavricka BM, et al. *Arch Dermatol* 2011; 147: 1325–6.

In this small study of 13 patients with biopsy-proven active classic LPP or variants, pruritus and pain improved in all patients who had these complaints before the treatment. Erythema reduced in five patients and decreased inflammatory lesions in seven patients. An increased growth of hair after 4–8 weeks was observed in three patients, with stable remission in two patients.

Lichen planopilaris treated with a peroxisome proliferator-activated receptor γ -agonist. Mirmirani P, Karnik P. *Arch Dermatol* 2009; 145: 1363–6.

A 47-year-old man with LPP recalcitrant to therapy responded to pioglitazone at a dose of 15 mg/day.

Because of the theoretical basis for the use of peroxisome proliferator-activated receptor agonists in LPP, further studies are warranted to determine whether this treatment is genuinely efficacious for the disorder.

The use of oral pioglitazone in the treatment of lichen planopilaris. Mesinkoyska NA, Tellez A, Dawes D, et al. *J Am Acad Dermatol* 2015; 72: 355–6.

Retrospective case analysis of the 22 patients who were prescribed pioglitazone hydrochloride (15 mg/day for a median of 10.5 months) showed that pioglitazone was effective in controlling the symptoms, inflammation, and disease progression in 16 patients (72.7% of the patients). Moreover, new hair regrowth was noted in six patients (27.3%). From the responders, only two patients (9%) experienced relapse after discontinuation of pioglitazone.

Response of lichen planopilaris to pioglitazone hydrochloride. Peterson EL, Gutierrez D, Brinster NK, et al. *J Drugs Dermatol* 2019; 18: 1276–9.

This retrospective analysis describes 23 patients with LPP treated with adjunctive pioglitazone. Most (18/25) demonstrated significant reduction in patient-reported symptoms and clinical signs of inflammation. No adverse effects were reported

Novel treatment using low-dose naltrexone for lichen planopilaris. Strazzulla LC, Avila L, Lo Sicco K, et al. *J Drugs Dermatol*. 2017; 16: 1140–2.

Naltrexone is licensed for the treatment of opiate and alcohol dependence. Its off-label use for autoimmune dermatologic conditions in low doses has been described. This retrospective study reports its use in four patients with LPP as adjuvant therapy. A small dose of 3 mg once per day of naltrexone was well tolerated. Reduction in pruritus, scalp inflammation, and disease progression was reported in all four patients at 1-month follow-up. Notably, three of the four patients were also prescribed pioglitazone.

Tofacitinib for the treatment of lichen planopilaris. Yang CC, Khanna T, Sallee B, et al. *Dermatol Ther* 2018; 31: 12656.

This retrospective study describes 10 patients with recalcitrant LPP. They received the Janus kinase (JAK) inhibitor tofacitinib either as monotherapy or adjunctive therapy to intralesional steroids, topical tacrolimus, or oral hydroxychloroquine. Eight of the 10 patients were found to have significant improvement. Four were on tofacitinib only, and four were receiving additional treatments. Tofacitinib was administered at 5 mg dose twice or three times daily for 9–12 months. The LPP Activity Index (LPPAI) was recorded before and after treatment; 30%–94% reduction in LPPAI score was reported.

Oral minoxidil improves background hair thickness in lichen planopilaris. Vañó-Galván S, Trindade de Carvalho L, Saceda-Corralo D, et al. *J Am Acad Dermatol* 2020; S0190-9622(20)30566-1.

In this retrospective study, 51 patients with LPP were treated with low-dose oral minoxidil: 0.5 mg for females and 2.5 mg for males daily. Independent of the duration of treatment 39% of patients had improved hair thickness, 53% remained stable, and 8% worsened. Mild adverse effects were reported in 37% of patients; these included hypertrichosis, postural hypertension, and tachycardia.

Hair transplant in frontal fibrosing alopecia: a multicenter review of 51 patients. Vañó-Galván S, Villodres E, Pigem R, et al. J Am Acad Dermatol 2019; 81(3): 865.

Patients with scarring alopecia may have poor long-term results with hair transplant. This retrospective study of 51 patients found that the mean graft survival rate reduced from 84% in year 1 to 41% in year 5.

Surgical options such as scalp reduction and hair transplant are other treatment options. Hair transplant requires sufficient healthy hair for donation and for the disease to be quiescent. Eventual graft failure in scarring alopecia is prevalent and the patient should be informed.

Lichen planus

Annie Dunn, Mark G. Lebwohl



Lichen planus (LP) is a pruritic, papulosquamous disease with characteristic histopathologic and clinical features. Classically, lesions are described with the 6 'P's: purple, pruritic, planar, polygonal, papule, and plaque. In some patients, fine white lines are visible across the surface of the lesions, known as *Wickham striae*. Oral erosive LP, a painful erosive condition affecting mucous membranes, is addressed in a separate chapter.

MANAGEMENT STRATEGY

Although LP can resolve spontaneously, treatment is often required because pruritus can be severe, interfering with quality of life. An association with underlying diseases such as hepatitis C remains controversial. Physicians should obtain a detailed medical history, as there are numerous reports of LP or lichenoid eruptions occurring after vaccinations, particularly hepatitis B, and after the use of certain medications.

In patients with localized disease, *superpotent corticosteroids* should be applied twice daily for 2–4 weeks. If the response is inadequate, *intralesional injection of corticosteroids* may be beneficial. Topical antipruritic agents containing *menthol*, *phenol*, *camphor*, *lidocaine*, *pramoxine*, or *doxepin hydrochloride* can be useful.

Traditionally, patients with extensive LP have been treated with systemic corticosteroids. *Oral prednisone* 30 to 60 mg daily for 2 to 6 weeks, or its equivalent, tapered over the ensuing 2 to 6 weeks, is often effective. However, relapses are frequent. If more than two courses of high-dose systemic corticosteroids are required over the span of a few months, alternative treatments should be sought. Fortunately, there is evidence in the literature for steroid-sparing treatments, including several agents that have been studied in clinical trials.

Oral metronidazole has emerged as a safe and effective alternative to systemic corticosteroids: 500 mg twice daily for 20–60 days has proved beneficial in many patients. A second 60-day course may be needed for complete response. *Sulfasalazine* has been studied in a randomized, double-blind trial. Patients are started on 500 mg twice daily, and the dosage is increased by 500 mg every 3 days until a dose of 2.5 g daily is reached, for a total of 3–6 weeks. The use of *narrowband ultraviolet B* (NB-UVB)

three times a week for 6 weeks has helped patients achieve partial and complete remission. *PUVA* (*psoralen + ultraviolet A*) has been particularly beneficial in the lichen planus–like eruption associated with graft-versus-host disease. However, in one retrospective study, the recurrence rate was higher in patients who received PUVA compared with NB-UVB. *Isotretinoin* in doses of 10 mg orally twice daily for 2 months has been reported to clear LP in several patients, and *acitretin* 30 mg daily for 2–4 months has also resulted in marked improvement or remission. Oral *methotrexate* (10–15 mg/week for adults and 0.25 mg/kg/week for children) has helped patients achieve complete remission after 24 weeks, with most side effects reported as mild. The use of subcutaneous *enoxaparin* (5 mg weekly for 8 weeks) enabled more patients to achieve complete remission compared with the use of oral prednisone (0.5 mg/kg). *Apremilast* (20 mg twice daily for 12 weeks) has helped some patients improve their Physician Global Assessment score, even 4 weeks after completing treatment.

For severe and refractory LP unresponsive to other therapies, antimicrobials (antibiotics, antifungals), immunosuppressive agents (mycophenolate mofetil, azathioprine, cyclosporin, leflunomide, antimalarials), tumor necrosis factor (TNF) blockers (adalimumab), thalidomide, topical calcineurin inhibitors, vitamin D analogs, and alitretinoin have been used with success.

Palmoplantar LP has been successfully treated with *acitretin* 35 mg/day (0.5 mg/kg) for 2 months, *UVA-1 laser therapy* three times a week for 4 weeks (100 J/cm²), and *cyclosporin* 3.5 mg/kg daily.

For *nail LP*, there are case reports detailing the use of 30 mg *alitretinoin* daily for 3 months, *cyclosporin* 3–6 mg/kg daily for 8 weeks, and *etanercept* (25 mg subcutaneous twice a week for 6 months and then 50 mg weekly for an additional 3 months).

Specific Investigations

- Detailed medication history
- Liver function tests
- Serology for hepatitis B and C

Association between HCV infection and cutaneous-mucosal lichen planus: an update. Pinelli S, Stefano B, Panici PB, et al. *Eur J Dermatol* 2017; 3: 329–31.

This systematic review regarding the prevalence of LP in patients with hepatitis C found the link between cutaneous and oral LP and HCV is supported by the data emerging from meta-analyses. This association varies widely among and within different countries.

Drug-induced Lichen Planus

Lichen planus and lichenoid dermatoses. Tziotzios C, Lee JYW, Brier T, et al. *J Am Acad Dermatol* 2018; 79: 789–818.

A large number of medications have been associated with lichenoid drug eruptions (LDEs), including immune checkpoint inhibitors, β -blockers, ACE inhibitors, furosemide, thiazides, methyl dopa, penicillamine, antimalarials, ketoconazole, antiretrovirals, tetracyclines, isoniazid, hepatitis B and influenza vaccinations, NSAIDs, allopurinol, sulfonylurea agents, phenytoin, carbamazepine, gold, lithium, mercury, TNF- α inhibitors, and tyrosine kinase inhibitors.

LDEs mirror cutaneous LP morphologically, but they tend to be more polymorphic, lack Wickham striae, and show more pronounced desquamation.

First-Line Therapies

- Topical corticosteroids **C**
- Intralesional corticosteroids **D**
- Antihistamines **C**

Betamethasone-17,21-dipropionate ointment: an effective topical preparation in lichen rubra planus. Bjornberg A, Hellgren L. *Curr Med Res Opin* 1976; 4: 212–7.

Patients with LP that had become resistant to betamethasone valerate ointment were treated with betamethasone dipropionate ointment once or twice daily for 2–3 weeks. Fourteen of 19 patients achieved better improvement with betamethasone dipropionate ointment.

Treatment of generalized cutaneous lichen planus with dipropionate and betamethasone disodium phosphate: an open study of 73 cases. Pitche P, Saka B, Kombate K, et al. *Ann Dermatol Venereol* 2007; 134: 237–40.

Injections of systemic corticosteroids performed at 2-week intervals for 6 weeks resulted in complete remission in 61 of 73 (83.6%) patients with LP; 8.2% of patients experienced partial remission, and another 8.2% failed this therapy. At 3 months, the relapse rate of initial responders was 23.3%, and at 6 months, 31.5% had relapsed.

Second-Line Therapies

- Metronidazole **B**
- Sulfasalazine **A**
- Systemic corticosteroids **B**
- Isotretinoin, acitretin **A**
- Narrowband or broadband UVB **B**
- PUVA **C**
- Methotrexate **B**

Efficacy of oral metronidazole in treatment of cutaneous and mucosal lichen planus. Rasi A, Behzadi AH, Davoudi S, et al. *J Drugs Dermatol* 2010; 9: 1186–90.

In this open trial of oral metronidazole 250 mg every 8 hours for 12 weeks, 20 of 49 patients (40.82%) had a complete response, 16 (32.65%) had a partial response, and 13 (26.53%) did not improve.

Metronidazole has also been studied in a dose of 500 mg twice daily for 20–60 days. Given the medication's favorable safety profile, many dermatologists use metronidazole as a first-line therapy.

Efficacy of sulfasalazine in the treatment of generalized lichen planus: randomized double-blinded clinical trial on 52 patients. Omidian M, Ayoobi A, Mapar MA, et al. *J Eur Acad Dermatol Venereol* 2010; 24: 1051–4.

Sulfasalazine doses were started at 1 g/day and increased by 0.5 g every 3 days until a dosage of 2.5 g daily was achieved. After 6 weeks of treatment, 19 of 44 patients (82.6%) in the sulfasalazine group achieved improvement compared with two patients (9.6%) in the placebo group. Mild response (<50% of lesions cleared) occurred in 21.7% of patients in the sulfasalazine group, moderate response (>50% of lesions cleared) in 52.2%, and excellent clearing of lesions (>80%) in 8.7%.

Although complete clearing occurred in a minority of patients, the authors did not continue this study beyond 6 weeks.

Treatment of lichen planus with acitretin. A double-blind, placebo-controlled study in 65 patients. Laurberg G, Geiger JM, Hjorth N, et al. *J Am Acad Dermatol* 1991; 24: 434–7.

Acitretin resulted in marked improvement or remission in 64% of patients compared with 13% of placebo-treated patients in a double-blind trial in 65 subjects. Acitretin doses of 30 mg daily were used for a duration of 8 weeks, leading to hyperlipidemia and dryness of the mouth and lips.

Isotretinoin in doses of 10 mg orally twice daily has been effective in the treatment of oral lichen planus, and anecdotal evidence suggests efficacy in generalized LP as well. Isotretinoin had fewer reported mucocutaneous side effects than acitretin. There are several case reports of alitretinoin 10–30 mg daily for 1–3 months improving nail, cutaneous, and oral LP.

Comparison of the narrow band UVB versus systemic corticosteroids in the treatment of lichen planus: a randomized clinical trial. Iraj F, Faghihi G, Asilian A, et al. *J Res Med Sci* 2011; 162: 1578–82.

Forty-six patients received either prednisolone 0.3 mg/kg for 6 weeks ($n = 23$) or NB-UVB three times a week for 6 weeks ($n = 23$) with a maximum dose of 9 J/cm². More patients in the NB-UVB group achieved complete response (12/23) compared with those in the steroid group (3/23) ($p < 0.05$). No side effects were reported.

Several other retrospective studies highlight the efficacy of UVB, especially NB-UVB, for the treatment of generalized cutaneous LP.

Psoralen plus UVA vs. UVB-311 nm for the treatment of lichen planus. Wackernagel A, Legat FJ, Hofer A, et al. *Photodermatol Photoimmunol Photomed* 2007; 23: 15–9.

This retrospective chart review compared 15 patients treated with PUVA with 13 patients treated with NB-UVB. Of the PUVA-treated patients 67% achieved complete remission, and 33% achieved a partial clinical response; 31% of patients treated with NB-UVB achieved complete remission and 46% a partial response. The mean duration of therapy was 10.5 weeks for PUVA and 8.2 weeks for NB-UVB. The mean number of treatments was 25.9 PUVA treatments compared with 22.5 NB-UVB treatments. LP recurred in 47% of PUVA-treated patients, but only in 30% of NB-UVB-treated patients.

Long-term efficacy of PUVA treatment in lichen planus: comparison of oral and external methoxsalen regimens. Helander I, Jansen CT, Meurman L. *Photodermatology* 1987; 4: 265–8.

Good or excellent clearing occurred in 10 of 13 patients after 8–46 bath-PUVA treatments, compared with 5 of 10 patients after 8–30 oral PUVA treatments. However, examination of patients months after PUVA suggested that treatment might prolong the duration of LP.

Effectiveness of oral methotrexate therapy versus systemic corticosteroid therapy in treatment of generalised lichen planus. Bakhtiar R, Noor SM, Paracha MM. *Journal of the College of Physicians and Surgeons Pakistan* 2018; 7: 505–8.

Randomized control trial of 158 patients with cutaneous LP treated with either methotrexate 10 mg once weekly for 8 weeks or oral corticosteroids 40 mg daily for 8 weeks followed by a taper. At 8 weeks 80% of the methotrexate group (63 patients) reported improvement compared with 72% of the corticosteroid group (57 patients).

Third-Line Therapies

• Trimethoprim-sulfamethoxazole	E
• Griseofulvin	A
• Itraconazole	C
• Terbinafine	E
• Antimalarials	D
• Leflunomide	E
• Azathioprine	E
• Ciclosporin, FK 506	E
• Etanercept	E
• Adalimumab	E
• 0.1% tacrolimus ointment	E
• Tofacitinib	E
• Calcipotriol ointment	A
• Thalidomide	A
• UVA1	D
• Tacrolimus 0.1% ointment	E
• Pimecrolimus cream	E
• Alitretinoin	D
• Low-molecular-weight heparin	B
• Dapsone	D

Antimicrobials

Treatment of lichen planus with Bactrim. Abdel-Aal H, Abdel-Aal MA. J Egypt Med Assoc 1976; 59: 547–9.

Oral trimethoprim-sulfamethoxazole, two tablets twice daily for 5 days, cleared LP within 2 weeks only to have the skin lesions relapse 2 months later. The trimethoprim-sulfamethoxazole was again effective when readministered to patients who experienced relapse.

Histopathological evaluation of griseofulvin therapy in lichen planus: a double-blind controlled study. Sehgal VN, Bikhchandani R, Koranne RV, et al. Dermatologica 1980; 161: 22–7.

Griseofulvin 500mg/day for 2 months was effective in 18 of 22 patients. Other antifungals including terbinafine and itraconazole have been used to treat LP. The use of griseofulvin has met with skepticism.

Pulsed itraconazole therapy in eruptive lichen planus. Khandpur S, Sugandhan S, Sharma VK. J Eur Acad Dermatol Venereol 2009; 23: 98–101.

Sixteen patients with eruptive LP were treated with itraconazole 200 mg twice daily pulsed for 1 week each month for 3 months. By the end of the first month, nine of 16 patients (56.25%) stopped developing new lesions. Only nine of the patients were followed for 3 months, and seven of those (77.7%) stopped developing new lesions. All nine patients reported improvement of pruritus, and five of them had complete relief of pruritus. By the end of 3 months, partial flattening was present in six of nine patients (66.66%) and complete flattening in three (33.33%).

Given the partial response seen at 3 months, longer therapy may be warranted.

Systemic Immunosuppressive Agents

A recalcitrant case of ulcerative lichen planus responsive to leflunomide. Sardana K, Gupta A. Clin Exp Dermatol 2019; 45(3): 340–341.

A 48-year-old woman with ulcerated LP on both legs refractory to oral and topical steroids, methotrexate, isotretinoin, dapsone, ciclosporin, and antibiotics. Leflunomide 20 mg OD per day was added to her regimen of methotrexate 12.5 mg/week and topical 0.05% clobetasol propionate ointment, and this combination resulted in marked improvement in lesions within a month.

Generalized severe lichen planus treated with azathioprine. Verma KK, Sirka CS, Khaitan BK. Acta Derm Venereol 1999; 79: 493.

Generalized severe LP has been successfully treated with azathioprine.

Palmoplantar lichen planus with umbilicated papules: an atypical case with rapid therapeutic response to ciclosporin. Karakatsanis G, Patsatsi A, Kastoridou C, Sotiriadis D. J Eur Acad Dermatol Venereol 2007; 21: 1006–7.

A 63-year-old woman with LP of the palms, forearms, soles, and feet was treated with ciclosporin 3.5 mg/kg daily. Pruritus improved within 2 weeks, and clinical improvement occurred within 4 weeks, at which point ciclosporin was tapered over the next 4 weeks.

In a different case report, a patient with 20 dystrophic fingernails noted improvement within 2 months of starting ciclosporin 3 mg/kg daily, but she required the addition of valsartan for hypertension.

Successful treatment of lichen planus with adalimumab. Holló P, Szakonyi J, Kiss D, et al. Acta Derm Venereol 2012; 92: 385–6.

A 39-year-old woman with extensive LP refractory to systemic corticosteroids, acitretin, and PUVA was treated with adalimumab 80 mg followed by 40 mg every other week. Pruritus decreased after 2 weeks, and skin lesions resolved within 2 months, leaving only hyperpigmentation.

There are a number of case reports of LP of the nails responding to treatment with TNF-α blockers. Unless the nail involvement is treated early, it is difficult to imagine that any therapy would reverse the pterygium that develops in late disease. There are also a number of reports of LP induced by TNF-α blockers.

Treatment of severe lichen planus with the JAK inhibitor tofacitinib. Damsky W, Wang A, Olamiju B, et al. J Allergy Clin Immunol 2020; S0091-6749(20)30120-2.

Three patients with erosive LP responded to tofacitinib 5 mg orally twice daily.

Other

A randomized controlled trial to compare calcipotriol with betamethasone valerate for the treatment of cutaneous lichen planus. Singapore Lichen Planus Study Group. Journal of Dermatological Treatment 2004; 15: 141–5.

A 31-patient randomized control trial comparing topical calcipotriol to betamethasone valerate for the treatment of cutaneous LP. The treatments prescribed were either calcipotriol 50 mcg/g ointment or betamethasone valerate 0.1% ointment applied twice daily for 12 weeks. Both agents showed modest efficacy.

Bacillus Calmette-Guerin, polysaccharide nucleic acid in the treatment of cutaneous and oral lichen planus. Nasr MM, Howyda EM, Khattab FM, et al. Dermatologic Therapy 2018; 3: e12591.

In this study, 13 patients with cutaneous LP received intradermal injection of Bacillus Calmette-Guérin polysaccharide nucleic acid (BCG-PCN) twice weekly for 3 weeks. A single lesion was injected with 0.5 mL of BCG-PCN twice weekly for 3 weeks. There was a complete response in 10 of the patients after 3 weeks, and one of the patients had a partial response. After 3 months, 10 of the 13 patients sustained a complete clinical response.

BCG-PCN was created for the purpose of this study and is an inactivated form of BCG vaccine – a live attenuated form of bovine tuberculosis.

Treatment of cutaneous lichen planus with thalidomide. Moura AK, Moure ER, Romiti R. Clin Exp Dermatol 2009; 34: 101–3.

Eight patients with cutaneous LP were treated with thalidomide 100 mg daily at bedtime. Three patients withdrew because of transient neuropathy of the legs and transient weakness that began shortly after the treatment started. Five patients noted improvement of pruritus within a few days after starting thalidomide. Skin lesions regressed in a mean of 4 weeks, and complete remission was achieved in a mean of 3 months.

Ultraviolet A1 in the treatment of generalized lichen planus: a report of 4 cases. Polderman MC, Wintzen M, van Leeuwen RL, et al. J Am Acad Dermatol 2004; 50: 646–7.

Four patients with refractory generalized LP were treated with UVA1 45 J/cm² 5 days per week for two 4-week treatment periods with a 3-week rest in between. All four improved.

Topical tacrolimus in the treatment of lichen planus in a child. Fortina AB, Giulioni E, Tonin E. Pediatr Dermatol 2008; 25: 570–1.

A child with LP did not respond to topical corticosteroids, but her condition resolved upon treatment with tacrolimus 0.03% ointment.

Tacrolimus 0.1% has also been used successfully to treat LP in adults. In addition, case reports describe the successful use of topical pimecrolimus for cutaneous LP.

Comparison of therapeutic effect of low-dose low-molecular-weight heparin (enoxaparin) vs. oral prednisone in treatment of patients with lichen planus: a clinical trial. Iraj F, Asilian A, Saeidi A, et al. Adv Biomed Res 2013; 2: 76.

Patients were given subcutaneous enoxaparin 5 mg weekly ($n=25$) or 0.5 mg/kg prednisone daily ($n=23$) until complete remission or a maximum of 8 weeks. The average time until improvement was 25.2 ± 13 days in the enoxaparin group compared with 9.7 ± 6 days in the oral prednisone group. In the enoxaparin group, eight patients (32%) achieved complete remission, and 10 (40%) experienced partial improvement. In the oral prednisone group, 16 patients (69.6%) had complete remission, and six patients (26.1%) had partial improvement. No serious complications were found in the enoxaparin group, whereas 22% of the patients on prednisone experienced side effects, with the most common being dyspepsia.

An open-label pilot study of apremilast for the treatment of moderate to severe lichen planus: a case series. Paul J, Foss CE, Hirano SA, et al. J Am Acad Dermatol 2013; 68: 255–61.

In this pilot study, 10 patients were treated with 20 mg apremilast twice daily for 12 weeks. After 12 weeks, three patients (30%) had at least a two-grade improvement in Physician Global Assessment, but all 10 patients had improvements in secondary end points such as lesion count. There was no loss of benefit when patients were assessed 28 days after the end of treatment.

Lichen planus in childhood: a series of 316 patients. Pandhi D, Singal A, Bhattacharya SN. Pediatr Dermatol 2014; 31: 59–67.

Dapsone was one of the most commonly prescribed medications for LP in this series of 316 childhood cases.

Lichen sclerosis

Fiona M. Lewis



Lichen sclerosis (LS) is a common dermatosis that has a predilection for the ano-genital skin. It occurs in both sexes but is more common in females and has two peaks of incidence – in girls before puberty and in women after menopause. It can also affect the extragenital skin in about 10% and particularly is seen on areas of friction and trauma. It appears to be lymphocyte-mediated and there is a strong association with other autoimmune disorders and the presence of circulating antibodies in females, but not in males. It is postulated that an inflammatory response to chronic exposure to urine in occluded skin may be an important aetiological factor in male genital LS, also called balanitis xerotica obliterans. There is a small risk of developing a squamous cell carcinoma (SCC) in atypical disease.

MANAGEMENT STRATEGY

The aims of management are to alleviate symptoms, reduce scarring and hence maintain function, and, by careful follow-up, to detect any premalignant and malignant change.

The most common symptom of LS in females is pruritus, but soreness and pain can occur if the skin fissures. In children, constipation is often the presenting symptom. White atrophic plaques are the typical clinical feature with ecchymosis being pathognomonic for the disease. Perianal involvement occurs in some females, but is hardly ever seen in men. If untreated, scarring will lead to changes in the vulval architecture. The labia minora may be resorbed and the clitoral hood can seal. Narrowing of the introitus can cause dyspareunia, and fusion of the labia minora may eventually lead to difficulties with micturition. In males, tightening of the foreskin causes phimosis and subsequently

problems with sexual function. Meatal stenosis leads to difficulties with micturition and requires expert urological intervention.

The first-line treatment for LS in adults and children of both sexes is an ultrapotent topical steroid. The general recommended induction regimen is *clobetasol propionate 0.05% ointment* once a day for a month, alternate days for a month and then twice weekly for a further month. After this 3-month period, the patient can apply treatment once daily if any symptoms recur, but some may require regular treatment such as once weekly. A 30g tube should last at least 3 months in an adult and 6 months in a child, but the majority of patients use much less than this. With successful treatment, the ecchymosis, fissuring and hyperkeratosis should resolve and scarring should not progress. The pallor will often remain and any scarring present before treatment starts will not reverse. There is some evidence that treatment can reduce the risk of developing an SCC.

Using an emollient as a soap substitute is helpful symptomatically and barrier preparations are recommended if there is urinary incontinence. *Stool softeners* can be helpful in children with constipation.

In women, surgery is only recommended for excision of any malignant lesion that develops, or to *release labial adhesions* that are causing severe introital narrowing. However, in males, *circumcision* may be a very helpful part of management.

Specific Investigations

- Biopsy
- Autoimmune screen if clinically indicated

A diagnosis of LS can often be made on the classic clinical appearances. Biopsy is mandatory if there are unusual or atypical features or in those who have failed to respond to first-line treatment.

British Association of Dermatologists' guidelines for the management of lichen sclerosis 2018. Lewis FM, Tatnall FM, Velangi SS, et al. *Br J Dermatol* 2018; 178: 839–53.

These up-to-date guidelines review all the evidence for investigation and treatment of LS in both sexes, adults, and children.

Association of autoimmune diseases with lichen sclerosis in 532 male and female patients. Kreuter A, Kryvosheyeva Y, Terras S, et al. *Acta Derm Venereol* 2013; 93(2): 238–41.

Concomitant autoimmune disease and circulating auto-antibodies were found significantly more often in females than males with LS.

First-Line Therapies

• Ultrapotent topical steroids	A
• Emollients	E
• Use of soap substitutes	E

Topical interventions of genital lichen sclerosis. Chi CC, Kitschig G, Baldo M, et al. *Cochrane Database Syst Rev* 2011; (7): CD008240.

A Cochrane review including seven randomly controlled trials with a total of 249 patients and investigating six treatments. This concluded that topical clobetasol propionate 0.05% and mometasone furoate were effective in treating LS, when compared with placebo. No significant benefit was found for topical testosterone, dihydrotestosterone, and progesterone.

A double-blind, randomized prospective study evaluating topical clobetasol propionate 0.05% versus topical tacrolimus 0.1% in patients with vulvar lichen sclerosis. Funaro D, Lovett A, Leroux N, et al. *J Am Acad Dermatol* 2014; 71: 84–91.

In this randomized, double-blind, controlled trial, 28 patients were treated with tacrolimus 1% ointment and 27 with clobetasol propionate 0.05% ointment once daily for 3 months. Signs and symptoms improved in both groups. However, clobetasol propionate was significantly more effective than tacrolimus.

The response of balanitis xerotica obliterans to local steroid application compared with placebo in children. Kiss A, Csontai A, Pirot L, et al. *Urol* 2001; 165: 219–20.

A double-blind, placebo-controlled, randomized study of 40 boys comparing 0.05% mometasone furoate against placebo. The application of a potent topical steroid produced clinical improvement in phimosis in histological early and intermediate disease and slowed deterioration in the late stages.

Treatment of vulval lichen sclerosis with topical corticosteroids in children: a study of 72 children. Casey G, Cooper S, Powell JJ. *Clin Exp Dermatol* 2015; 40: 289–92.

Of a group of 72 girls, 62 were treated prospectively with clobetasol propionate 0.05% ointment for 3 months; the remaining 10 responded to a moderately potent steroid. In comparison to a study of 31 patients who had used a moderately potent steroid where symptom clearance was 32.2%, 72.6% of the first group had complete resolution of symptoms.

First randomized trial of clobetasol propionate and mometasone furoate in the treatment of vulvar lichen sclerosis: results of efficacy and tolerability. Virgili A, Minghetti S, Corazza M, et al. *Brit J Dermatol* 2014; 171(2): 388–96.

Fifty-four patients were randomized to apply clobetasol propionate 0.05% or mometasone furoate 0.1% on a tapering regimen for 12 weeks. Both showed equal efficacy with a response rate of 89% and were well tolerated.

Continuous versus tapering application of the potent topical corticosteroid mometasone furoate in the treatment of vulvar lichen sclerosis: results from a randomized trial. Borghi A, Corazza M, Minghetti S, et al. *Brit J Dermatol* 2015; 173: 1381–6.

Sixty-four patients applied mometasone furoate 0.1% ointment on a reducing regimen over 12 weeks or continuously for 5 days per week. The response rate as reported by objective and subjective scores showed similar efficacy in both regimens. This confirms that a tapering regimen is equally effective as continuous treatment.

Long-term management of adult vulvar lichen sclerosis: a prospective cohort study of 507 women. Lee A, Bradford J, Fischer G. *JAMA Dermatol* 2015; 151: 1061–7.

Prepubertal-onset vulvar lichen sclerosis: the importance of maintenance therapy in long-term outcomes. Ellis E, Fischer G. *Pediatr Dermatol* 2015; 32: 461–7.

These two studies are comparative studies of the use of topical steroids in adults and children. Both show that good control of the inflammation in the long term reduces scarring in both groups and the risk of malignancy in adults.

Second-Line Therapies

• Topical pimecrolimus	A
• Topical tacrolimus	B
• Circumcision	B

A double-blind, randomized controlled trial of clobetasol versus pimecrolimus in patients with vulvar lichen sclerosis. Goldstein AT, Creasey A, Pfau R, et al. *J Am Acad Dermatol* 2011; 64: 99e–104e.

A group of 38 women were treated for 12 weeks. Clobetasol propionate 0.05% was superior in improving inflammation as seen in posttreatment biopsies. Both treatments showed improvement in symptoms and a decreased clinical evaluation score.

Multicentre, phase II trial on the safety and efficacy of topical tacrolimus ointment for the treatment of lichen sclerosis. Hengge UR, Krause W, Hofmann H, et al. *Br J Dermatol* 2006; 155: 1021–8.

A prospective study of 84 patients (49 women, 32 men, and three girls) were treated with 0.1% topical tacrolimus ointment twice daily for up to 24 weeks. Of these, 36% had a complete, and 29% a partial, clinical response.

Because of concerns about infection and malignancy, the use of topical calcineurin inhibitors is controversial.

Lichen sclerosis of the male genitalia and urethra: surgical options and results in a multi-centre international experience of 215 patients. Kulkarni S, Barbagli G, Kirpekar D, et al. *Eur Urol* 2009; 55: 945–54.

A large, retrospective, observational study comparing circumcision and/or meatotomy, one or two stage penile oral mucosal graft urethroplasty, and definitive perineal urethrostomy. Circumcision alone or together with meatotomy was successful in 100% of cases, meatotomy alone in 80%, and various forms of urethroplasty in 73–91%.

It is not stated whether any of these patients who required surgery for persistent phimosis had received any topical treatment first.

Current treatment of lichen sclerosis and stricture. Chung ASJ, Suarez OA. *World J Urol* 2020; 38: 3061–7.

A review of the management of urethral stricture in men where surgical intervention is required. Oral mucosal grafts were shown to be the graft of choice. Skin grafts should be avoided as they are prone to develop further LS on the graft.

Third-Line Therapies

• Acitretin	A
• CO ₂ laser	B
• Photodynamic therapy	B

Acitretin for severe lichen sclerosis of male genitalia: a randomized, placebo controlled study. Ioannides D, Lazaridou E, Apalla Z, et al. *J Urol* 2010; 183: 1395–9.

Men ($n = 52$) with severe longstanding LS were treated with acitretin 35 mg/day or placebo for 20 weeks. A complete response was achieved in 36.4% vs. 6.3% of controls.

The double-blind nature of this study is limited because of the expected side effects of oral acitretin as opposed to placebo.

Is carbon dioxide laser treatment of lichen sclerosus effective in the long run? Windahl T. Scand J Urol Nephrol 2006; 40: 208–11.

A retrospective review of 62 men who had failed to respond adequately to a topical steroid, although the potency is not specified. They were treated with CO₂ laser (15–20 W output with defocused beam) with vaporization of macroscopically abnormal areas on the glans penis. Of 50 patients who were contacted up to 14 years after treatment, 80% had no symptoms or visible lesions. Two men were found to have SCC at follow-up.

Comparison of 5-aminolevulinic acid photodynamic therapy and clobetasol propionate in treatment of vulvar lichen sclerosus. Shi L, Miao F, Zhang LL, et al. Acta Derm Venereol 2016; 96(5): 684–8.

Forty-three patients were randomized to treatment with 5-aminolevulinic acid photodynamic therapy (ALA-PDT) or clobetasol propionate 0.05%. Twenty patients in each group completed treatment and results reported less relapse in the PDT group. However, follow-up was only 6 months.

Other Therapies	
• Topical calcipotriol	B
• Topical tretinoin	B
• Oxatomide gel	B
• Topical testosterone	B
• Oral stanozolol	B
• Low-dose UVA1 phototherapy	C
• Non-ablative laser therapy	B
• Antibiotics	D
• Intralesional triamcinolone	D
• Cryosurgery	D
• Ciclosporin	D
• Potassium <i>p</i> -aminobenzoate	D
• Adipose-derived mesenchymal cells and platelet-rich plasma	D
• Focused ultrasound therapy	D
• Hydroxycarbamide	E
• Hydroxyurea	E
• Methotrexate	E
• Oral calcitriol	E
• Extracorporeal photophoresis	E
• Intralesional adalimumab	E

Low-dose ultraviolet A1 phototherapy for extragenital lichen sclerosus: results of a preliminary study. Kreuter A, Gambichler T, Avermaete A, et al. J Am Acad Dermatol 2002; 46: 251–5.

A series of 10 patients (8 female and 2 male) were treated with low-dose UVA1 four times a week for 10 weeks with a cumulative UVA1 dose of 800 J/cm². A marked reduction in clinical score, decrease in skin thickness, and increase in dermal density was seen in all patients who also reported a subjective improvement.

UVA1 phototherapy for genital lichen sclerosus. Beattie PE, Dawe RS, Ferguson J, et al. Clin Exp Dermatol 2006; 31: 343–7.

Five out of seven patients had moderate (3 patients) or minimal (2 patients) improvement after at least 15 treatments with UVA1 three to five times weekly.

The extragenital lesions of LS appear to respond better to UVA1. There are also concerns about an increased potential for the development of SCC with phototherapy.

Efficacy of non-ablative laser therapy for lichen sclerosus: a randomized control trial. Bizjk Ogrinu U, Senčar S, Luzar B, et al. J Obstet Gynaecol Can 2019; 41(2): 1717–25.

Forty patients were randomized to receive laser treatment or topical steroids. An improvement was seen in the laser group, but they were also treated with a potent topical steroid and this was not double-blind randomization. This therefore introduces significant problems with the conclusions that laser may be helpful.

A randomized double-blind placebo-controlled trial of autologous platelet-rich plasma intradermal injections for the treatment of vulvar lichen sclerosus. Goldstein AT, Mitchell L, Govind V, et al. J Am Acad Dermatol 2019; 80(6): 1788–9.

Thirty patients were randomized to receive placebo or platelet-rich plasma (PRP) injections. PRP was shown to be inadequate in controlling the inflammation in LS.

Chronic lichen sclerosus successfully treated with intralesional adalimumab. Feig JL, Gribetz ME, Lebwohl MG. Br J Dermatol 2016; 174: 687–9.

Intralesional adalimumab for the treatment of refractory balanitis xerotica obliterans. Lowenstein EB, Zeichner JAMA Dermatol 2013n; 149: 23–4.

These are two case reports about rapid response of longstanding balanitis xerotica obliterans to intralesional tumor necrosis factor blockers, enough to infiltrate the affected area. In both patients, adalimumab 40 mg was injected intralesionally every other week until normalization of epithelium, which began within 2 weeks for both.

Lichen simplex chronicus

Michael A. Renzi Jr., Lacy L. Sommer,
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Lichen simplex chronicus (LSC, or neurodermatitis circumscripta) is characterized by pruritic, lichenified plaques that most often occur on the neck, anterior tibias, ankles, wrists, and anogenital region in response to chronic localized scratching or rubbing. Primary LSC evolves on apparently normal skin from pruritus of unclear etiology, whereas secondary LSC is superimposed upon preexisting dermatoses, particularly atopic dermatitis, psoriasis, or dermatophytosis.

Psychogenic factors can play an important contributory role, and psychopathology, such as anxiety and obsessive-compulsive disorder, have been found at higher rates in LSC groups compared with control groups. An association between longstanding LSC on the limbs and chronic cervical or lumbar radiculopathy has been reported.

MANAGEMENT STRATEGY

The objective of treatment is to remove environmental triggers, break the itch-scratch cycle, and treat any underlying cutaneous or systemic disease. Patients' understanding of their role in the itch-scratch cycle is essential to enlisting their cooperation in avoiding scratching, thereby facilitating a more complete and permanent recovery. Recurrences are frequent, and complete resolution often requires multiple approaches to therapy. Environmental triggers such as harsh skin care products or bathing regimens, friction, and excessive moisture or dryness should be minimized or eliminated. High-potency *topical corticosteroids*, such as clobetasol, diflorasone, and betamethasone, as creams or ointments, are the initial treatments of choice. The potency and/or frequency of application of topical corticosteroids should be decreased as the lesion resolves to avoid atrophy with long-term use. Adjunctive therapies, such as *doxepin cream*, may be introduced if topical corticosteroids are not easily tapered. Occlusion has been found to be a successful aid to therapy because

it provides a physical barrier to prevent scratching and permits enhanced and prolonged application of topical medications. *Occlusive plastic film* or *hydrocolloid dressings* have been used alone or over mid-potency corticosteroids. *Flurandrenolide tape* is very effective as both an occlusive and antiinflammatory measure. It is typically changed once daily, although a short occlusion-free period each day will help minimize the side effects of occlusion therapy. In chronic, difficult cases on the lower leg, an Unna boot (a gauze roll impregnated with zinc oxide) may be applied for up to 1 week, provided there is no concomitant infection of the occluded area. *Calcineurin inhibitors* such as *tacrolimus* and *pimecrolimus* also have been successfully used as monotherapy to treat LSC and offer a good alternative for treatment in steroid-sensitive areas such as the genitalia.

Intralesional injections of triamcinolone at monthly intervals can rapidly induce involution. Although highly effective, repeated injections may cause depigmentation or thinning of the epidermis; therefore, other therapies should be used if several treatments with intralesional corticosteroids do not clear LSC. Transcutaneous pneumatic injection devices can decrease pain and increase the efficacy of intralesional injections. Secondary infections should be treated with appropriate topical or systemic antibiotics. Intralesional *botulinum toxin* has been reported to offer lasting relief in patients with recalcitrant LSC.

A variety of other therapies have been reported to be effective in the management of LSC. *Doxepin cream*, *capsaicin cream*, and *aspirin/dichloromethane solution* are occasionally of value as monotherapy but are probably best used as adjunctive therapy when LSC does not quickly clear with topical or intralesional corticosteroids. *Oral antihistamines* may be useful for their sedative effect on patients who scratch during their sleep. *Surgical excision* has been used infrequently to treat nodular LSC. Non-invasive *transcutaneous electrical nerve stimulation (TENS)* has emerged as a possible effective treatment for pruritic dermatoses such as LSC. Pruritus and neuralgia of varying etiologies have responded to the anticonvulsant *gabapentin*, which may explain its usefulness in treating LSC. In more severe or recalcitrant conditions, *psychotherapy* and/or the use of *psychopharmacologic agents* may be needed for sustained improvement. *Benzodiazepines*, *amitriptyline*, *pimozide*, and *doxepin* have been used to treat neurotic excoriations and severe neurodermatitis. Neurodermatitis has improved with habit-reversal *behavioral therapy*, *biofeedback*, and *hypnotherapy* in certain individuals. *Acupuncture* and *electroacupuncture* are labor intensive but have been effective in treating some cases of LSC. *Alitretinoin* was used successfully in a single case of LSC on the hands. Adjunctive therapy with *narrowband ultraviolet B (UVB) phototherapy* may prove useful for cases of vulvar LSC. Focused ultrasound therapy has also been shown to be effective for vulvar LSC, although this modality is not widely available and requires general anesthesia.

Specific Investigation

- Skin biopsy with periodic acid-Schiff stain

LSC that is atypical in appearance or poorly responsive to therapy should be biopsied and cultured to look for preexisting dermatoses and underlying cutaneous malignancy or infection. Squamous cell carcinoma, though rare, has been reported to develop within longstanding LSC. Lesions should be surveyed carefully, and fixed plaques or proliferating nodules should raise suspicion for malignant transformation.

First-Line Therapies

- Topical corticosteroids **A**
- Occlusion – flurandrenolide tape **C**
- Intralesional corticosteroids **C**
- Transcutaneous pneumatic injection **E**

A double-blind, multicenter trial of 0.05% halobetasol propionate ointment and 0.05% clobetasol 17-propionate ointment in the treatment of patients with chronic, localized atopic dermatitis or lichen simplex chronicus. Datz B, Yawalkar S. *J Am Acad Dermatol* 1991; 25: 1157–60.

In 127 patients with chronic, localized atopic dermatitis or LSC, healing was reported in 65.1% of those treated with halobetasol propionate ointment (a superpotent group I topical corticosteroid) compared with 54.7% of those treated with clobetasol propionate (a weaker group I topical corticosteroid). Success rates, early onset of therapeutic effect, and adverse effects were similar in the two treatment groups.

Group I topical corticosteroids should not be used for more than 2 weeks. They are therefore best combined with adjuvant therapies such as topical doxepin or pimecrolimus cream.

Flurandrenolone tape in the treatment of lichen simplex chronicus. Bard JW. *J Ky Med Assoc* 1969; 67: 668–70.

Of the 18 patients in the study, 10 used flurandrenolone tape, and eight used a topical corticosteroid preparation without occlusion. Lasting remissions were seen in 70% of those using the tape versus 25% of those using topical corticosteroids without occlusion. Duration of therapy is not mentioned.

The use of occlusion with topical corticosteroids is considered the treatment of choice for LSC despite the lack of adequate clinical trials.

Update on intralesional steroid: focus on dermatoses. Richards RN. *J Cutan Med Surg* 2010; 14: 19–23.

In the absence of any formal clinical studies since the 1960s, Richards compiled a review of peer-reviewed literature, six standard dermatology textbooks, and questionnaires from dermatologists to summarize the available information on the use of intralesional steroids in localized dermatoses. Pooled clinical experience is presented in this review, which suggests that triamcinolone acetonide 2.5 mg/mL administered in total doses of 7.5–20 mg intralesionally every 3–4 weeks has proven to be a safe, economical, and highly effective treatment for localized dermatoses such as LSC.

Corticosteroid injections are considered first-line therapy despite the lack of adequate controlled clinical trials.

Less painful and effective intralesional injection method for lichen simplex chronicus. Jung HM, Eun SH, Lee JH, et al. *J Am Acad Dermatol* 2018; 79: e105–6.

Clinical Pearl discussing utilization of a transcutaneous pneumatic device to deliver triamcinolone 0.4 mg/mL at consistent quantities and depths. Each injection was spaced 2 cm apart. The authors reported significant efficacy 1 month after a single treatment to lesions that previously failed to respond to potent topical steroid application.

Second-Line Therapies

- Doxepin cream **B**
- Pimecrolimus cream **C**
- Tacrolimus ointment **B**
- Capsaicin cream **E**

The antipruritic effect of 5% doxepin cream in patients with eczematous dermatitis. Doxepin Study Group. Drake LA, Millikan LE. *Arch Dermatol* 1995; 131: 1403–8.

A multicenter, double-blind trial conducted to evaluate the safety and antipruritic efficacy of 5% doxepin cream in patients with LSC ($n = 136$), nummular eczema ($n = 87$), or contact dermatitis ($n = 86$). Patients treated with doxepin versus vehicle had significantly greater pruritus relief. Of doxepin-treated patients, 60% experienced relief from pruritus within 24 hours with a response rate of 84% by the end of the study.

Pimecrolimus 1% cream for pruritus in postmenopausal diabetic women with vulvar lichen simplex chronicus: a prospective noncontrolled case series. Kelekci HK, Uncu HG, Yilmaz B, et al. *J Dermatolog Treat* 2008; 19: 274–8.

Twelve postmenopausal diabetic women with vulvar LSC were treated with pimecrolimus 1% cream twice daily for 3 months. All patients experienced a statistically significant reduction in pruritus when evaluated at 4 weeks and 12 weeks. After 3 months of treatment, 10 women (83.3%) had a complete cure, and the pruritus was improved in the two remaining women.

Effective treatment of scrotal lichen simplex chronicus with 0.1% tacrolimus ointment: an observational study. Tan ES, Tan AS, Tey HL. *J Eur Acad Dermatol Venereol* 2015; 29: 1448–9.

In this prospective, observational study, 29 men presenting with scrotal LSC were treated with 0.1% tacrolimus ointment twice daily for 6 weeks. After treatment, there were statistically significant improvements ($p \leq 0.001$) in mean itch score, mean itch frequency, mean sleep score, degree of skin modification, and mean affected scrotal surface area. The mean onset of action was 3.5 days. Six patients experienced intolerable burning sensation and discontinued treatment.

Treatment of prurigo nodularis, chronic prurigo and neurodermatitis circumscripta with topical capsaicin. Tupker RA, Coenraads PJ, van der Meer JB. *Acta Derm Venereol* 1992; 72: 463.

In this small, open study, two patients with corticosteroid-unresponsive neurodermatitis circumscripta were treated with 0.25% capsaicin, applied five times daily, resulting in flatter lesions and marked relief of itching.

Third-Line Therapies

- Transcutaneous electrical stimulation **B**
- Acupuncture and electroacupuncture **C**
- Botulinum toxin **D**
- Aspirin **A**
- Gabapentin **D**
- Psychotherapy **E**
- Hypnosis **E**
- Psychopharmacotherapy **E**
- Surgical excision **E**
- Alitretinoin **E**
- Phototherapy **C**
- Focused ultrasound therapy **B**

Use of transcutaneous electrical nerve stimulation for chronic pruritus. Mohammad Ali BM, Hegab DS, El Saadany HM. *Dermatol Ther* 2015; 28: 210–5.

Ten patients with atopic dermatitis (group I), 20 patients with LSC (group II), and 16 with chronic intractable pruritus from chronic liver disease (group III) had their most pruritic, distressing

lesions treated with TENS. Treatment occurred during three 30-minute sessions each week and continued for a maximum of 12 sessions or until symptomatic resolution was obtained. The results showed statistically significant mean reductions in visual analog scale (VAS) scores at weeks 2 and 4 compared with baseline for all groups. At the 1-month follow-up, mean reductions in VAS itch scores from baseline remained statistically significant for groups I and II but were found to be statistically insignificant for group III.

Acupuncture treatment of 139 cases of neurodermatitis. Yang Q. *J Tradit Chin Med* 1997; 17: 57–8.

Acupuncture was used to treat 96 patients with localized neurodermatitis and 43 patients with generalized neurodermatitis. A course of treatment was 10 days, with 3- to 5-day rest periods between multiple courses of therapy. An 81% cure rate and 14% improvement rate were reported, but the number of courses of therapy and long-term follow-up were not specified.

Acupuncture and electroacupuncture (where acupuncture needles are stimulated with low-voltage, high-frequency stimulation) may be used to reduce the proinflammatory neuropeptide state in pruritic and inflamed skin and thereby promote a more normal state of neuropeptide homeostasis.

Botulinum toxin type A injection in the treatment of lichen simplex: an open pilot study. Heckmann M, Heyer G, Brunner B, et al. *J Am Acad Dermatol* 2002; 46: 617–9.

Four patients received 20 units of botulinum toxin type A (100 U/mL) per 2 cm × 2 cm area of an LSC plaque. One week after injection, there was a noticeable reduction in pruritus. Three patients were free of itching, and the remaining patient had >50% reduction in itching. After 12 weeks, three patients remained asymptomatic.

The effect of topically applied aspirin on localized circumscribed neurodermatosis. Yosipovitch G, Sugeng M, Chan YH, et al. *J Am Acad Dermatol* 2001; 45: 910–3.

In this double-blind, crossover, placebo-controlled study, 29 patients with LSC were randomized to receive aspirin/dichloromethane solution treatment followed by placebo or vice versa. In the aspirin/dichloromethane treatment group, 46% achieved a significant response, and 12% of the placebo group achieved a comparable improvement.

Therapeutic hotline: treatment of prurigo nodularis and lichen simplex chronicus with gabapentin. Gencoglan G, Inanir I, Gunduz K. *Dermatol Ther* 2010; 23: 194–8.

Five patients with LSC and four with prurigo nodularis refractory to antihistamines, corticosteroids, phototherapy, and antidepressants were treated with gabapentin. Gabapentin therapy was initiated at 300 mg/day and titrated up by 300 mg/day every 3 days to a final dose of 900 mg/day. Doses were subsequently decreased during a total treatment period ranging from 4 to 10 months. After 2 months, some reduction in pruritus was noted in all patients. Clinical improvement was maintained during the 3-month follow-up period after patients discontinued gabapentin. All patients had improvement in their pruritus, with residual itching responding to topical lubricants. Side effects were limited to tolerable sedation in some patients.

The behavioral treatment of neurodermatitis through habit-reversal. Rosenbaum MS, Ayllon T. *Behav Res Ther* 1981; 19: 313–8.

Four patients with neurodermatitis received a single treatment session in which they learned to substitute a competing response for their urges to scratch. There was a rapid reduction in scratching in all patients. At 6 months, scratching had been eliminated in one patient and markedly reduced in three patients.

Brief hypnotherapy of neurodermatitis: a case with 4-year followup. Lehman RE. *Am J Clin Hypn* 1978; 21: 48–51.

One patient with extensive neurodermatitis was treated with eight sessions of hypnotherapy. She was clear within 2 weeks after her last session and remained clear at 4-year follow-up.

Improvement of chronic neurotic excoriations with oral doxepin therapy. Harris BA, Sherertz EF, Flowers FP. *Int J Dermatol* 1987; 26: 541–3.

Two patients with chronic neurotic excoriations had improvement in symptoms and in clinical signs of their skin condition within several weeks of receiving oral doxepin (30–75 mg daily).

Nodular lichen simplex of the scrotum treated by surgical excision. Porter WM, Bewley A, Dinneen M, et al. *Br J Dermatol* 2001; 144: 343–6.

Two patients with nodular LSC of the scrotum were treated by surgical excision of LSC plaques with remission lasting over 12 months.

Efficacy of treatment with oral alitretinoin in patient suffering from lichen simplex chronicus and severe atopic dermatitis of hands. D'Erme AM, Milanesi N, Angoletti AF, et al. *Dermatol Ther* 2014; 27: 21–3.

One patient with LSC of the hands and underlying atopic dermatitis received alitretinoin 30 mg daily and topical emollients for 12 weeks. Substantial clinical improvement was achieved with no recurrence observed 4 months after the end of treatment.

The efficacy and safety of targeted narrowband UVB therapy: a retrospective cohort study. Esen Salman K, Kivanç Altunay İ, Salman A. *Turk J Med Sci* 2019; 49: 595–603.

Single-center retrospective cohort of 26 patients with LSC who received targeted narrowband UVB (NB-UVB) therapy. Eighteen were treated with NB-UVB monotherapy while the remaining patients received combination therapy with topical tacrolimus, corticosteroids, or antihistamines. Patients were treated 2–3 times per week for a mean number of 29 sessions. Of the 13 subjects that completed follow-up, 11 (84.6%) showed a moderate or better response and seven (53.8%) showed a complete response.

Short- and long-term efficacy of focused ultrasound therapy for non-neoplastic epithelial disorders of the vulva. Wu C, Zou M, Xiong Y, et al. *BJOG* 2017; 124(Suppl 3): 87–92.

Eighty-five patients with vulvar LSC received a single session of focused ultrasound under intravenous anesthesia in an operating room. Treatment parameters were power 3.5 W, frequency 10 MHz, and pulses 1000 Hz. Patients were treated for 15–30 minutes until a clinical end point of mild congestion, swelling, and hyperthermia was achieved. The authors reported a 48.24% cure rate for LSC. Nineteen (22.35%) patients experienced recurrence after treatment.

Linear IgA bullous dermatosis

Gérôme Bohelay, Frédéric Caux



Linear IgA bullous dermatosis is a clinically and immunologically heterogeneous, subepidermal autoimmune blistering disease. It is defined by pure or predominant IgA linear deposits at the epidermal basement membrane zone of skin or mucous membrane. This rare disease also known in childhood as *chronic bullous disease of childhood* has a mean age of onset of 5 years; it occurs in adults around 55 years and often is chronic. It may be idiopathic or drug-induced, mainly by vancomycin in adults. The cutaneous manifestations include papules, vesicles, or blisters with a characteristic sign known as 'string of pearls' (peripheral vesiculation on annular plaques). These lesions occur on the face around the mouth, the perineal area, and the limbs in children; in adults, involvement of buttocks, elbow, and knee as seen in dermatitis herpetiformis can be encountered but bipolar distribution (face, extremities) can also arise. The oral, genital, and ocular mucosae are commonly involved. Skin biopsy shows a subepidermal blister and a neutrophilic dermal infiltrate, and direct immunofluorescence showing linear isolated or predominant IgA deposits on the basement membrane zone establish the diagnosis. Several target antigens recognized by circulating IgA autoantibodies have been identified using immunoblot: LABD97 and LAD-1, which are proteolytic fragments of BP180 antigen, full length and NC16a region of BP180 antigen, BP230 antigen, laminin-332, laminin- γ 1, integrin α 6 β 4, and type VII collagen. The clinical presentation probably is related to the recognized target antigen(s) explaining the absence of a unique phenotype.

MANAGEMENT STRATEGY

A detailed medical history should be obtained because there are some reports of linear IgA bullous dermatosis occurring after vaccinations, infections, or use of drugs. Moreover, associated diseases such as ulcerative colitis, Crohn disease, and lymphoproliferative

malignancies have been rarely reported but should be detected. In case of ocular or ear, nose, and throat (ENT) functional signs, patients should be evaluated by an ophthalmologist or otolaryngologist to delineate mucosal lesions, which may influence the treatment. In patients with mucosal involvement who are at risk of chronic evolution, immunologic investigations (BP180 ELISA, BP230 ELISA, type VII collagen ELISA, immunoblotting) must be performed.

Even if spontaneous remission of linear IgA bullous dermatosis may occur, treatment is required to control flare of blisters. If drug-induced disease is considered, the suspect trigger drug must be withdrawn. Treatment of linear IgA bullous dermatosis is dictated by the severity of disease and the areas of involvement. No therapeutic recommendations exist, and all drugs are used off-label. Because linear IgA bullous dermatosis tends to be chronic, it is important to be aware of the potential, not only for short-term but also for long-term, toxicities in any treatment used.

Despite the absence of controlled trials evaluating dapsone in linear IgA bullous dermatosis, this is the first-line therapy. The majority of patients with disease limited to the skin will respond well, with the mucous membrane lesions being more resistant. Dapsone generally works quite rapidly, with responses often occurring in the first few days of starting the drug. Prior to prescribing dapsone, patients should be screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency because those with a deficiency in this enzyme can develop severe hemolysis and should avoid this drug.

The dosage of dapsone should be individually titrated to determine the best dose that effectively controls the disease. Typically, initial dosage is low (< 0.5 mg/kg) and slowly increased (25 mg per month while monitoring full blood count and liver function tests) until control of blistering is achieved. A dose of 2.5–3.0 mg/kg is usually considered maximal. After disease control is attained, the dosage can then be slowly reduced to the minimum that maintains appropriate control.

All patients treated with dapsone will experience some degree of hemolysis that is usually dose dependent. A reduction of approximately 2–3 g of hemoglobin is often observed. As long as this decrease is relatively gradual and patients have no history of cardiovascular disease or anemia, this is usually well tolerated. Methemoglobinemia, which is also dosage dependent, occurs in most patients but is usually asymptomatic. More worrisome toxicities include bone marrow suppression and even agranulocytosis, which usually happens early in the course of therapy, and a dapsone-induced neuropathy, which appears more commonly in patients treated for several years with more than 200 mg of dapsone daily. Less commonly, hepatitis, nephritis, pneumonitis, erythema multiforme, and dapsone hypersensitivity syndrome have all been reported.

For those patients who fail to achieve satisfactory control of their disease with dapsone as first-line therapy, it is often of value to add corticosteroids. This combination is considered second-line therapy. Topical corticosteroids could be added in mild disease and can even be effective as a sole agent. Systemic corticosteroids may be associated in moderate-to-severe disease; the dosage of prednisone required is often in the 20–40-mg daily range but may be higher. The benefit–risk balance for systemic corticosteroids in children has to be evaluated since these patients are more prone to develop complications arising from the use of steroids.

Alternatives to dapsone are the sulfonamides: *salazosulfapyridine* (a.k.a. *sulfasalazine*) and *sulfapyridine*. Salazosulfapyridine, which is also effective in treating ulcerative colitis and Crohn disease, may be successful given at a dose of 15–60 mg/kg/day. The side effects are similar to dapsone. If the patient is intolerant to dapsone, it is not recommended to use sulfonamides even if

some experts mention it is possible. Similarly it is not advised to use dapsone in case of sulfa allergy.

Other applicable second-line therapies include *erythromycin* at doses of approximately 1.5–3 g daily in adults and 50 mg/kg/day in children, and *colchicine*, which has been reported to be beneficial at doses of 1.0–1.5 mg daily. Often, erythromycin is used while awaiting confirmation of the diagnosis of linear IgA bullous dermatosis as this drug may have a beneficial effect in the first few months of treatment.

Third-line therapies include *sulfamethoxypyridazine*, which is available in the UK; antibiotics (*dicloxacillin*, *oxacillin*, *flucloxacillin*, *trimethoprim-sulfamethoxazole*, and *tetracycline* combined with *niacinamide*); immunosuppressants (*mycophenolate mofetil*, *methotrexate*, *azathioprine*, *cyclophosphamide*, *ciclosporin*); and biologic agents (*intravenous immunoglobulin (IVIG)*, *rituximab*, *omalizumab*). Toxicity profiles and financial considerations favor using antibiotics before treatment with the immunosuppressive agents or IVIG. However, in the case of life-threatening mucous membrane involvement or blindness risks (ocular, pharyngeal, esophageal, and laryngeal mucosae), immunosuppressive agents may be necessary. In severe or recalcitrant linear IgA bullous dermatosis, rituximab has been reported to be beneficial but necessitating several infusions and having a longer delay of action than in pemphigus.

The efficacy of treatments such as thalidomide, miconazole, interferon- α , infliximab, tacrolimus ointment, botulinum toxin A, and immunoabsorption has been reported in solitary case reports, making it difficult to draw a conclusion on their therapeutic effect.

Specific Investigations

- Detailed medication history
- Skin biopsy of blister for histology
- Perilesional skin biopsy for direct immunofluorescence
- Indirect immunofluorescence on human salt-split skin
- Consider ophthalmology and ENT consult if functional signs
- Consider G6PD level before dapsone use

Linear immunoglobulin A bullous dermatosis. Fortuna G, Marinkovich MP. Clin Dermatol 2012; 30: 38–50.

The diagnosis of linear IgA bullous dermatosis requires routine histologic studies as well as direct and indirect immunofluorescence studies. Once the diagnosis is confirmed, laboratory studies to be obtained will depend on the severity of the disease and specific treatment anticipated.

Autoantibody profile of a cohort of 54 Italian patients with linear IgA bullous dermatosis: LAD-1 denoted as a major auto-antigen of the lamina lucida subtype. Cozzani E, Di Zenzo G, Gasparini G, et al. Acta Derm Venereol 2020 Feb 29; 100(4): adv00070. doi: 10.2340/00015555-3415.

Drug-induced linear immunoglobulin A bullous dermatosis: a French retrospective pharmacovigilance study of 69 cases. Garel B, Ingen-Housz-Oro S, Afriat D, et al. Br J Clin Pharmacol 2019; 85: 570–9.

In this large series of drug-induced linear IgA bullous dermatosis, 20% of patients had lesions mimicking toxic epidermal necrolysis, which are not encountered in spontaneous linear IgA bullous dermatosis. Vancomycin was the suspected drug in 57% of cases.

Culprit drugs reported in the literature are in order of frequency: vancomycin, phenytoin, trimethoprim-sulfamethoxazole, penicillins,

cephalosporins, rifampin, metronidazole, moxifloxacin, diclofenac, acetaminophen, naproxen, piroxicam, ketoprofen, buprenorphine, amiodarone, atorvastatin, candesartan, captopril, furosemide, ciclosporin, lithium, glibenclamide, infliximab, verapamil, enoxaparin, minocycline, and vibramycin. Route of administration of vancomycin is usually parenteral but could be oral or intraarticular (vancomycin-loaded bone cement).

First-Line Therapy

• Dapsone	C

Idiopathic linear IgA bullous dermatosis: prognostic factors based on a case series of 72 adults. Gottlieb J, Ingen-Housz-Oro S, Alexandre M, et al. Br J Dermatol 2017; 177: 212–22.

In this large series age >70 years and lack of mucous membrane involvement were significantly associated with complete remission. First-line therapy was topical steroid, combined with dapsone and/or sulfasalazine.

Second-Line Therapies

• Dapsone and topical corticosteroids	D
• Dapsone and systemic corticosteroids	D
• Salazosulfapyridine	C
• Sulfapyridine	C
• Erythromycin	D
• Colchicine	D

Linear IgA bullous dermatosis in adults and children: a clinical and immunopathological study of 38 patients. Genovese G, Venegoni L, Fanoni D, et al. Orphanet J Rare Dis 2019; 14: 115. doi.org/10.1186/s13023-019-1089-2.

Successful treatment of a case of idiopathic linear IgA bullous dermatosis with oral sulfasalazine. Yang Z, Liu ZH, Sun CQ, Shen H. Dermatol Ther 2020; 33: e13210.

Is erythromycin an effective treatment for chronic bullous disease of childhood? A national survey of members of the British Society for Paediatric Dermatology. Farrant P, Darley C, Carmichael A. Pediatr Dermatol. 2008; 25: 479–82.

Treatment of linear IgA bullous dermatosis of childhood with colchicine. Ang P, Tay YK. Pediatr Dermatol 1999; 16: 50–2.

Third-Line Therapies

• Sulfamethoxypyridazine	E
• Dicloxacillin	D
• Flucloxacillin	E
• Trimethoprim-sulfamethoxazole	E
• Tetracycline and niacinamide	E
• Mycophenolate mofetil	D
• Methotrexate	E
• Azathioprine	E
• Cyclophosphamide	E
• Ciclosporin	E
• IVIG	D
• Rituximab	E
• Omalizumab	E

Linear IgA bullous dermatosis of childhood: good response to antibiotic treatment. de las Heras MN. Clin Exp Dermatol 2014; 39: 395–7.

Chronic bullous disease of childhood: successful treatment with dicloxacillin. Siegfried EC, Sirawan S. J Am Acad Dermatol 1998; 39: 797–800.

Treatment of linear IgA bullous dermatosis of childhood with flucloxacillin. Alajlan A, Al-Khawajah M, Al-Sheikh O, et al. J Am Acad Dermatol 2006; 54: 652–6.

In this case series of seven children complete remission without relapse was obtained in four cases and remission with relapse after flucloxacillin discontinuation in three cases.

Linear IgA bullous dermatosis responsive to trimethoprim-sulfamethoxazole. Peterson JD, Chan LS. Clin Exp Dermatol 2007; 32: 756–8.

A case of linear IgA dermatosis successfully treated with tetracycline and niacinamide. Shan XF, Zhang FR, Tian HQ, et al. Int J Dermatol. 2016; 55: e216–7.

An adult was successfully treated with the use of 1.5 g of tetracycline and 1.8 g of nicotinamide daily. Tetracyclines should not be used in children under 8 years of age because they can permanently stain teeth.

Refractory linear IgA bullous dermatosis successfully treated with mycophenolate sodium. Marzano AV, Ramoni S, Spinelli D, et al. J Dermatolog Treat 2008; 19: 364–7.

Linear IgA bullous dermatosis associated with ulcerative proctitis: treatment challenge. Yetto T, Burns C. Dermatol Online J 2018; 24: 13030/qt46421332.

One patient with concomitant ulcerative colitis was treated by mesalamine and methotrexate, which controlled both the gastrointestinal and skin issues.

Linear IgA disease. Smith JR, Kupa A, Coster DJ. Aust N Z J Ophthalmol 1999; 27: 443–6.

Prednisolone 1 mg/kg/day and cyclophosphamide 100 mg/day permitted to control severe ocular involvement of linear IgA disease in one woman.

Linear IgA disease: successful treatment with cyclosporine. Young HS, Coulson IH. Br J Dermatol 2000; 143: 204–5.

Ciclosporin 3 mg/kg/day was useful to control a patient who developed side effects of first-line and second-line treatments.

High-dose intravenous immunoglobulins for the treatment of autoimmune mucocutaneous blistering diseases: evaluation of its use in 19 cases. Segura S, Iranzo P, Martínez-de Pablo I, et al. J Am Acad Dermatol 2007; 56: 960–7.

One patient with linear IgA dermatosis in this series of autoimmune blistering diseases was controlled with the use of IVIG therapy in addition to colchicine and prednisone 15 mg/day. Five cycles of 2 g/kg/cycle permitted to discontinue prednisone.

Linear IgA bullous dermatosis treated with rituximab. Pinard C, Hebert V, Lecuyer M, et al. JAAD Case Rep 2019; 5: 124–6.

Two case reports suggest the efficacy of rituximab in recalcitrant linear IgA dermatosis.

Linear IgA bullous dermatosis successfully treated with omalizumab: a case report. Maalouf N, Hanna D. JAAD Case Rep 2019; 5: 966–9.

Lipodermatosclerosis

Ayman A. Grada, Tania J. Phillips



Lipodermatosclerosis (LDS) refers to the 'woody' indurated skin of the lower extremities in patients with longstanding venous disease. LDS is a form of fibrosing panniculitis that results from chronic inflammation and progressive fibrotic process of the skin and subcutaneous tissue secondary to chronic venous insufficiency. The diagnosis is based on clinical findings. LDS more often affects middle-aged to elderly, obese women with venous abnormalities. It is usually located above the medial malleolus on the lower leg. Venous ulcers may develop within LDS. Pain is the most consistent presenting symptom. There is a clinical continuum of LDS ranging from acute to chronic disease. The acute form presents with painful, tender, and slightly indurated plaques. Lesions are usually well-demarcated from normal skin. Acute LDS can be confused with cellulitis, thrombophlebitis, erythema nodosum, or inflammatory morphea. The chronic variant, which is strongly associated with venous insufficiency, is densely indurated with pronounced hyperpigmentation, and less painful than the acute form. In its late stages, chronic LDS alters the shape of the leg, making it look like an 'inverted champagne bottle.' Bilateral involvement can be seen in up to 50% of cases. Extreme fibrosis may lead to limitation in muscle pump function and ankle joint mobility, which may worsen the condition.

MANAGEMENT STRATEGY

The current treatment of choice is the combination of *stanazolol* and *compression therapy*. However, patients with acute LDS often find compression therapy painful. In this case *stanazolol* is used alone. *Stanazolol*, a synthetic anabolic steroid, is contraindicated

in patients with uncontrolled hypertension and heart failure. Of note, although *stanazolol* is no longer commercially available in the United States, *danazol* has been used as an alternative. However, *stanazolol* is still available in Europe, and its purchase is unregulated online. *Pentoxifylline* is an alternative that stimulates fibrinolysis but may cause gastrointestinal upset. *Niacin* has some fibrinolytic properties and has also been used. Other treatments, such as *antibiotics*, *antiinflammatory agents*, *antimetabolites*, and *long-term cimetidine*, have also been proposed. Intraleisional *triamcinolone*, platelet-rich plasma, and topical *capsaicin* may be helpful. *Surgical approaches* include *subfascial perforator endoscopic surgery (SEPS)*, *perforator vein sclerotherapy*, *ultrasound therapy*, and *complete excision of LDS followed by split-thickness skin graft repair*. Other simple lifestyle measures include weight loss, increased leg elevation, and increased exercise to improve calf muscle pump function.

Specific Investigations

- Biopsy
- Duplex ultrasound
- Laser Doppler scanning
- Ultrasound indentometry
- Capillary microscopy
- Magnetic resonance imaging (MRI)

The clinical spectrum of lipodermatosclerosis. Kirsner RS, Pardes JB, Eaglstein WH, et al. *J Am Acad Dermatol* 1993; 28: 623–7.

The diagnosis of LDS is based on clinical findings. In most cases, biopsy is not advised because 50% of biopsy sites do not heal.

Acute lipodermatosclerosis is associated with venous insufficiency. Greenberg A, Hasan A, Montalvo BM, et al. *J Am Acad Dermatol* 1996; 35: 566–8.

One-third to one-fifth of patients with acute LDS lack evidence of venous disease with routine venous evaluation. Chronic LDS may present after, or independently of, acute LDS.

Lipodermatosclerosis: the histologic spectrum with clinical correlation to the acute and chronic forms. Hurwitz D, Kirsner RS, Falanga V, et al. *J Clin Pathol* 1996; 23: 78.

Biopsy specimens of acute LDS showed little epidermal change or capillary proliferation. In the subcutis, there was lobular and septal panniculitis with eosinophils, fibrin thrombi, and purpura. Biopsies of chronic LDS showed dermal changes associated with venous insufficiency, including capillary proliferation, hemosiderin deposition, and fibrosis. Epidermal hypertrophy was also found.

Lipodermatosclerosis: a clinicopathological study of 25 cases. Walsh SN, Santa Cruz DJ. *J Am Acad Dermatol* 2010; 62: 1005–12.

Biopsies may distinguish LDS from other fibrosing entities. Most cases show pseudoxanthoma elasticum-like elastic fiber calcification within the septae.

Skin iron deposition characterises lipodermatosclerosis and leg ulcer. Caggiati A, Rosi C, Casini A, et al. *Eur J Vasc Endovasc Surg* 2010; 40: 777–82.

Lipodermatosclerosis is always accompanied by hemosiderin deposition.

Duplex venous imaging: role for a comprehensive lower extremity examination. Badgett DK, Comerota MC, Khan MN, et al. *Ann Vasc Surg* 2000; 14: 73–6.

Results of duplex scanning of 205 lower extremities with varices: 106 not previously operated and 99 previously operated for varicose veins. Egeblad K, Baekgaard N. *Ugeskr Laeger* 2003; 3016–8.

Color duplex ultrasound can accurately detect the specific location of lower extremity venous insufficiency that often leads to LDS.

Quantifying fibrosis in venous disease: mechanical properties of lipodermatosclerosis and healthy tissue. Geyer MJ, Brienza DM, Chib V, et al. *Adv Skin Wound Care* 2004; 17: 131–42.

Ultrasound indentometry was used to quantify fibrotic tissue in LDS.

Excision of lipodermatosclerotic tissue: an effective treatment for non-healing venous ulcer. Ahnlied I, Bjellerup M, Akesson H. *Acta Derm Venereol* 2000; 80: 28–30.

In seven cases, laser Doppler scanning showed an increase in blood flow in lipodermatosclerotic skin, which decreased after surgical removal of the affected area.

Microangiopathy in chronic venous insufficiency: quantitative assessment by capillary microscopy. Howlader MH, Smith PD. *Eur J Vasc Endovasc Surg* 2003; 26: 325–31.

Advanced venous disease (LDS and healed ulcer) was associated with a reduced number of capillaries and increased capillary convolution.

Magnetic resonance imaging as a diagnostic tool for extensive lipodermatosclerosis. Chan CC, Yang CY, Chu CY. *J Am Acad Dermatol* 2008; 58: 525–7.

In a single case, MRI was in agreement with histopathologic findings. Additional studies are necessary to validate this technique.

First-Line Therapies

• Compression therapy	A
• Stanazolol	B
• Compression therapy plus stanazolol	B
• HR (O-[beta-hydroxymethyl]-rutosides)	B
• Leg elevation	C

The clinical spectrum of lipodermatosclerosis. Kirsner RS, Pades J, Eaglstein WH, et al. *Am Acad Dermatol* 1993; 28: 623–7.

Traditionally LDS has been treated with compression using graded stockings or elastic bandages. The authors suggest open-toe and below-the-knee graded stockings, with 30- to 40-mmHg pressure. Stockings with a zipper in the back are easier for elderly patients to use. Patients with acute LDS often have too much pain to use compression stockings; in these patients, stanazolol 2 mg twice daily dramatically reduced pain and tenderness.

Graduated compression stockings reduce lipodermatosclerosis and ulcer recurrence. Vandongen YK, Stacey MC. *Phlebology* 2000; 25: 33–7.

A randomized, controlled trial of 150 patients showed that elastic stockings alone can improve the skin changes of LDS and lower risk of recurrence.

Removal of dermal edema with class I and II compression stockings in patients with lipodermatosclerosis. Gniadecka M, Karlsmark T, Bertram A. *J Am Acad Dermatol* 1998; 39: 966–70.

In this study, ultrasonography demonstrated that low levels of compression, class I (18–26 mmHg), in lipodermatosclerosis are as effective as class II (26–36 mmHg) in the removal of dermal edema.

Venous lipodermatosclerosis: treatment by fibrinolytic enhancement and elastic compression. Burnand K, Clemen-son G, Morland M, et al. *Br Med J* 1980; 280: 7–11.

Stanozolol 5 mg twice daily with compression was shown to reduce extravascular fibrin and area of LDS but not leg dimensions. Patients reported improvement in LDS but could not distinguish response during placebo from stanazolol treatment.

Patients taking stanazolol should be carefully monitored for excessive fluid retention, hirsutism, acne, liver function, and plasma fibrinogen concentration. Stanazolol is contraindicated in patients with uncontrolled hypertension or congestive heart failure.

Acute lipodermatosclerosis: an open clinical trial of stanazolol in patients unable to sustain compression. Vesikovic J, Medenica LJ, Pavlovic MD. *Dermatol Online J* 2008; 14: 1.

In an open trial of 17 patients, stanazolol 2 mg twice daily, without compression, decreased pain and dermal thickness.

HR (Paroven, Venoruton; O-(beta-hydroxyethyl)-rutosides) in venous hypertensive microangiopathy. Incandela L, Belacaro G, Renton S, et al. *J Cardiovasc Pharmacol Ther* 2002; 7: S7–10.

HR reduced signs and symptoms of chronic venous insufficiency and LDS.

Effect of leg elevation on the skin microcirculation in chronic venous insufficiency. Abu-Own A, Scurr JH, Smith PD. *J Vasc Surg* 1994; 20(5): 705–10.

In this study of 15 patients with lipodermatosclerosis, leg elevation resulted in a 41% median increase in blood flow velocity as measured by Doppler fluximetry.

Second-Line Therapies

• Superficial venous surgery	B
• Subfascial perforator endoscopic surgery (SEPS)	C
• Pentoxifylline	C

Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial. Gohel MS, Barwell JR, Taylor M, et al. *BMJ* 2007; 335: 83.

Surgical correction of superficial venous reflux (saphenous vein ablation) with compression reduced ulcer recurrence at 4 years compared with treatment with compression alone.

The effects on LDS were not specifically mentioned in this study.

Midterm results of endoscopic perforator vein interruption for chronic venous insufficiency: lessons learned from the North American Subfascial Endoscopic Perforatory Surgery registry. Gioviczki P, Bergan JJ, Rhodes JM, et al. *J Vasc Surg* 1999; 29: 489–502.

In this prospective registry of 148 patients who underwent SEPS ablations for LDS, patients reported improved overall LDS symptoms, including less pain, edema, and hyperpigmentation, as well as more rapid ulcer healing. Seventy-one percent of patients had a concomitant venous procedure (e.g., saphenous vein ablation).

Pentoxifylline for treating venous leg ulcer. Jull AB, Waters J, Arroll B. Cochrane Database Syst Rev 2002; 1: CD001733.

Pentoxifylline is a dimethylxanthine derivative that increases erythrocyte flexibility and reduces blood viscosity. The dose of 400 mg three times daily may be increased to 800 mg three times daily if no improvement occurs.

Pentoxifylline is a good alternative in those intolerant to stanozolol. Side effects include nausea, dizziness, heartburn, and, occasionally, vomiting.

Third-Line Therapies

• Ultrasound	D
• Excision of lipodermatosclerotic tissue	D
• Intralesional triamcinolone injections	D
• Hydroxychloroquine	D
• Danazol	E
• Oxandrolone	E
• Niacin	E
• Sclerotherapy	E
• Intralesional platelet-rich plasma	E
• Topical capsaicin	E

Ultrasound therapy for lipodermatosclerosis. Damian DL, Yiasemides E, Gupta S, et al. Arch Dermatol 2009; 145: 330–2.

Eight patients treated with 3-MHz continuous ultrasound three times weekly for 4–8 weeks showed decreased skin hardness and erythema. Patients also wore grade II compression stockings.

Excision of lipodermatosclerotic tissue: an effective treatment for nonhealing venous ulcer. Ahnlied I, Bjellerup M, Akesson H. Acta Derm Venereol 2000; 80: 28–30.

In this combined retrospective and prospective study, six of seven patients' non-healing venous ulcers healed after excision of lipodermatosclerotic tissue and split-skin graft.

Surgical removal of ulcer and lipodermatosclerosis followed by split-skin grafting (shave therapy) yields good long-term results in 'non-healing' venous leg ulcers. Schmeller W, Gaber Y. Acta Derm Venereol 2000; 80: 267–71.

In 41 patients with LDS and recalcitrant leg ulcers, despite prior treatment with compression and surgical venous ablation, shave excision with meshed split-thickness skin grafts demonstrated 67% ulcer healing at an average follow-up of 2.4 years.

Intralesional triamcinolone in the management of lipodermatosclerosis. Campbell LB, Miller OF 3rd. J Am Acad Dermatol 2006; 55: 166–8.

A retrospective chart review of 28 patients showed improvement in pain, erythema, edema, and induration after one to three intralesional injections of 5–10 mg/mL triamcinolone.

Adjunct therapies were used in the majority of the patients.

Lipodermatosclerosis: improvement noted with hydroxychloroquine and pentoxifylline. Choonhakarn C, Chaowattapanit S. J Am Acad Dermatol 2012; 66: 1013–4.

A retrospective chart review of 32 patients showed improvement in pain, erythema, edema, and induration after treatment with hydroxychloroquine (maximum <6.5 mg/kg/day) and pentoxifylline (1200 mg/day) within 2 weeks to 6 months.

An acute case of lipodermatosclerosis successfully treated with danazol. Hammerman S, Mamakos L, Falanga V. J Am Acad Dermatol 2012; 66 (Suppl 1): AB42.

One patient with LDS resistant to leg elevation, aspirin, and niacin was treated with oral danazol, with improvement of pain and disease extension. With 100 mg twice daily, erythema and induration also improved. After 4 months, the patient transitioned to compression only without recurrence of LDS.

Danazol is an anabolic androgen, with fibrinolytic and immunomodulatory properties similar to stanozolol. Monitoring for liver function should be performed.

Treatment of lipodermatosclerosis with oxandrolone in a patient with stanozolol-induced hepatotoxicity. Segal S, Cooper J, Bologna J. J Am Acad Dermatol 2000; 43: 558–9.

Oxandrolone is another anabolic androgen similar to stanozolol with known fibrinolytic activity but with a lower incidence of hepatotoxicity. A single patient with LDS initially improved within 2 weeks with stanozolol (2 mg daily) but developed hepatotoxicity. Oxandrolone 10 mg twice daily reduced pain and induration of the legs with 3 months of treatment.

Lipid lowering and enhancement of fibrinolysis with niacin. Holvoet P, Collen D. Circulation 1995; 92: 698–9.

Niacin, at 100–150 mg three to five times a day, improved the hyperlipidemia often associated with LDS. In large doses it causes vasodilation and stimulates fibrinolysis.

Niacin is another alternative for patients who cannot tolerate stanozolol.

The effect of ultrasound-guided sclerotherapy (UGS) of incompetent perforator veins on venous clinical severity and disability scores. Masuda EM, Kessler DM, Lurie F, et al. J Vasc Surg 2006; 43: 551–6.

In this 68-patient series, UGS was an effective modality in the treatment of incompetent perforator veins and associated venous hypertension.

Refractory lipodermatosclerosis treated with intralesional platelet-rich plasma. Jeong K, Shin M, Kim N. J Am Acad Dermatol 2011; 65: e157–8.

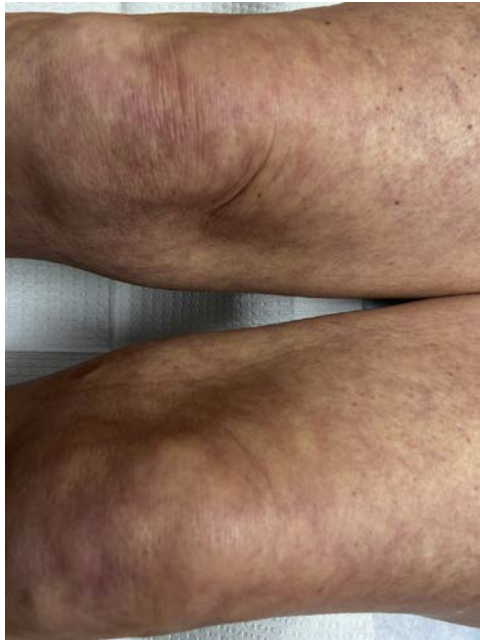
This is a single case report of LDS and recalcitrant venous leg ulcer treated intralesionally with the patient's own platelet-rich plasma. Ulcer healing occurred with improvement in LDS and no ulcer recurrence over 6 months.

Topical capsaicin for the treatment of acute lipodermatosclerosis and lobular panniculitis. Yosipovitch G, Mengesha Y, Faclaru D, et al. J Dermatolog Treat 2005; 16: 178–80.

Two cases of acute LDS resolved with topical capsaicin 0.075% applied five times daily to an area pretreated with topical anesthetic EMLA (eutectic mixture of lidocaine 2.5% and prilocaine 2.5%). Mechanism of action is unclear.

Livedo reticularis

Ruwani P. Katugampola, Andrew Y. Finlay



Livedo reticularis (LR) is the netlike, mottled, violaceous discoloration of the skin secondary to dilatation and stagnation of blood within dermal capillaries. The unaffected normal-colored islands of skin are the areas where blood supply is sufficient; in the network areas the supply is insufficient. This commonly occurs on the legs, arms, and trunk, but can be diffuse and generalized (livedo racemosa) and is more pronounced after exposure to cold. LR can be physiologic (cutis marmorata), can occur as a primary phenomenon (idiopathic LR), or can be secondary to a number of diseases that cause dermal vessel wall thickening and/or lumen occlusion. Secondary causes of LR include infections (hepatitis B and C, HIV, meningococcus, mycoplasma, tuberculosis), systemic lupus erythematosus, polyarteritis nodosa, antiphospholipid syndrome, cryoglobulinemia, oxalosis, cholesterol emboli, hypercalcemia (secondary to malignancy, hyperparathyroidism, renal failure), underlying malignancy (as a paraneoplastic phenomenon), endocrinological crisis (pheochromocytoma), and medications. Idiopathic LR may be congenital (cutis marmorata telangiectatica congenita) or associated with painful ulcers (livedoid vasculitis) or with cerebrovascular involvement (Sneddon syndrome). LR has been reported as a paraneoplastic phenomenon associated with metastatic breast cancer, renal cell carcinoma, and multiple myeloma. LR has also been reported as a complication of accidental intraarterial filler injections, such as hyaluronic acid fillers and use of silicone implants for soft tissue augmentation.

MANAGEMENT STRATEGY

The etiology of physiologic and primary LR is unknown, and no definitive treatment is available. The management of primary LR

depends on the presence of associated ulcers, anomalies (congenital form), and systemic involvement (Sneddon syndrome). In secondary LR, the underlying cause needs to be identified and treated.

Physiologic LR, which occurs in healthy children and adults in response to cold weather, is diffuse, mild, temporary, and usually asymptomatic. No specific treatment is required for this condition except *avoidance of cold exposure*, protection from cold exposure with *warm clothing*, and *rewarming* the affected area.

Cutis marmorata telangiectatica congenita is rare and presents at birth or soon after birth. A small proportion of affected children have associated congenital anomalies, such as hemangiomas, glaucoma, limb atrophy, cardiac malformation, or psychomotor retardation, that need to be identified and referred for appropriate specialist care. The LR in these children usually spontaneously disappears or markedly improves with age.

Patients with Sneddon syndrome are at risk of cerebrovascular disease and may benefit from antiplatelet or *antithrombotic treatment*. The timing of such treatment is debated, as LR may precede the neurologic events by up to 10 or more years. Advice regarding decreasing or eliminating risk factors predisposing to cerebrovascular events such as smoking, obesity, hypertension, and oral contraceptives is important.

Although multiple agents, including antiplatelet and anticoagulant therapy, danazol, pentoxifylline, and systemic steroids, have been used to treat ulcers associated with LR, no single agent has been shown to completely resolve the LR itself.

Several medications, including those used in dermatology, have been associated with LR. The decision to withdraw the suspected medication should be based on clinical judgment, alternative treatments, and other side effects rather than the appearance of LR per se.

Specific Investigations

- Skin biopsies for microscopy and direct immunofluorescence (adults)
- Full blood count and renal function
- Rheumatologic serologic tests
- Cryoglobulin level
- Anticardiolipin antibodies
- Coagulation screen
- Serum lipid profile
- Serum calcium
- Infection screen

A detailed clinical history followed by physical examination is essential, especially in diagnosing Sneddon syndrome, identifying congenital anomalies in infants, and in excluding secondary causes of LR. The histology of LR is non-inflammatory thickening of dermal vessel walls with eventual occlusion of the lumen.

Livedo reticularis: a review of the literature. Sajjan VV, Lunge S, Swamy MB, et al. Indian Dermatol Online J 2015; 6: 315–21.

This review of LR includes an extensive list of its systemic associations. The authors conclude that management of secondary LR should be directed toward the underlying cause and that all patients with either primary or secondary LR should be encouraged to avoid the use of tobacco and vasoconstricting medications.

The histopathological characteristics of livedo reticularis. In SI, Han JH, Kang HY, et al. J Cutan Pathol 2009; 36: 1275–8.

A survey of 16 patients with LR concluded that multiple skin biopsies from both the peripheral erythematous and central whitish areas in LR increase diagnostic yield.

Diagnostic impact and sensitivity of skin biopsies in Sneddon's syndrome. A report of 15 cases. Wohlrab J, Fisher M, Wolter M, et al. *Br J Dermatol* 2001; 145: 285–8.

Deep 4-mm punch biopsies from the central white part of the LR demonstrated a sensitivity of 27% with one biopsy, 53% with two biopsies, and 80% with three biopsies of diagnosing Sneddon syndrome in clinically suspected cases. The authors concluded that the positive histology was important for commencing prophylaxis of cerebrovascular events in patients initially presenting with LR.

Livedo reticularis: an underutilized diagnostic clue in cholesterol embolization syndrome. Chaudhary K, Wall BM, Rasberry RD. *Am J Med Sci* 2001; 321: 348–51.

Six out of eight patients with unexplained acute renal failure due to suspected cholesterol emboli syndrome (CES) demonstrated cholesterol emboli in skin biopsies of LR. Deep skin biopsies of LR are proposed as a safe diagnostic procedure to confirm CES, thus avoiding increased morbidity associated with biopsy of visceral organs.

Livedo reticularis: a cutaneous clue to an underlying endocrine crisis. Shrikrishnapalasuriyar N, Noyvirt M, Evans P, et al. *Endocrinol Diabetes Metab Case Rep* 2018; 17-0179. doi: 10.1530/EDM-17-0170 [eCollection 2018].

This case report of a 54-year old woman presenting with pheochromocytoma crisis in association with diffuse LR affecting the lower half of her body and limbs highlights that LR can be a rare but significant cutaneous marker of an endocrine crisis. LR in this setting is thought to develop due to catecholamine-induced arteriolar vasospasm resulting in pooling of blood in the surrounding venules.

First-Line Therapies

• Warfarin	D (Sneddon syndrome associated with positive antiphospholipid antibodies)
• Aspirin or clopidogrel	D (Sneddon syndrome in the absence of antiphospholipid antibodies)

Sneddon syndrome: a comprehensive overview. Samanta D, Cobb S, Arya K. *J Stroke Cerebrovasc Dis* 2019; 28: 2098–108.

This comprehensive overview recommends that Sneddon syndrome associated with positive antiphospholipid antibodies should be treated with the high-dose antithrombotic agent, warfarin, aiming for an international normalized ratio of >3, to reduce the risk of thrombosis. Although treatment of antiphospholipid antibodies negative Sneddon syndrome is more controversial, antiplatelet agents (aspirin or clopidogrel) and warfarin are thought to have similar efficacy in preventing thrombotic cerebral events.

Second-Line Therapies

• Corticosteroids	D
• Psoralen plus ultraviolet A phototherapy (PUVA)	D
• Pentoxifylline + methylprednisolone	E
• Pentoxifylline + nifedipine	E

Cholesterol emboli syndrome in type 2 diabetes: the disease history of a case evaluated with renal scintigraphy. Piccoli GB, Sargiotto A, Burdese M, et al. *Rev Diabetic Stud* 2005; 2: 92–6.

A 75-year-old obese, diabetic, hypertensive man with moderate dyslipidemia who developed CES after endovascular intervention manifesting as acute renal failure and LR of both feet. Methylprednisolone 300 mg intravenously for 3 days followed by oral prednisolone 25 mg daily and tapered over 2 months, commenced in view of deteriorating renal function, resulted in improvement in serum creatinine and disappearance of LR within 2 days of starting treatment.

Livedo reticularis and livedoid vasculitis responding to PUVA therapy. Choi HJ, Hann SK. *J Am Acad Dermatol* 1999; 40: 204–7.

Two patients with ulcers due to livedoid vasculitis of the lower legs resistant to treatment with other systemic treatment, including aspirin, prednisolone, and pentoxifylline, were treated with systemic PUVA using methoxsalen. Only the lower legs were exposed to UVA initially with 4 J/cm² three times a week and subsequent 1 J/cm² increments. No significant ulcers had recurred at 3- and 6-months' follow-up of the two patients after the last treatment. Improvement in the discoloration of the skin affected by LR was noted in one of the patients at completion of PUVA treatment.

Widespread livedoid vasculopathy. Marzano AV, Vanotti M, Alessi E. *Acta Derm Venereol* 2003; 83: 457–60.

A 37-year-old woman with widespread LR and recurrent painful ulcers on all limbs, trunk, and scalp was treated with intravenous methylprednisolone 80 mg/day for 5 days, followed by an intramuscular and subsequent tapering oral dose to 32 mg/day and with pentoxifylline 400 mg twice daily for 2 months. There was a marked clinical improvement within 2 weeks of treatment, and the intensity of the LR faded but did not completely resolve.

Generalized livedo reticularis: a rare variety. Goyal P, Dayal S, Sahu P. *Indian J Dermatol* 2019; 64: 59–61.

A 40-year old man with a 4-year history of asymptomatic generalized LR with no associated underlying cause was treated with oral pentoxifylline 400 mg three times daily and oral nifedipine 10 mg twice daily. Mild improvement in LR was noted after 6 weeks of treatment; patient was subsequently lost to follow-up.

Third-Line Therapies

• Chemical lumbar sympathectomy	C
• Withdrawal of causative medications (minocycline, interferon- α_{2b} , or amantadine)	D
• Simvastatin	E

Chemical lumbar sympathectomy in the treatment of idiopathic livedo reticularis. Wang WH, Zhang L, Li X, et al. *J Vasc Surg* 2015; 62: 1018–22.

Ten women with idiopathic LR were treated with L3–4 chemical lumbar sympathectomy (CLS) using 5% phenol, 2 mL in each injection site. Seven patients were 'clear or almost clear' of LR after CLS; LR recurred in two of these patients ≤ 1 year during follow-up but achieved 'clear or almost clear' skin after repeat CLS.

The women recruited for this study were bothered by the social inhibition caused by LR and 'showed a very strong desire for treatment by seeking medical treatment at least twice and waiting for at least 1 week to make a decision' [to have the procedure].

Livedo reticularis associated with interferon α therapy in two melanoma patients. Ruiz-Genao DP, García-F-Villalta MJ, Hernández-Núñez A, et al. *J Eur Acad Dermatol Venereol* 2005; 19: 252–4.

Two patients treated with subcutaneous interferon- α_{2b} as adjuvant therapy for malignant melanoma (American Joint Committee on Cancer stages IIA and IIB, respectively) developed LR on the legs and trunk 2 weeks after commencing treatment. LR cleared completely with no further recurrence after treatment was discontinued for other reasons.

Amantadine-induced livedo reticularis – case report. Quaresma MV, Gomes AC, Serruya A, et al. *An Bras Dermatol* 2015; 90: 745–7.

A 79-year-old man with Parkinson disease treated with amantadine, carbidopa, and levodopa developed LR. This resolved with the discontinuation of amantadine. Amantadine is one of the more common drugs to cause LR.

Amantadine-induced livedo reticularis in a child treated off label for neurobehavioral disorders. Helmandollar KJ, Hoverson KR, Meyerle JH. *Cutis* 2018; 102: E8–9.

An 8-year-old boy with attention deficit hyperactivity disorder, bipolar disorder, and autism spectrum treated with amantadine developed LR. The LR improved 5 months after discontinuation of amantadine. This case is presented to highlight that amantadine, which has been reported to cause LR, is often used off-label for treatment of several pediatric neurobehavioral conditions.

Livedo reticularis caused by cholesterol embolization may improve with simvastatin. Finch TM, Ryatt KS. *Br J Dermatol* 2000; 143: 1319–20.

A 69-year-old man with LR without ulceration of the legs extending to the lower abdomen due to cholesterol embolization failed to respond to low-dose aspirin and low-fat diet. Fasting serum cholesterol was 6.9 mmol/L⁻¹ and serum triglyceride was normal. Three months after initiation of simvastatin 10 mg daily, the serum cholesterol decreased to 4.9 mmol/L⁻¹ with associated reduction in extent and prominence of the LR.

Livedoid vasculopathy

Molly J. Youssef, Bethany R. Hairston,
Mark D.P. Davis



Livedoid vasculopathy, or livedoid vasculitis, is a painful ulcerative condition of the lower extremities with characteristic clinical and histopathologic features. Pain is a prominent feature, associated with tiny infarctive, shallow ulcerations most often involving the legs around the feet and ankles. This condition is difficult to treat and often recalcitrant to therapy. Healed ulcers have the non-specific appearance of atrophie blanche, characterized by smooth, porcelain-white lesions surrounded by punctate telangiectasia and hyperpigmentation; this appearance also may be seen in the context of healed ulcers due to venous insufficiency.

MANAGEMENT STRATEGY

Clinicopathologic correlation for a diagnosis of livedoid vasculopathy is necessary before treatment options can be considered. Histologic identification of the characteristic segmental hyalinized appearance of the dermal blood vessels is important to exclude other causes of lower extremity ulcers. Increasing numbers of reports suggest that the disease has a procoagulant predisposition, with both hereditary and acquired hypercoagulable states; therefore, a comprehensive coagulation screen is recommended.

Typically shallow and numerous, the ulcers in livedoid vasculopathy are painful and slow healing. *Wound care* is an important facet of treatment. Excellent *dressings* and *topical products* are available to treat chronic ulcerative diseases, and selection depends on the moisture content of the wound and the possibility of superinfection. *Pain management* is also essential.

Because of the increasing evidence supporting procoagulant mechanisms involved in disease etiology, medical therapy involves prevention and treatment of dermal vessel thrombosis and improvement of vascular perfusion. Medical management has included *aspirin* (acetylsalicylic acid), *niacin* (nicotinic acid), *pentoxifylline*,

dipyridamole, *warfarin*, *minidose heparin*, *subcutaneous low-molecular-weight heparin injections*, *danazol*, and more recently *direct-acting oral anticoagulants* such as *rivaroxaban*. Systemic corticosteroids are not considered a primary therapy; however, some patients' conditions have improved with immunosuppressants in combination therapy. *Psoralen with ultraviolet A (PUVA)* has also been used. Patients with livedoid vasculitis recalcitrant to traditional management have been treated with *certain prostanoids*, *intravenous immunoglobulin (IVIG)*, and a *tissue-type plasminogen activator (tPA)*.

Specific Investigations

- Skin biopsy, including routine histology and direct immunofluorescence
- Wound and tissue cultures
- Full blood count
- Serum homocysteine
- Cryoglobulin
- Thrombophilia investigations: anticardiolipin antibody, anti- β_2 -glycoprotein I antibodies, factor V Leiden R506Q and prothrombin G20210A mutations, biologic activity and antigen levels of protein C and S, functional and immunologic levels of antithrombin III protein, detection of lupus anticoagulant, lipoprotein(a), and fibrinogen A levels
- Non-invasive venous and arterial function testing: continuous-wave Doppler, venous duplex imaging, plethysmography, and transcutaneous oximetry

Livedoid vasculopathy: an intriguing cutaneous disease. Criado PR, Rivitti EA, Sotto MN, et al. *An Bras Dermatol* 2011; 86: 961–77.

Livedoid vasculopathy was originally described as a clinical expression of vasculitis; however, current understanding of the main pathogenetic mechanism suggests a vasoocclusive phenomenon due to intraluminal thrombosis of dermal vessels. The authors review etiologic associations, publications on livedoid vasculopathy associated with hypercoagulable conditions, and options for treatment.

Livedoid vasculopathy: an in-depth analysis using a modified Delphi approach. Alavi A, Hafner J, Dutz JP, et al. *J Am Acad Dermatol* 2013; 69: 1033–42.

This article reviews nomenclature changes with this condition. An illustrative approach to diagnosis and review of treatments are well presented.

Association between peripheral vascular endothelial dysfunction and livedoid vasculopathy. Yang CH, Shen SC, Hui RC, et al. *J Am Acad Dermatol* 2012; 67: 107–12.

Sixteen patients diagnosed with livedoid vasculopathy were compared to 16 matched control subjects in this prospective study using flow-mediated vasodilation of the brachial artery, an indicator of vascular endothelial function, using high-resolution, two-dimensional ultrasonic imaging. Peripheral vascular endothelial dysfunction was demonstrated in patients, providing some evidence of endothelial dysfunction in the development of the disease. Decreased nitric oxide bioavailability may be the main reason for this dysfunction; however, the authors noted that more studies are needed to clarify the mechanism.

Livedoid vasculopathy: further evidence for procoagulant pathogenesis. Hairston BR, Davis MD, Pittelkow MR, et al. *Arch Dermatol* 2006; 142: 1413–8.

This retrospective study of 45 patients with biopsy-proven livedoid vasculopathy analyzed the presence of coagulation abnormalities. The laboratory results revealed numerous heterogeneous coagulation abnormalities, including factor V Leiden mutations, protein C or S abnormalities, prothrombin G20210A gene mutations, lupus anticoagulant, anticardiolipin antibodies, and elevated homocysteine, thus providing further evidence of procoagulant mechanisms for this disease.

Livedoid vasculopathy: the role of hyperhomocysteinemia and its simple therapeutic consequences. Meiss F, Marsch WC, Fischer M. *Eur J Dermatol* 2006; 16: 159–62.

Hypercoagulability due to hyperhomocysteinemia was recognized as a potentially contributing factor to livedoid vasculopathy in a 49-year-old woman.

Livedoid vasculopathy and its association with factor V Leiden mutation. Yong AA, Tan AW, Giam YC, et al. *Singapore Med J* 2012; 53: 258–60.

Two cases of livedoid vasculopathy with factor V Leiden mutations are described.

Livedoid vasculopathy associated with heterozygous protein C deficiency. Boyvat A, Kundakci N, Babikir MO, et al. *E. Br J Dermatol* 2000; 143: 840–2.

Livedoid vasculitis in association with protein C deficiency is described in one patient.

Livedoid vasculitis: a manifestation of the antiphospholipid syndrome. Acland KM, Darvay A, Wakelin SH, et al. *Br J Dermatol* 1999; 140: 131–5.

Four patients with ulcerative livedoid vasculitis are described, all of whom had associated elevated anticardiolipin antibody levels but no other evidence of systemic disease.

First-Line Therapies

• Wound care (including bed rest and leg elevation)	C
• Aspirin	C
• Dipyridamole	C
• Pentoxifylline	D

Atrophie blanche: a clinicopathological study of 27 patients. Yang LJ, Chan HL, Chen SY, et al. *Changcheng Yi Xue Za Zhi* 1991; 14: 237–45.

Twenty-seven patients were reviewed with respect to mean age at onset, disease duration, natural course, and clinical morphology. Thirteen patients responded to local wound care, bed rest, and low-dose aspirin plus dipyridamole as treatment for the first attack or recurrent episodes.

Livedoid vasculopathy associated with sickle cell trait: significant improvement on aspirin treatment. El Khoury J, Taher A, Kurban M, et al. *Int Wound J* 2012; 9: 344–7.

The authors describe a patient with sickle cell trait diagnosed with livedoid vasculopathy; treatment with aspirin led to significant improvement in the cutaneous ulcers.

Livedo vasculitis: therapy with pentoxifylline. Sams WM Jr. *Arch Dermatol* 1988; 124: 684–7.

Eight patients with disease unresponsive to a variety of medications were treated with pentoxifylline. Three experienced

complete healing and four were much improved, whereas only one was unchanged after treatment.

Second-Line Therapies

• Low-molecular-weight heparin	C
• Warfarin	D
• Hyperbaric oxygen	D
• Danazol	D
• Rivaroxaban	C

Frequency of thrombophilia determinant factors in patients with livedoid vasculopathy and treatment with anticoagulant drugs – a prospective study. Di Giacomo TB, Hussein TP, Souza DG, et al. *J Eur Acad Dermatol Venereol* 2010; 24: 1340–6.

Thirty-four patients diagnosed with livedoid vasculopathy were tested for prothrombin time, activated partial thromboplastin time, antithrombin activity, protein C and S activity, anticardiolipin antibodies, lupus anticoagulant, prothrombin gene mutation, factor V Leiden mutation, methylenetetrahydrofolate reductase mutation, plasma homocysteine, and fibrinogen; 18 (52%) presented laboratory abnormalities of procoagulant conditions. Thirteen of the 34 patients were treated with anticoagulant drugs (either warfarin or heparin), with clinical improvement in 11 patients.

Livedoid vasculopathy in a pediatric patient with elevated lipoprotein(a) levels: prompt response to continuous low-molecular-weight heparin. Goerge T, Weishaupt C, Metze D, et al. *Arch Dermatol* 2010; 146: 927–8.

The authors describe a pediatric patient with livedoid vasculopathy who had elevated levels of lipoprotein(a). Treatment with low-molecular-weight heparin (enoxaparin) showed remission of the ulcers and pain.

Treatment of livedoid vasculopathy with low-molecular-weight heparin: report of 2 cases. Hairston BR, Davis MD, Gibson LE, et al. *Arch Dermatol* 2003; 139: 987–90.

Two patients with livedoid vasculitis recalcitrant to conventional first- and second-line therapies had a beneficial response to subcutaneous injections of low-molecular-weight heparin.

Ulcerations caused by livedoid vasculopathy associated with a prothrombotic state: response to warfarin. Davis MD, Wysokinski WE. *J Am Acad Dermatol* 2008; 58: 512–5.

Warfarin therapy healed ulcerations in a 50-year-old woman who had a lifelong history of painful ulcerations; the patient was a heterozygous carrier of factor V Leiden and prothrombin gene mutations.

A case of livedoid vasculopathy associated with factor V Leiden mutation: successful treatment with oral warfarin. Kavala M, Kocaturk E, Zindanci I, et al. *J Dermatol Treat* 2008; 19: 121–3.

A 19-year-old man with a 4-year history of recurrent leg ulcers had rapid improvement with oral warfarin therapy after laboratory diagnosis of protein C and factor V Leiden mutations.

Livedoid vasculopathy: long-term follow-up results following hyperbaric oxygen therapy. Juan WH, Chan YS, Lee JC, et al. *Br J Dermatol* 2006; 154: 251–5.

Eight patients completed a prospective study evaluating the efficacy of hyperbaric oxygen on healing the ulcers of livedoid

vasculopathy. Leg ulcers in all eight patients healed completely at a mean of 3.4 weeks; however, six patients had relapses of ulcers but responded to additional hyperbaric oxygen therapy.

Livedoid vasculopathy and high levels of lipoprotein(a): response to danazol. Criado PR, de Souza Espinell DP, et al. *Dermatol Ther* 2015; 28: 248–53.

The authors present four patients with livedoid vasculopathy who were successfully treated with low-dose danazol (200 mg daily orally); clinical characteristics and laboratory workup, including the level of lipoprotein(a), are also presented.

Low-dose danazol in the treatment of livedoid vasculitis. Hsiao GH, Chiu HC. *Dermatology* 1997; 194: 251–5.

Six of seven patients treated with low-dose danazol (200 mg daily orally) had rapid cessation of new lesion formation, prompt reduction in pain, and healing of active ulceration.

Rivaroxaban prevents painful cutaneous infarctions in livedoid vasculopathy. Kerk N, Drabik A, Luger TA, et al. *Br J Dermatol* 2013; 168: 898–9.

Three patients were treated with rivaroxaban (10 mg daily) for livedoid vasculopathy. Pain levels and the frequency of new ulcers were noted to improve significantly within 1 month and 3 months, respectively.

Anticoagulation with rivaroxaban for livedoid vasculopathy (RILIVA): a multicentre, single-arm, open-label, phase 2a, proof-of-concept trial. Weishaupt C, Strölin A, Kahle B, et al. *Lancet Haematol* 2016; 3: e72–9.

Twenty patients with livedoid vasculitis were treated with rivaroxaban 10 mg twice daily. Median pain on the visual analog scale decreased significantly after 12 weeks. Six of 20 patients received backup treatment with enoxaparin due to insufficient efficacy of rivaroxaban; however, these patients were later able to be maintained on rivaroxaban.

Third-Line Therapies

• Tissue plasminogen activator	C
• Intravenous immunoglobulin	C
• PUVA	C
• Sulfapyridine	D
• Cilostazol	E
• Apixaban	E
• Dabigatran	E
• Prostanoids (PGE-1, prostacyclin)	E

Tissue plasminogen activator for treatment of livedoid vasculitis. Klein KL, Pittelkow MR. *Mayo Clin Proc* 1992; 67: 923–33.

In a prospective study, six patients who had non-healing ulcers caused by livedoid vasculitis and in whom numerous conventional therapies had failed were treated with low-dose tPA. In five of the six patients, dramatic improvement with almost complete healing of the ulcers occurred during hospitalization. Several were maintained with warfarin therapy after their inpatient treatment.

Successful long-term use of intravenous immunoglobulin to treat livedoid vasculopathy associated with plasminogen activator inhibitor-1 promoter homozygosity. Tuchinda P, Tammara A, Gaspari AA. *Arch Dermatol* 2011; 127: 1224–5.

A 33-year-old patient diagnosed with livedoid vasculopathy associated with plasminogen activator inhibitor-1 promoter

homozygosity was treated with IVIG after failing antiinflammatory, antiplatelet, and tPA therapies. She was successfully treated for over 4 years without complications with IVIG, 0.5 g/kg every 2 weeks, given intravenously by an implanted Port-A-Cath.

Efficacy of intravenous immunoglobulins in livedoid vasculopathy: long-term follow-up of 11 patients. Monshi B, Posch C, Vujic I, et al. *J Am Acad Dermatol* 2014; 71: 738–44.

In this retrospective study, the authors analyzed IVIG therapy in 11 patients. Most patients received IVIG added to an existing regimen, primarily aspirin, oral anticoagulants, or low-molecular-weight heparin, alone or in combination. Reduction of disease activity and improved quality of life were achieved after six rounds of IVIG.

Refractory livedoid vasculitis responding to PUVA: a report of four cases. Tuchinda C, Leenutaphong V, Sudtim S, et al. *Photodermatol Photoimmunol Photomed* 2005; 21: 154–6.

Four patients with refractory livedoid vasculopathy responded to PUVA therapy; however, two of the four patients had recurrent lesions within a few months after cessation of therapy.

Livedoid vasculitis responding to PUVA therapy. Lee JH, Choi HJ, Kim SM, et al. *Int J Dermatol* 2001; 40: 153–7.

Eight patients treated with systemic PUVA had rapid cessation of new lesion formation, notable symptom relief, and complete healing of primary lesions without unacceptable adverse effects.

Clinical studies of livedoid vasculitis (segmental hyalinizing vasculitis). Winkelmann RK, Schroeter AL, Kierland RR, et al. *Mayo Clin Proc* 1974; 49: 746–50.

Clinical, laboratory, and histologic studies of 37 patients with livedoid vasculitis were presented. Treatment options included niacin (nicotinic acid), which was effective because of the inhibiting effect of nicotinate on contraction of vascular smooth muscle of the skin. Nine of 12 patients had sustained remission of their livedoid vasculopathy. Rest and wet-dressing therapy produced short remissions. Six of 11 patients responded to sulfapyridine, and three of eight responded to guanethidine.

Cilostazol: a novel agent in recalcitrant livedoid vasculopathy. Mendiratta V, Malik M, Yadav P, et al. *Indian J Dermatol Venereol Leprol* 2016; 82: 222–4.

A 25-year-old woman with recalcitrant livedoid vasculopathy was initially treated with oral cilostazol (50 mg daily), with reduction in pain and burning and improvement of the ulcers, then twice daily for a short time during a flare. Within a few months, medication was tapered off, and no relapse was noted within a year.

Rapid remission of severe pain from livedoid vasculopathy by apixaban. Yamaguchi Y, Nakazato S, Izumi K, et al. *J Eur Acad Dermatol Venereol* 2017; 31: e45–6.

A 73-year-old Japanese woman presented with a 1-year history of livedoid vasculopathy. She was treated with oral apixaban 10 mg daily. Pain improved in 1 day, and ulcers were almost epithelialized at 8 weeks with no recurrence at 5-month follow-up.

Dabigatran in the management of livedoid vasculopathy. Sawada T, Suehiro M. *Clin Exp Dermatol* 2017; 42: 237–9.

A 44-year-old woman with livedoid vasculopathy was treated with numerous topical agents, as well as oral aspirin and clopidogrel, with worsening ulcers. She remained on aspirin, but clopidogrel was switched to dabigatran 220 mg daily. Pain improved within 1 week, and ulcers healed within 4 months without recurrence.

Treatment of livedoid vasculopathy with alprostadil (PGE-1): case report and review of published literature. Mofarrah R, Aberer W, Aberer E. *J Eur Acad Dermatol Venereol* 2013; 27: 252–4.

This article discusses the diagnosis and treatment of livedoid vasculopathy in patients. It examines a 47-year-old patient

with livid reticular discoloration and ulceration on both legs. It informs of a vasodilatory effect of prostaglandins and that prostaglandin E1 (PGE-1) is a promising drug used for the treatment of livedoid vasculopathy.

Lyme borreliosis

Sarah Rawi, Matthew Grant, David Banach



Lyme disease is a multisystem illness caused by spirochetes of the genus *Borrelia*. In North America, the causative agent is *Borrelia burgdorferi*, whereas in Europe, disease is caused primarily by *B. afzelii* and *B. garinii*. Clinical manifestations of Lyme disease depend on the stage of illness and may be limited to the skin or involve the nervous system, joints, or heart. Lyme disease is the most common vectorborne disease in the United States (USA). It is endemic in the northeast, the mid-Atlantic, and parts of Wisconsin and Minnesota. The most common vector for Lyme disease in the USA is the *Ixodes scapularis* tick. *I. pacificus* has been linked to transmission of *B. burgdorferi* in the northwestern USA.

Mice and deer are the major reservoirs of *B. burgdorferi*. After hatching in the spring, tick larvae acquire *B. burgdorferi* while feeding on white-footed mice. The following spring, the larvae develop into nymphs and are then capable of transmitting infection. Nymph or adult female forms slowly deposit spirochetes into human skin during feeding. Ticks must remain attached and feed for over 36 hours to transmit a sufficient inoculum of spirochetes for illness to occur.

MANAGEMENT STRATEGY

Routine antimicrobial prophylaxis or serologic testing after a tick bite is not recommended. It is recommended to offer single-dose prophylaxis to patients residing in endemic areas (i.e., prevalence of *B. burgdorferi*-infected tick $\geq 20\%$) who remove engorged *I. scapularis* ticks attached for >36 hours. This recommendation is based on result of a randomized trial of single-dose doxycycline (200 mg), which prevented 87% of Lyme infections if administered within 72 hours of tick removal. Regardless of whether prophylaxis is taken, patients who remove a tick attached for more than a day should be monitored for up to 30 days for the occurrence of local skin lesions or fever.

The best mode of preventing Lyme disease is avoidance of tick-infested areas. If tick exposure is unavoidable, then one should ideally wear permethrin treated clothes with long sleeves and long pants tucked into socks. Exposed skin should be treated with a $\geq 20\%$ DEET-based repellent, which has activity against ticks in

addition to mosquitoes and most biting insects. After outdoor activities, clothes can be placed in the dryer on high heat for approximately 6–60 min in order to kill *I. scapularis*. Skin self-inspection within 36 hours of tick exposure and bathing within 2 hours of exposure have both been associated with decreased risk of developing Lyme borreliosis. Daily inspection of the entire body, including the scalp, is recommended since attached ticks removed within 24–36 hours are unlikely to transmit *B. burgdorferi*. *Ixodes* ticks are small: larvae are less than 1 mm in size and adult females are 2–3 mm in size. Attached ticks should be removed with tweezers by carefully pulling on the mouth apparatus close to the skin, taking care not to retain mouth parts of the embedded tick.

Lyme disease generally occurs in stages, with different signs and symptoms at each stage. Therapeutic recommendations vary depending on the stage of disease and the presence of extracutaneous manifestations.

Early Localized Lyme Disease

The most common clinical manifestation of early Lyme disease is erythema migrans (EM). This characteristic skin lesion occurs at the site of the bite a median of 10 days after inoculation, beginning as an erythematous papule and evolving into an expanding annular patch with a distinct edge. Although central clearing of erythema leading to a bullseye or targetoid appearance is characteristic, many lesions do not demonstrate this finding and absence of central clearing should not exclude an EM diagnosis. It is important to note that in individuals with darker skin, EM can appear as a bruise, hypo/hyperpigmentation without erythema, which may be misdiagnosed as cellulitis. The lesion may be accompanied by non-specific symptoms including fever, regional lymphadenopathy, arthralgias, fatigue, and headache. About 75% of patients with Lyme disease in the USA are diagnosed during the early localized Lyme stage with a single primary lesion. Untreated lesions usually fade within 3–4 weeks. In the southeast and south central areas of the USA, the southern tick-associated rash illness (STARI) can be indistinguishable from Lyme's EM.

Administration of doxycycline 100 mg twice daily for 10 days, or, amoxicillin 500 mg three times daily, or cefuroxime axetil 500 mg twice daily for 14 days is recommended for early localized or early disseminated Lyme disease associated with EM. Doxycycline has the advantage of also treating human granulocytic anaplasmosis caused by *Anaplasma phagocytophilum*, which can be cotransmitted by *I. scapularis* bites. Doxycycline can cause photosensitivity and is contraindicated during pregnancy or breastfeeding. Traditionally it was also contraindicated for children; however, the American Academy of Pediatrics has now supported courses less than 3 weeks for children younger than eight years old.

A rare skin manifestation of early Lyme infection described predominantly in Europe is Borrelial lymphocytoma (BL). This solitary, bluish-red nodule occurs at the site of a tick bite typically preceding or concomitantly with EM. Commonly involved sites are the ear lobes in children and near or on the nipple in adults. BL may develop within weeks to months after a tick bite and if untreated can persist for months to years. Treatment regimens used to treat EM can be used to treat BL.

Early Disseminated Lyme Disease

Early dissemination of the spirochete occurs via blood or lymphatics over several weeks in untreated infection. Multiple

annular skin lesions resembling primary EM can arise when spirochetes are deposited at skin sites remote from the initial bite – notably these lesions are generally smaller. However, it is important to keep in mind that multiple areas of EM are most commonly associated with spirochetemia, rather than multiple tick bites. Other common symptoms include fever, lethargy, myalgias, headache, and neck stiffness. Patients may present with atrioventricular (AV) conduction disturbances, iritis or uveitis, aseptic meningitis (lymphocytic pleocytosis in cerebral spinal fluid with normal glucose), cranial nerve palsies (notably facial nerve palsies), or peripheral radiculopathy. In adults, intravenous ceftriaxone 2g daily for 14–21 days is recommended for early Lyme disease presenting with neurologic or advanced cardiac conduction abnormalities. Parenteral penicillin or cefotaxime are second-line agents. Temporary pacing may be required for patients with high-degree AV block (PR interval ≥ 0.30 seconds). Insertion of a permanent pacer is not necessary as conduction defects usually resolve with medical treatment alone. Isolated facial nerve palsy and first degree AV block can be treated with oral doxycycline.

Late Lyme Disease

Late Lyme disease can occur months to years after previously untreated or inadequately treated initial infection. Lyme arthritis is the most common manifestation of late Lyme disease, although decreasing in incidence due to improved recognition of early disease. Lyme arthritis is oligoarticular and presents as recurrent swelling of large joints, primarily the knees. Persistent swelling is atypical. Positive serologic testing is required to confirm the diagnosis. Positive polymerase chain reaction (PCR) results from synovial fluid can strengthen the diagnosis (sensitivity ranges 71%–100%).

Late neuroborreliosis is rare and can manifest as peripheral neuropathy, encephalomyelitis, or a subacute encephalopathy characterized by memory disturbances, mood alterations, and somnolence.

A rare dermatologic finding associated with late Lyme disease is acrodermatitis chronica atrophicans (ACA). ACA has been predominantly described in elderly female patients and has rarely been seen in the USA but is more common in European patients with *B. afzelii*. ACA presents months to years after initial infection with a poorly demarcated area of violaceous discoloration and swelling of involved skin. These lesions usually involve the extensor surfaces of the extremities including the dorsum of hands. Over time the lesions become atrophic, with a characteristic hyperpigmented, hairless, translucent appearance. Involvement of peripheral nerves can also result in sensory neuropathy.

Lyme arthritis without neurologic symptoms can be treated with a 28-day oral regimen of either doxycycline 100mg twice daily or amoxicillin 500mg three times daily. Adults with evidence of concurrent neurologic involvement should receive intravenous ceftriaxone. Recurrent or persistent joint swelling after an oral regimen can be re-treated with another 28-day course of oral antimicrobials or with a 2–4-week parenteral regimen. Adults with late neurologic disease should be treated with a parenteral regimen for 2–4 weeks. Repeated or prolonged therapy is not recommended.

Diagnosis

In cases of early Lyme disease that present as skin lesions consistent with EM with potential exposure to infectious ticks in a Lyme

disease-endemic area, clinical diagnosis is recommended. Serology (around 40% sensitivity) and skin biopsy culture (40%–60% sensitivity) is not recommended to confirm skin lesions as EM. In non-cutaneous disease or in the presence of skin lesions that are suggestive of but atypical for EM, if the clinical history and physical examination support Lyme disease as a leading diagnosis, then testing is recommended. Traditionally, two-step testing with enzyme-linked immunosorbent assay (ELISA) and Western immunoblot was the gold standard for diagnosing later stages of Lyme disease. In 2019, the Centers for Disease Control and Prevention (CDC) updated the two-test methodology to using a sensitive enzyme immunoassay (EIA) or immunofluorescence assay (IFA) as the first test, then a second EIA as the second test, rather than the Western immunoblot assay. This is now called the modified 2-tier test (MTTT).

Posttreatment Symptoms

Persistent arthritic complaints appear to be immunologically mediated and are most common in individuals with the HLA-DR4 haplotype. Research studies have not consistently demonstrated microbiological persistence of *Borrelia* in patients with symptoms following completion of treatment for Lyme. Moreover, prolonged or multiple courses of antimicrobials are unhelpful and may be harmful. Symptomatic treatment with non-steroidal agents, intraarticular corticosteroids, disease modifying antirheumatic drugs, or, in severe non-remitting cases, arthroscopic synovectomy may provide relief.

Reinfection and Vaccination

Patients treated for early Lyme disease, specifically EM, do not develop protective immunity and if reexposed may become reinfected. The clinical presentation associated with reinfection is similar to primary infection. At this time there is no vaccine available to protect against Lyme disease.

SPECIFIC INVESTIGATIONS

Testing

Evaluation of modified 2-tiered serodiagnostic testing algorithms for early Lyme disease. Branda JA, Strle K, Nigrovic LE, et al. Clin Infect Dis 2017; 64: 1074–80.

This case-control study compared sensitivities and specificities of using two first-tier tests (whole-cell sonicate [WCS] EIA, C6 EIA, or variable major protein-like sequence, expressed [VlsE] chemiluminescence immunoassay [CLIA]) with the traditional two-tier model (EIA and Western blot). Serum samples of the acute phase ($n=55$) and the convalescent phase ($n=47$) were obtained in patients who were diagnosed with EM. Patients referred for Lyme but diagnosed with other illnesses ($n=50$) and healthy asymptomatic individuals ($n=1227$) were used as controls. Using two first-tier tests was called the modified 2-tiered testing (MTTT) protocol. The MTTT protocol had a 36%–54% sensitivity compared with 25% in the traditional model; moreover, it had similar specificity (99.3%–99.5%) compared with 99.5% in the traditional model. This study concluded that the MTTT protocol had greater sensitivity than the traditional model; thus, it should be the preferred diagnosis pathway, eliminating the need for Western blots.

Automated detection of erythema migrans and other confounding skin lesions via deep learning. Burlina PM, Joshi NJ, Ng E, et al. Comput Biol Med 2019; 105: 151–6.

This study looked at the difference between a computer model (artificial intelligence) diagnosing EM compared with non-medically trained humans. A dataset of 1834 images of EM, tinea corporis, herpes zoster, and normal skin was used. The machine had an accuracy of 86.53% (95% CI error margin 2.70), which exceeded the specificity and sensitivity of human performance. This could lead to faster physician recognition/referral and earlier diagnosis to help reduce the risk of late complications.

Prevention

Peridomestic Lyme disease prevention. Results of a population based case-control study. Connally NP, Durante AJ, Yousey-Hindes M, et al. *Am J Prev Med* 2009; 37: 201–6.

This was a 32-month case-control study comparing 364 patients with Lyme disease with neighborhood-matched controls to evaluate the impact of prevention measures on risk. In multivariate analysis checking for ticks within 36 hours after spending time in the yard, bathing within 2 hours after exposure, and fencing around the yard were associated with decreased risk of EM.

Prophylaxis

Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an *Ixodes scapularis* tick bite. Nadelman RB, Nowakowski J, Fish D, et al.; Tick Bite Study Group. *N Engl J Med* 2001; 345: 79–84.

In this investigation, 482 patients were randomized to receive 200 mg doxycycline or placebo within 72 hours of removal of an *I. scapularis* tick. One of 235 subjects (0.4%) who received doxycycline, as compared with eight of 247 (3.2%) who received placebo, developed EM. No asymptomatic seroconversions occurred, and no subject developed extracutaneous Lyme disease. Prophylaxis was effective at decreasing the development of Lyme disease. More gastrointestinal symptoms occurred with doxycycline.

Topical azithromycin for the prevention of Lyme borreliosis: a randomized, placebo-controlled, phase 3 efficacy trial. Schwameis M, Kündig T, Huber G, et al. *The Lancet Inf Dis* 2017; 17: 322–9.

This multicenter trial of 28 sites looked at the use of 10% topical azithromycin to prevent Lyme borreliosis within 72 hours of a tick bite. Patients were only included if they did not have seroconversion at time of treatment and either had the tick still attached or collected and presented. At 8 weeks 2% of both the azithromycin and placebo group had treatment failure, defined as EM and/or seroconversion. The number of adverse events were also equal in each group and mostly mild; however, the study was stopped early because the primary end point of reduction of patients with EM and/or seroconversion compared to the placebo was not achieved at eight weeks.

Treatment

Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease. Lantos PM, Rumbaugh J, Bockenstedt LK, et al. *Clin Infect Dis* 2020; 722: e1–48.

First-Line Therapies

Early localized disease (erythema migrans)^a

- Doxycycline^b 100mg twice daily or 200 mg once daily for 10 days **A**
- Amoxicillin 500mg three times daily for 14 days **A**
- Cefuroxime axetil 500mg twice daily for 14 days **A**

Early neurological (meningitis or radiculopathy)

- Ceftriaxone 2g IV daily for 14–21 days **B**
- Doxycycline 100mg twice daily for 14–21 days **B**

Cardiac disease including atrioventricular block

- Can be treated with oral or parenteral regimens recommended for early localized or early neurologic disease for 14 days^c **C**

Lyme arthritis without neurologic involvement

- Doxycycline^b 100mg twice daily for 28 days **B**
- Amoxicillin 500mg three times daily for 28 days **B**

Lyme arthritis with neurologic involvement

- Ceftriaxone 2g IV daily for 14–28 days **B**

Recurrent arthritis

- Retreatment with a 28-day course of oral antibiotics **D**

Late neuroborreliosis

- Ceftriaxone 2g IV daily for 14–21 days **B**
- Penicillin G 18–24 million units IV daily (divided and dosed every 4 hours) for 14–21 days **B**

Acrodermatitis chronic atrophicans

- Doxycycline 100mg twice daily for 21 days **C**
- Amoxicillin 500mg three times daily for 21 days **C**
- Cefuroxime axetil 500mg twice daily for 21 days **D**

^aLevel B recommendation for borrelia lymphocytoma and early Lyme disease with isolated cranial nerve palsy.

^bDoxycycline is contraindicated in pregnancy and in children <8 years old if duration of treatment is greater than 21 days.

^cInitial treatment with parenteral regimen recommended in hospitalized patients.

Second-Line Therapies

Early localized disease

- Azithromycin 500mg daily for 7 days **B**

Neurologic involvement or advanced cardiac conduction block

- Doxycycline 100mg twice a day for 14–28 days **B**

Second-line therapies are to be used in the setting of contraindication to first-line treatments (e.g., severe allergy).

Comparison of phenoxymethylpenicillin, amoxicillin, and doxycycline for erythema migrans in general practice. A randomized controlled trial with a 1-year follow-up. Eliassen K, Reiso H, Berild D, et al. *Clin Microbiol Infect* 2018; 24: 1290–6.

In a Norwegian primary care setting, a randomized control study compared the use of phenoxymethylpenicillin (PCV), amoxicillin, and doxycycline for the treatment of EM in 188

individuals. The duration of EM was the primary outcome after treatment for 14 days. Among all three groups the median duration of EM was 14 days. No one in either group was diagnosed with late stage or disseminated Lyme. Thus, this study concluded that there was no significant difference in efficacy or safety profile between these three antibiotics.

Comparison of cefuroxime axetil and doxycycline in the treatment of early Lyme disease. Nadelman RB, Luger SW, Frank E, Wisniewski M, et al. *Ann Intern Med* 1992; 117: 273–80.

A randomized, multicenter, investigator-blinded trial treated 123 patients with EM for 20 days with either cefuroxime axetil 500 mg twice daily ($n=63$) or doxycycline 100 mg twice daily ($n=60$). Cure or improvement was achieved in 51 of 55 (93%) evaluable patients treated with cefuroxime axetil and in 45 of 51 (88%) patients treated with doxycycline. At 1 year posttreatment, the percentage of patients who achieved a satisfactory outcome was comparable between the two groups. Cefuroxime was associated with more diarrhea than doxycycline and is more expensive than doxycycline or amoxicillin.

Azithromycin compared with amoxicillin in the treatment of erythema migrans. A double-blind, randomized, controlled trial. Luft BJ, Dattwyler RJ, Johnson RC, et al. *Ann Intern Med* 1996; 124: 785–91.

In this report, 246 adults with EM were randomized to either amoxicillin 500 mg three times daily for 20 days or azithromycin 500 mg once daily for 7 days. Those treated with amoxicillin were more likely to achieve complete resolution of disease at day 20 (88% for amoxicillin compared with 76% for azithromycin;

$p = 0.024$). More azithromycin recipients (16%) than amoxicillin recipients (4%) had relapses.

Treatment of erythema migrans with doxycycline for 10 days versus 15 days. Stupica D, Lusa L, Ruzić-Sabljic E, et al. *Clin Infect Dis* 2012; 55: 343–50.

In this study 117 patients with EM received doxycycline 100 mg twice daily for 10 or 15 days. Resolution of EM was similar in both groups and at 12 months 93% of the 15 day group and 92% of patients in the 10-day group showed complete response and most had complete response within 2 months. There was a higher rate of photosensitivity in the 15-day group.

Randomized trial of longer-term therapy for symptoms attributed to Lyme disease. Berende A, ter Hofstede HJM, Vos FJ, et al. *N Engl J Med* 2016; 374: 1209–20.

This study included 280 patients over the course of almost 3 years to determine if longer antibiotic treatment improves quality of life. Each individual in this study was diagnosed with Lyme and treated with 2 weeks of IV ceftriaxone, then split into three groups: continued treatment with 12 weeks of doxycycline; clarithromycin and hydroxychloroquine; or placebo. The primary outcome was measured by the physical component of the RAND-36 Health Status Inventory. These scores were not significantly different in the prolonged antibiotic group compared with the placebo. Thus, in patients with persistent symptoms from Lyme, long-term antibiotics did not result in added benefit or improved quality of life.

Lymphangioma circumscriptum

Patrick O.M. Emanuel, Erika Romero Sandoval



Lymphangioma circumscriptum (LC) is an uncommon lymphatic malformation. It presents on the skin surface as grapelike groups of thin-walled, translucent, lymph-filled vesicles, often compared with frog spawn. Hemorrhage within the lesions can create a deep red or black appearance.

Commonly congenital, they are typically noted at birth or appear during childhood. They are most commonly found around the shoulder girdle and proximal limbs. There is a morphologically identical acquired variant related to lymphatic obstruction (consequence of surgery, radiation, or malignancy).

MANAGEMENT STRATEGIES

Although observation is an appropriate option for many cases, cosmetic concern is the typical indication for treatment. Other indications may include persistent leakage of lymphatic fluid or blood and recurrent infection. The risk of developing angiosarcoma and squamous cell carcinoma is trivial and should not be used to rationalize full surgical excision.

Treatment is challenging and often thwarted by local recurrences due to the persistence of deep lymphatic cisterns. Consequently, there is disagreement in the literature as to which treatment option is the most effective. Although *complete surgical excision* has the lowest recurrence rates, it has the highest rate of complications; more extensive lesions may be deemed inoperable.

Sclerotherapy using a variety of sclerosants has been advocated as a less invasive and effective treatment modality, which is either a first-line alternative or an adjunct to surgery.

Other authorities suggest that after definitive diagnosis and radiologic mapping, surgical excision and postoperative histologic assessment of excision margins provide the most effective treatment options.

Resurfacing of the lesions can be attempted and achieved even if proper surgical excision is not possible and/or sclerotherapy fails, but recurrence rates are usually higher than with other therapies. The high-energy, short-pulse CO₂ laser has been found to yield functionally and cosmetically acceptable results. This seals communicating channels to the deeper cisterns by vaporizing the superficial lymphatics and is said to have fewer complications than more aggressive treatment alternatives. Other laser methods, particularly the pulsed dye laser, have also been shown to be effective in selected superficial cases.

Specific Investigations

- Biopsy
- Imaging studies
- Magnetic resonance imaging (MRI)
- Lymphangiography
- Ultrasound

In most cases the clinical diagnosis is straightforward. In some, the differential diagnosis may be broad: genital lesions are often associated with verrucous changes, which give them a warty appearance and are often confused with viral warts or squamous cell carcinoma; discoloration of the vesicles can lead to confusion with hemangiomas and even malignant melanoma; herpetic infection and dermatitis herpetiformis are less frequent differential diagnoses. Biopsy is diagnostic for clinically unusual cases and exhibits numerous thin-walled, dilated lymphatic channels encroaching onto the epidermis (which may become hyperkeratotic), expanding the papillary dermis and extending deep into the dermis and subcutis. Immunostaining with VEGFR3 and D2-40 decorates the vessels and confirms their lymphatic origin.

MRI can define the entire anatomy of a lesion and can help prevent unnecessarily extensive or incomplete surgical resection. Computed tomography (CT), ultrasound, and lymphoscintigraphy have also been useful in determining the extent of a lesion.

Secondary lesions may be investigated for an underlying cause. Lymphangiomas may be associated with rare disorders such as Proteus, Cobb, and Klippel-Trénaunay syndromes, and so appropriate investigations and consultations should be sought.

First-Line Therapies

- Conservative/observation
- Antibiotics
- Sclerotherapy
- OK-432
- Hyperosmolar saline
- Sodium tetradecyl sulfate
- Surgery

A
D
A
A
D
E
A

Intralesional sclerotherapy with group A *Streptococcus pyogenes* of human origin (OK-432) has emerged as an effective sclerosing agent.

OK-432 therapy in 64 patients with lymphangioma. Ogita S, Tsuto T, Nakamura K, et al. *J Pediatr Surg* 1994; 29: 784–5.

A case of unresectable lymphangioma circumscriptum of the vulva successfully treated with OK-432 in childhood. Ahn SJ, Chang SE, Choi JH, et al. *J Am Acad Dermatol* 2006; 55: S106–7.

Treatment of lymphangioma in children: our experience of 128 cases. Okazaki T, Iwatani S, Yanai T, et al. *J Pediatr Surg* 2007; 42: 386–9.

The main advantage of OK-432 over other sclerosing agents is the absence of perilesional fibrosis. OK-432 is an effective agent for cases of a single or limited numbers of vesicles. In larger lesions the technique is useful as a pretreatment adjunct to surgical excision.

Treatment of lymphangioma circumscriptum with sclerotherapy: an ignored effective remedy. Al Ghamdi KM, Mubki TF. *J Cosmet Dermatol* 2011; 10: 156–8.

Lymphangioma circumscriptum: treatment with hypertonic saline sclerotherapy. Bikowski JB, Dumont AM. *J Am Acad Dermatol* 2005; 53: 442–4.

Hypertonic saline has been reported to be effective for the management of lymphangioma circumscriptum to the shoulder, although wider use of this agent in comparison with other treatments has not been reported.

Percutaneous sclerotherapy of lymphangioma. Molitch HI, Unger EC, Witte CL, et al. *Radiology* 1995; 194: 343–7.

Five patients with unresectable lymphangiomas of the pelvis, neck, abdomen, or leg were treated with sclerotherapy, using doxycycline as the sclerosant.

Treatment of unusual vascular lesions: usefulness of sclerotherapy in lymphangioma circumscriptum and acquired digital arteriovenous malformation. Park CO, Lee MJ, Chung KY. *Dermatol Surg* 2005; 31: 1451–3.

Two cases of LC were treated with a sclerosant, sodium tetradecyl sulfate, and were almost cleared with several treatments of sclerotherapy.

Surgery treatment of lymphangioma in children: our experience of 128 cases. Okazaki T, Iwatani S, Yanai T, et al. *J Pediatr Surg* 2007; 42: 386–9.

Lymphangioma circumscriptum treated with combination of bleomycin sclerotherapy and radiofrequency ablation. Khurana A, Gupta A, Ahuja A, et al. *J Cosmet Laser Ther* 2018; 1–4.

Primary surgical excision was significantly more successful than sclerotherapy, but the results are often unsatisfactory because of complications, including damage to surrounding structures, scarring, and recurrence due to incomplete excision. Ultrasound and MRI demonstrate deep cysts, thereby ensuring deeper excision of these structures and less risk of recurrence.

Surgical management of 'lymphangioma circumscriptum'. Browse NL, Whimster I, Stewart G, et al. *Br J Surg* 1986; 73: 585–9.

Confirmation of the completeness of excision can be obtained using frozen section analysis of the lateral and deep margins.

Lymphangioma circumscriptum of the vulva mimicking genital wart: a case report and review of literature. Sah SP, Yadav R, Rani S. *J Obstet Gynaecol Res* 2001; 27: 293–6.

The patient required extensive vulval surgery, and there was no recurrence after 16 months.

Surgical management of penoscrotal lymphangioma circumscriptum. Latifoglu O, Yavuzer R, Demir Y, et al. *Plast Reconstr Surg* 1999; 103: 175–8.

An extensive LC of the penis and scrotum that was successfully treated by wide excision in single-stage surgery.

Lymphangioma circumscriptum: pitfalls and problems in definitive management. Bond J, Basheer MH, Gordon D. *Dermatol Surg* 2008; 34: 271–5.

Two cases of surgical excision with no recurrence at 1 and 2 years. Imaging of deep communicating structures and histologic assessment of excision margins provide the greatest chance of nonrecurrence.

Second-Line Therapies

• CO ₂ laser	D
• Pulsed dye laser	D
• Radiotherapy	E
• Cryotherapy	D
• Argon laser	D
• Suction-assisted lipectomy	D
• Topical imiquimod	D
• Microneedle radiofrequency	D
• Electrocoagulation	D

Lymphangioma circumscriptum: review and evaluation of carbon dioxide laser vaporization. Eliezri YD, Sklar JA. *J Dermatol Surg Oncol* 1988; 14: 357–64.

Three patients were treated with CO₂ laser vaporization, with good to excellent cosmetic results and complete resolution of their symptoms.

CO₂ laser therapy of vulval lymphangiectasia and lymphangioma circumscriptum. Huilgol SC, Neill S, Barlow RJ. *Dermatol Surg* 2002; 28: 575–7.

Focal recurrence and an area of localized persistence were noted in both patients with LC treated with CO₂ laser therapy.

CO₂ laser therapy of vulval lymphangiectasia and lymphangioma circumscriptum. Haas AF, Narurkar VA. *Dermatol Surg* 1998; 24: 893–5.

A difficult case of LC was treated successfully with CO₂ laser after two failed surgical excisions.

CO₂ laser ablation of lymphangioma circumscriptum of the scrotum. Treharne LJ, Murison MS. *Lymphat Res Biol* 2006; 4: 101–3.

Widespread disease of the scrotum had excellent symptomatic relief after treatment with the CO₂ laser.

Treatment of lymphangioma circumscriptum with the intense pulsed light system. Thissen CA, Sommer A. *Int J Dermatol* 2007; 46: 16–8.

An intense pulsed light source led to good cosmetic results.

Treatment of lymphangioma circumscriptum with combined radiofrequency current and 900 nm diode laser. Lapidot M, Ackerman L, Amitai DB, et al. *Dermatol Surg* 2006; 32: 790–4.

Treatment was rated as ‘excellent’ in four patients and ‘good’ in two. Swelling, erythema, and pain were present in all patients and ulcers and scarring in two.

Lymphangioma circumscriptum treated with pulsed dye laser. Lai CH, Hanson SG, Mallory SB. *Pediatr Dermatol* 2001; 18: 509–10.

A child with a symptomatic LC was treated with pulsed dye laser, with good results.

Radiotherapy in congenital vulvar lymphangioma circumscriptum. Yildiz F, Atahan IL, Ozhar E, et al. *Int J Gynecol Cancer* 2008; 18: 556–9.

A patient was treated successfully with a course of external radiotherapy after failed attempts with sclerosing agents and surgery.

Radiotherapy is a useful treatment for lymphangioma circumscriptum: a report of two patients. Denton AS, Baker-Hines R, Spittle MF. *Clin Oncol (R Coll Radiol)* 1996; 8: 400–1.

Treatment of lymphangioma circumscriptum with topical imiquimod 5% cream. Wang JY, Liu LF, Mao XH. *Dermatol Surg* 2012; 38: 1566–9.

Microneedle radiofrequency treatment of lymphangioma circumscriptum. Kim S-J, Seo Y-J, Lee J-H. *Dermatol Surg* 2019; 45(10): 1333–5.

A 17-year-old man was successfully treated with a fractional radiofrequency microneedling system.

Acquired lymphangioma circumscriptum of the penis treated by electrocoagulation. Bonini J, Ducharme O, Ponroy B, et al. *Case Rep Dermatol* 2019; 11(3): 260–3.

A 69-year-old man was treated with one session of electrocoagulation therapy with an almost complete regression of the lesion without recurrence.

Lymphedema

Peter C. Lambert, Giuseppe Micali, Maria R. Nasca, Robert A. Schwartz



Lymphedema is a chronic, progressive, and debilitating condition due to abnormal accumulation of protein-rich lymphatic fluid in interstitial spaces. Lymphedema is classified into primary and secondary types.

Primary lymphedema is caused by a developmental malformation of the lymphatic system. It may be classified by age of onset into *congenital lymphedema*, *lymphedema praecox*, and *lymphedema tarda*. *Primary congenital lymphedema*, or *Milroy disease*, occurs at age less than 2 years and is an uncommon autosomal dominant disorder due, in some families, to one of several known missense mutations that interfere with vascular endothelial growth factor-3 (VEGF-3) signaling, resulting in abnormal vascular lymphatic function. *Lymphedema praecox*, also known as *Meige disease*, has its onset between age 2 and 35 years, with a marked tendency to arise during puberty or during pregnancy. Finally, *lymphedema tarda* has an age of onset later than 35 years.

Secondary lymphedema is due to obstruction or damage to an otherwise normal lymphatic system. Common causes are *malignancy*, *surgery*, *radiation therapy*, *traumatic injuries*, *recurrent infections*, and, globally, *filariasis*. Breast cancer patients are among the largest groups of patients with lymphedema. Genital lymphedema secondary to severe *hidradenitis suppurativa* has also been reported in a patient under treatment with adalimumab.

Once lymphedema has become established, biophysical influences, such as the law of La Place (which causes dilated structures to expand, regardless of what caused them to begin with) and pathophysiologic responses, such as tissue induration, make it progressively worse and difficult to treat. Chronic Th2 inflammatory responses activate a feed-forward mechanism, with expression of cytokines (IL-4, IL-13, IFN- γ , TGF- β), that causes inhibition of lymphatic pumping function and collateral lymphatic vessel formation, with worsening of lymphatic dysfunction and progressive fibrosis, that ultimately lead to disease progression. In addition, chronic lymphedema may lead to striking verrucous proliferative changes in the overlying skin known as *elephantiasis nostra*. Lymphedema may also predispose

the affected tissue to recurrent infection and to a usually aggressive form of *angiosarcoma*, in a condition known as the *Stewart-Treves syndrome*.

MANAGEMENT STRATEGIES

Lymphedema must be distinguished from cutaneous and soft tissue lymphedema due to other causes, particularly of cardiac, hepatic, or renal etiology. Not infrequently, there may be more than one cause acting simultaneously or in sequence. Chronic lymphedema is characterized clinically by brawny, non-pitting edema, unlike lymphedema due to cardiac, hepatic, or renal causes, which tend to produce pitting edema.

Lymphoscintigraphy (LSG) using an isotope as a radiotracer (usually Technetium-99) is a first-line standard imaging modality useful to evaluate and diagnose disorders of lymphatic vasculature. *Near-infrared fluorescence* (NIRF) imaging, usually with *indocyanine green* (ICG), also known as ICG lymphography, is a preferred technique for real-time imaging of the superficial lymphatic network. *Computed tomography* (CT) is helpful for volumetric measurements and tissue analysis. *Magnetic resonance imaging* (MRI) either using contrast (gadolinium) and non-contrast techniques is useful both for the diagnosis and treatment planning of surgery of lymphedema. Finally, there are a variety of experimental technologies, such as photoacoustics, specific tracer targeting to the lymphatic system, and new contrast agents.

The goal of therapy for lymphedema is to reduce stasis of protein-rich lymph in the interstitium and to improve outflow of the lymphatic circulation.

The primary treatment step should be a conservative approach with medical and physical therapy.

Complex decongestive therapy (CDT) is an effective first-line treatment option. CDT is a four-component plan comprising *multi-layer compression bandaging*, *manual lymphatic drainage*, *skin care*, and *exercise*. Therapeutic efficacy is highly dependent on patient compliance. Because of this, strict adherence to the treatment protocol should be encouraged. Weight loss, obtained through nutritional counseling and exercise programs, is also important to decrease the disease severity.

Pneumatic compression therapy has been widely used to control lymphedema as a second-line alternative approach. Because of its poor outcomes as a monotherapy, however, its use has become limited. Compression therapy is contraindicated in acute inflammatory conditions (such as cellulitis), congestive heart failure, acute venous thrombosis, severe ischemia, or peripheral arterial occlusive disease, as well as in cases of venous insufficiency.

Recent advances in these modalities have produced beneficial results. In contrast, medications, such as *diuretics* and *biologics*, have been ineffective, showing limited or no benefit. *Meticulous skin care* and *hygiene* may reduce the incidence of secondary bacterial and fungal infections. If infection does occur, *topical or systemic antibiotics* should be initiated at the first sign of the infection, as infections may lead to further lymphatic injury.

Surgery is traditionally reserved for patients refractory to conservative management, although early microsurgical procedures have recently emerged in the prevention of secondary lymphedema. Surgical treatment may be aimed at removing excess fibroadipose tissue (*reductive techniques*) or restoring lymphatic outflow (*microsurgical techniques*). *Reductive techniques*, including *surgical excision* and *liposuction*, are indicated to reduce limb size and to improve mobility in patients with advanced disease with a prominent fibroadipose component. *Microsurgical techniques* include *lymphatic-venous anastomoses* (LVA), which bypass superficial lymphatic drainage to adjacent regional venules, and

vascularized lymph node transfer (VLNT), in which healthy lymph nodes with the associated arteriovenous supply contained in a soft tissue flap are transferred from an unaffected region of the body to the lymphedematous area to restore lymphatic drainage function. Both techniques have also been used in combination with promising results. LVA are useful, especially to repair traumatic injury, and are most effective in patients with early-stage lymphedema; they have also been performed prophylactically in patients undergoing lymph node dissection as a *lymphedema microsurgical preventive healing approach (LYMPHA)*. LVA are often preferred as a less risky and invasive option compared with VLNT.

The scheme proposed here, outlining a two-step conservative therapy and a third-step surgical approach, is for a hypothetical, average patient. However, no such individual exists. The preferred therapy varies widely and should be shaped to meet the specific needs of each patient.

Specific Investigations

- Lymphoscintigraphy (LSG)
- Near-infrared fluorescence imaging with indocyanine green (NIRF-ICG)
- CT
- MRI

New diagnostic modalities in the evaluation of lymphedema. O'Donnell TF Jr, Rasmussen JC, Seveck-Muraca EM. *J Vasc Surg Venous Lymphat Disord* 2017; 5: 261–73.

A comprehensive and updated review on imaging techniques (duplex ultrasound, lymphoscintigraphy, NIRF imaging, CT, and MRI) used for the diagnosis and evaluation of primary or secondary lymphedema.

Lymphoscintigraphy for the diagnosis of extremity lymphedema: current controversies regarding protocol, interpretation, and clinical application. Pappalardo M, Cheng MH. *J Surg Oncol* 2020; 121: 37–47.

Lymphoscintigraphy (LSG) allows a global anatomic and functional assessment of the lymphatic network, identifying sites of obstruction and leakage. The limits of lymphoscintigraphy are the exposure to ionizing radiation, a relatively slow tracer kinetics, an inadequate visualization of small lymphatic vessels and of subdermal lymphatics due to poor spatial resolution, and the lack of a standardized protocol shared by all nuclear medicine centers.

Non-contrast magnetic resonance lymphangiography: an emerging technique for the study of lymphedema. Cellina M, Oliva G, Menozzi A, et al. *Clin Imaging* 2019; 53: 126–33.

Non-contrasted MRI represents a promising and safer alternative tool that enables mapping of both superficial and deep lymphatics with high spatial resolution and can accurately measure lymphatic vessel caliber. However, further investigations on larger series of patients are needed in order to validate its use.

First-Line Therapy

- Complex (or complete) decongestive therapy (CDT) **B**

Physiotherapeutic rehabilitation of lymphedema: state-of-the-art. Tzani I, Tschlakis M, Zerva E, et al. *Lymphology* 2018; 51: 1–12.

This systematic review summarizes current evidence in the literature for conservative physiotherapeutic management of lymphedema, including complete decongestive therapy, manual lymphatic treatment, rehabilitation exercises, skin care, compression therapy, and intermittent pneumatic compression. Other options, such as elevation, thermotherapy, cryotherapy, kinesio-taping, and aqua lymphatic therapy, are also discussed.

Manual lymphatic drainage for lymphedema following breast cancer treatment. Ezzo J, Manheimer E, McNeely ML, et al. *Cochrane Database Syst Rev* 2015; (5): CD003475.

Manual lymphatic drainage is safe and may offer additional benefit to compression bandaging for swelling reduction in patients with breast cancer-related lymphedema, especially in those with a mild-to-moderate lymphedema degree.

Second-Line Therapy

- Pneumatic compression therapy **B**

The cutaneous, net clinical, and health economic benefits of advanced pneumatic compression devices in patients with lymphedema. Karaca-Mandic P, Hirsch AT, Rockson SG, et al. *JAMA Dermatol* 2015; 151: 1187–93.

This retrospective analysis on a large series of patients with cancer (374 patients) and non-cancer-related (344 patients) lymphedema suggests that advanced pneumatic compression devices may improve clinical outcomes and prevent cellulitis. The study also found significant reductions in outpatient care and costs.

Intermittent pneumatic compression devices for the management of lymphedema: a review of clinical effectiveness and guidelines [Internet]. Tran K, Arg  ez C. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 May 12.

The pooled analysis of the findings from a systematic review and two randomized controlled trials showed that low-level evidence of current trials fails to unequivocally support efficacy of the use of intermittent pneumatic compression devices in combination with routine management of lymphedema.

Third-Line Therapies

- Low-level laser therapy **A**
- Surgery **B**
- Stem cell therapy **B**

Effects of photobiomodulation therapy on breast cancer-related lymphoedema: a systematic review and meta-analysis of randomised controlled trials. Chen HY, Tsai HH, Tam KW, et al. *Complement Ther Med* 2019; 47: 102200.

Treatment with low-level laser therapy, also known as photobiomodulation therapy (infrared wavelengths between 808 and 905 nm), used at a dosage ranging from 1.5 to 2.4 J/cm² and administered as 20-min sessions three times per week for 4–12 weeks in most studies, demonstrated a slight improvement in reducing limb volume in breast cancer-related lymphedema, with no obvious side effects. However, a recent meta-analysis and systematic review concluded that further fully powered randomized controlled trials (RCTs) on large series of patients with uniform and well-designed protocols of laser treatment and follow-up schedules are required to definitively assess its efficacy and long-term safety.

Surgical treatment of lymphedema. Schaverien MV, Coroneos CJ. *Plast Reconstr Surg* 2019; 144: 738–58.

This review gives evidence-based decision aid with indications on algorithmic surgical approach, with special regard to lymphovenous bypass anastomosis techniques and to vascularized lymph node flap transplant procedures.

Surgical intervention for lymphedema. Gallagher K, Marulanda K, Gray S. *Surg Oncol Clin N Am* 2018; 27: 195–215.

Treatment options, their indications, and operation procedures are discussed in detail. Early application of microsurgery procedures may be performed to prevent late lymphedema worsening, whereas poor results are advisable in advanced disease with irreversibly damaged, non-functional lymphatics. Surgical excision should be reserved for end-stage, disfiguring disease that is not amenable to other procedures.

Liposuction treatment of lymphedema. Schaverien MV, Munnoch DA, Brorson H. *Semin Plast Surg* 2018; 32: 42–7.

Microinvasive suction-assisted lipectomy may be an option to remove hypertrophied adipose tissue. It is contraindicated in patients with pitting edema related to lymph stasis, which can be removed by conservative treatment, in those with untreated or uncontrolled cancer, or in those who are not candidates for

safe surgery. Postoperative lifelong use of compression garments is crucial to reduce the risk of relapse.

Stem cell therapy using bone marrow-derived mononuclear cells in treatment of lower limb lymphedema: a randomized controlled clinical trial. Ismail AM, Abdou SM, Abdelnaby AY, et al. *Lymphat Res Biol* 2018; 16: 270–7.

Twenty randomly selected patients with chronic lymphedema treated with autologous bone marrow-derived mononuclear cells were compared with 20 control patients treated with compression therapy. Stem cell therapy significantly decreased limb circumference and lymphedema symptoms compared to the control group.

Genital lymphedema associated with hidradenitis suppurativa unresponsive to adalimumab treatment. Musumeci ML, Scilletta A, Sorci F, et al. *JAAD Case Rep* 2019; 5: 326–8.

In this case report, treatment with adalimumab improved the inflammatory lesions of hidradenitis suppurativa (HS), but was ineffective on the associated lymphedema, likely resulting from extensive scarring and fibrosis. Patients with HS undergoing treatment with adalimumab should therefore be advised that lymphedema may progress despite medical treatment, and that in such cases combination with surgery should be considered.

Lymphocytoma cutis

Fiona J. Child



Lymphocytoma cutis (cutaneous B-cell lymphoid hyperplasia, cutaneous B-cell pseudolymphoma, Spiegler-Fendt sarcoid) is an entity encompassing a spectrum of benign B-cell lymphoproliferative diseases that share clinical and histopathologic features that may mimic cutaneous low-grade B-cell lymphoma. Various antigenic stimuli can induce lymphocytoma cutis, but in most cases the cause is not known. It is more common in females, with a female-to-male ratio of approximately 2:1. Most cases are characterized by localized erythematous, plum-colored nodules and plaques. Less frequently the generalized form may present with multiple miliary papules measuring a few millimeters in diameter. Lymphocytoma cutis secondary to *Borrelia* infection is most frequently seen at sites where skin temperature is low, such as the earlobes, nipples, nose, and scrotum.

MANAGEMENT STRATEGY

A skin biopsy for histopathology and immunohistochemistry is required to confirm the diagnosis, but the distinction between lymphocytoma cutis and cutaneous B-cell lymphoma may be difficult. There are no agreed histologic criteria; however, features that suggest lymphocytoma cutis include an unaffected epidermis, separated by a grenz zone, below which are well-formed, non-expanded, reactive germinal centers. The majority of the infiltrate consists of small, round B-lymphocytes with admixed T-cells (usually <30%), without cellular atypia, and polytypic expression of kappa and lambda light chains. A further feature is the presence of numerous tangible-body macrophages within the lymphoid follicles. Molecular analysis of the immunoglobulin heavy chain gene has shown that a significant proportion harbor B-cell clones, which suggests that many cases previously thought to be lymphocytoma cutis represent indolent, low-grade, primary cutaneous B-cell lymphomas (PCBCL). In cases where the diagnosis is in doubt, including those with unusual manifestations, such as multiple nodules, monotypic expression of immunoglobulin light chains, or the detection of B-cell or T-cell clonality by molecular techniques, careful evaluation to exclude systemic disease (a

thorough clinical examination, thoracoabdominopelvic computed tomography [CT] scan, or positron emission tomography (PET) scan) is required, with adequate long-term follow-up.

A history of possible stimuli known to cause lymphocytoma cutis should be sought; these include *Borrelia burgdorferi* infection, *Leishmania* infection, trauma, vaccinations, allergy hyposensitization injections, drugs, arthropod bites, acupuncture, gold pierced earrings, tattoos, treatment with leeches (*Hirudo medicinalis*), and post-herpes zoster scars, but in most cases the etiology is unknown.

The course of the disease varies but tends to be chronic and indolent; some lesions may resolve spontaneously without treatment. There is no therapy of proven value for lymphocytoma cutis, with only anecdotal case reports and small series reported and no clinical trials in the literature.

If a cause can be identified, the causative agent should be removed. If infection with *B. burgdorferi* is suspected, treatment with appropriate antibiotics (for adults: doxycycline 100 mg twice per day, or amoxicillin 500–1000 mg three times per day for 21 days, or, alternatively azithromycin 500 mg once daily for 17 days; doses vary for children depending on age and weight) should be initiated.

Localized disease can be treated by simple excision and may respond to intralesional injection of corticosteroids, local irradiation, or intralesional interferon- α . More widespread (generalized) disease is traditionally treated with oral antimalarials, most commonly hydroxychloroquine (maximum dose 6.5 mg/kg/day); however, lesions may fail to respond to treatment or may recur after cessation of therapy. Other treatment modalities include subcutaneous interferon- α and oral thalidomide. Effective responses to destructive therapies, including cryotherapy and the argon laser, have been reported. A subtype of generalized lymphocytoma cutis may be exacerbated by light, and therefore sun avoidance and the use of sun block are important.

Specific Investigations

- Serology for *B. burgdorferi* (antibodies identified in 50% of patients with borrelial lymphocytoma)
- Skin biopsy for histology, immunophenotype, and immunoglobulin gene analysis
- Patch testing (if a possible contact allergen is suspected)

The spirochetal etiology of lymphadenosis benigna cutis solitaria. Hovmark A, Asbrink E, Olsson I. Acta Derm Venereol 1986; 66: 479–84.

Of 10 patients investigated, four reported a previous tick bite. Positive *Borrelia* serology was found in six of nine patients, and spirochetes were cultured from one of two skin biopsies.

***Borrelia burgdorferi*-associated lymphocytoma cutis: clinicopathologic, immunophenotypic, and molecular study of 106 cases.** Colli C, Leinweber B, Müllegger R, et al. J Cutan Pathol 2004; 31: 232–40.

A total of 106 cases of *B. burgdorferi*-associated lymphocytoma cutis in a region endemic for *Borrelia* infection were studied retrospectively. The most common sites affected were the earlobe, genital area, and nipple (these locations may be due to the predilection of *B. burgdorferi* spirochetes for cooler body sites). In some cases the histopathologic, immunophenotypic, and molecular features were misleading, and it was concluded that integration of all data is necessary to obtain the correct diagnosis.

Borrelial lymphocytoma in adult patients. Maraspin V, Nahtigal Kleišar M, Ruzic-Sabljic E, et al. Clin Infect Dis 2016; 63: 914–21.

Cases of borrelial lymphocytoma diagnosed in 144 adults from a single institution were followed for 1 year. Breast and earlobe were the most common sites of involvement, and 72% had concomitant erythema migrans. Ninety percent of patients responded to a course of antibiotics. Those with features of disseminated Lyme borreliosis were most likely to fail treatment, but all responded to re-treatment.

Differential diagnosis of cutaneous infiltrates of B lymphocytes with follicular growth pattern. Leinweber B, Colli C, Chott A, et al. Am J Dermatopathol 2004; 26: 4–13.

The histopathologic, immunophenotypic, and molecular features of *B. burgdorferi*-associated lymphocytoma cutis, primary cutaneous follicle center cell lymphoma, and primary cutaneous marginal zone lymphoma were compared. Features that favored lymphocytoma cutis were the presence of tangible-body macrophages, strong proliferation rate of follicular cells, BCL-2-negative follicular cells, and the absence of monoclonality.

Immunophenotypic and genotypic analysis in cutaneous lymphoid hyperplasias. Hammer E, Sanguenza O, Suwanjindar P, et al. J Am Acad Dermatol 1993; 28: 426–33.

Of 11 patients with histologic and immunophenotypic features of lymphocytoma cutis, clonal rearrangements were detected in two, both of whom subsequently developed B-cell lymphoma.

A review of 55 cases of cutaneous lymphoid hyperplasia: reassessment of the histopathologic findings leading to reclassification of 4 lesions as cutaneous marginal zone lymphoma and 19 as pseudolymphomatous folliculitis. Arai E, Shimizu M, Hirose T. Hum Pathol 2005; 36: 505–11.

The histopathologic features of 55 cases of cutaneous lymphoid hyperplasia were reassessed. Of these, nine were reclassified as marginal zone lymphoma, distinguished by patchy or diffuse centrocyte-like cells, with plasma cells at the periphery of the infiltrate, monotypic light chain restriction, and a clonal immunoglobulin heavy chain gene rearrangement.

Clonality assessment of cutaneous B-cell lymphoid proliferations: a comparison of flow cytometry immunophenotyping, molecular studies, and immunohistochemistry/in situ hybridization and review of the literature. Schafernak KT, Variakojis D, Goolsby CL, et al. Am J Dermatopathol 2014; 36: 781–95.

Flow cytometry immunophenotyping, which is not routinely applied to the skin, was performed on 73 cutaneous lymphoid infiltrates; B-cell clones were detected in 68% of infiltrates diagnosed as B-cell lymphoma, in contrast to none of the 14 cases of cutaneous lymphoid hyperplasia.

Cutaneous pseudolymphoma – a review on the spectrum and a proposal for a new classification. Mitteldorf C, Kempf W. J Cut Pathol 2020; 47: 76–97.

The clinical and histopathological spectrum of benign cutaneous lymphoid infiltrates is wide and a new classification for cutaneous pseudolymphomas is proposed. Lymphocytoma cutis is included as a nodular pseudolymphoma.

Lymphomatoid contact reaction to gold earrings. Fleming C, Burden D, Fallowfield M, et al. Contact Derm 1997; 37: 298–9.

A rare entity characterized by nodules at sites of piercing with gold jewelry and the histologic features of lymphocytoma cutis. Patch tests to gold sodium thiosulfate are positive.

Cutaneous pseudolymphoma after patch test to gold sodium thiosulfate in two patients. Garcia-Arpa M, Gomez-Torrigos E, Relea-Calatayud E, et al. Contact Dermatitis 2020; 82: 322–4.

Two patients developed cutaneous lymphoid hyperplasia at the site of gold sodium thiosulfate in a patch test series. No clinical relevance to gold was present in either patient.

Vaccination-induced cutaneous pseudolymphoma. Maubec E, Pinquier L, Viguier M, et al. J Am Acad Dermatol 2005; 52: 623–9.

Nine patients developed cutaneous lymphoid hyperplasia at the site of hepatitis vaccinations. Aluminum deposits were identified in all nine biopsy specimens, and the authors suggest that cutaneous lymphoid hyperplasia is a possible adverse effect of vaccinations that include aluminum oxide as an adjuvant.

Ipilimumab/nivolumab-induced pseudolymphoma in a patient with malignant melanoma. Ayoubi N, Haque A, Vera N, et al. J Cutan Pathol 2020; 47: 390–3.

A 38-year-old man developed painful nodules on his hands and face, confirmed on biopsy as pseudolymphoma, during adjuvant treatment for metastatic melanoma. The lesions resolved with treatment interruption and a tapering dose of oral prednisolone, and did not recur when nivolumab alone was restarted. It is unclear as to whether ipilimumab was the culprit or whether the lesions occurred as a result of immune dysregulation induced by anti-CTLA4/PD1 combination therapy.

Cutaneous pseudolymphoma as a rare adverse effect of medicinal leech therapy; a case report and review of the literature. Sepaskhah M, Yazdanpanah N, Aslani FS, et al. Cureus 2020; 12(4): e7517. doi: 10.5579/cureus.5517.

A 44-year-old woman with erythematous, pruritic lesions on right shin, confirmed histologically as pseudolymphoma, following leech therapy for treatment of erythema nodosum. The lesions resolved with oral steroids given for erythema nodosum. Seven previous cases reported in the literature are reviewed; all responded to topical or intralesional steroids or cryotherapy.

First-Line Therapies

Localized

• Excision	E
• Topical corticosteroids	E
• Intralesional corticosteroids	E
• Oral antibiotics (if positive <i>Borrelia</i> serology)	E
• CO ₂ or Nd:YAG laser (if occurring within a tattoo)	E

Generalized

• Antimalarials	E
• Sun avoidance/sun block (light exacerbated)	E

Treatment of cutaneous pseudolymphoma with hydroxychloroquine. Stoll DM. J Am Acad Dermatol 1983; 8: 696–9.

A case report of a 40-year-old woman with generalized lymphocytoma cutis that cleared with 400mg hydroxychloroquine daily.

Cutaneous lymphoid hyperplasia (pseudolymphoma) in tattoos: a case series of 7 patients. Kluger N, Vermeulen C, Moguelet P, et al. *J Eur Acad Dermatol Venereol* 2010; 24: 208–13.

Two of seven patients with cutaneous lymphoid hyperplasia occurring within their tattoos were treated with CO₂ or Nd:YAG laser with improvement.

Second-Line Therapies

Localized

• Superficial radiotherapy	E
• Intralesional interferon- α	E
• Argon laser	E
• Cryotherapy	D
• Topical 0.1% tacrolimus ointment	E
• Intralesional rituximab	E
• Topical photodynamic therapy	E

Generalized

• Subcutaneous interferon- α_{2b}	E
• Thalidomide	E
• Methotrexate	E

Cutaneous lymphoid hyperplasia: results of radiation therapy. Olson LE, Wilson JE, Cox JD. *Radiology* 1985; 155: 507–9.

Four cases of lymphocytoma cutis were treated with radiation therapy. Over a follow-up period of 8 months to 7 years there were no recurrences.

Local orthovolt radiotherapy in primary cutaneous B-cell lymphoma. Pimpinelli N, Vallecchi C. *Skin Cancer* 1999; 14: 219–24.

Data from 115 patients with PCBCL produced a 98.2% complete remission rate and a median disease-free period of 55 months; recurrences were mostly limited to the skin. In view of the difficulties in distinguishing between PCBCL and lymphocytoma cutis, many groups have used superficial radiotherapy in cases of lymphocytoma cutis, although evidence remains anecdotal.

In our experience these cases are relatively radioresistant compared with PCBCL.

Treatment of cutaneous pseudolymphoma with interferon alfa-2b. Tomar S, Stoll HL, Grassi MA, et al. *J Am Acad Dermatol* 2009; 60: 172–4.

One patient with multiple nodules and plaques was treated with intralesional interferon- α_{2b} (1 MU in 1 mL saline) every 2 weeks for a total of 5 weeks with complete resolution of all lesions except for one that was subsequently excised.

Role of the argon laser in treatment of lymphocytoma cutis. Wheeland RG, Kantor GR, Bailin PL, et al. *J Am Acad Dermatol* 1986; 14: 267–72.

The argon laser improved cosmetic appearance and alleviated symptoms of lymphocytoma cutis but failed to provide complete histologic clearing in a young man who had failed to respond adequately to initial therapy with hydroxychloroquine.

Lymphocytoma cutis: a series of five patients successfully treated with cryosurgery. Kuflik AS, Schwartz RA. *J Am Acad Dermatol* 1992; 26: 449–52.

Five patients with lymphocytoma cutis underwent therapy with liquid nitrogen to individual lesions using a single cycle of

15–20 seconds per lesion, with complete clinical resolution of all lesions treated within 3–6 weeks.

Spiegler–Fendt type lymphocytoma cutis: a case report of two patients successfully treated with interferon alfa-2b. Hervonen K, Lehtinen T, Vaalasti A. *Acta Derm Venereol* 1999; 79: 241–2.

Two men who had generalized lymphocytoma cutis and had failed to respond to other therapies were treated with subcutaneous interferon- α_{2b} 2.5 MU three times per week, with complete resolution of all lesions by 3 months. However, lesions recurred in both men between 6 and 23 months after the completion of treatment.

Subcutaneous interferon alfa for the treatment of cutaneous pseudolymphoma. Singletary HL, Salim A, Olsen E. *Arch Dermatol* 2012; 148: 572–4.

A 28-year-old female with plaques on the face, ear, and arms had a complete response to subcutaneous interferon- α_{2b} (3 MU three times per week) after 3 months of treatment, having failed multiple previous therapies. The lesions recurred on cessation of treatment but responded to reintroduction of interferon- α_{2b} .

A once-weekly pegylated version of subcutaneous interferon- α_{2b} has replaced the three times weekly interferon- α_{2b} , which has been withdrawn from the market.

Treatment of cutaneous lymphoid hyperplasia with thalidomide: report of two cases. Benchikhi H, Bodemer C, Fraïtag S, et al. *J Am Acad Dermatol* 1999; 40: 1005–7.

Two cases of lymphocytoma cutis involving the nose that showed complete regression after treatment with thalidomide for 3 months at a dose of 100 mg once daily for 2 months and 50 mg once daily for the third month. There was no recurrence at 36 and 31 months' follow-up, respectively.

Disseminated cutaneous lymphoid hyperplasia of 12 years' duration triggered by vaccination. Pham-Ledard A, Vergier B, Doutre MS, et al. *Dermatology* 2010; 220: 176–9.

A 17-year-old girl with longstanding hepatitis B vaccination-induced cutaneous lymphoid hyperplasia was treated with oral thalidomide with a complete clinical response.

Sustained remission of recalcitrant cutaneous lymphoid hyperplasia after thalidomide treatment. Erickson SP, Nahmias Z, Rosman IS, et al. *JAAD Case Reports* 2018; 4: 345–7.

A 66-year-old man with cutaneous lymphoid hyperplasia affecting the face, who had failed to respond adequately to multiple treatment modalities, was treated with thalidomide 50 mg daily for 1 month, uptitrated to 100 mg, with complete resolution at 4 months. Thalidomide was stopped at that stage due to mild peripheral neuropathy, and he remained in clinical remission 6 months later.

Cutaneous lymphoid hyperplasia arising in pre-existing morphea plaques treated with methotrexate. Dairi M, Arnault J-P, Dadban A, et al. *JAAD Case Rep* 2019; 16: 127–30.

A patient with generalized morphea developed scattered erythematous nodules on the scapula and upper back diagnosed as B-cell cutaneous lymphoid hyperplasia on histology. Methotrexate 25 mg/week resulted in resolution of the nodules in addition to reduced induration of the plaques of morphea.

Lymphocytoma cutis treated with topical tacrolimus. El-Dars LD, Statham BN, Blackford S, et al. *Clin Exp Dermatol* 2005; 30: 305–7.

Two cases of lymphocytoma cutis affecting the face were treated with topical tacrolimus 0.1% twice daily. In both cases the lesions completely resolved after 8 months' application.

Treatment of cutaneous lymphoid hyperplasia with the monoclonal anti-CD20 antibody rituximab. Martin SJ, Duvic M. Clin Lymphoma Myeloma Leuk 2011; 11: 286–8.

One case of lymphocytoma cutis was treated with intralesional rituximab with notable clinical improvement. Persistent and

recurrent erythematous areas were subsequently treated with topical tacrolimus with further improvement.

Successful treatment of lymphadenosis benigna cutis with topical photodynamic therapy with delta-aminolevulinic acid.

Takeda H, Kaneko T, Harada K, et al. Dermatology 2005; 211: 264–6.

Two females were treated with five treatments of topical δ -aminolevulinic acid photodynamic therapy (ALA-PDT) with dramatic clinical and histopathologic improvement.

Lymphogranuloma venereum

Antonios Kanelleas, Vasileios Papaefthymiou



Lymphogranuloma venereum (LGV) is an uncommon sexually transmitted infection occurring mainly in the tropics. It is caused by one of the three serovars (L1, L2, L3) of the intracellular bacterium *Chlamydia trachomatis*. The incubation period is 1–4 weeks, after which three subsequent stages can follow: a primary stage with transient genital ulceration, a secondary stage with painful, suppurative inguinal lymphadenopathy, and a tertiary fibrotic stage complicated with lymphatic obstruction and genital elephantiasis.

LGV can be associated with extragenital manifestations such as erythema nodosum, myalgia, reactive arthritis, fever, malaise, and weight loss.

In recent years, developed countries have experienced a shift in LGV epidemiological patterns and clinical presentation. Since 2003, LGV has emerged in Europe and North America as a leading cause of proctitis and proctocolitis in men who have sex with men (MSM). Endemic acquired cases of LGV in heterosexuals are extremely rare in Europe and there is no evidence of transmission of LGV within the European heterosexual population. Among MSM, about 25% of the anorectal LGV infections are asymptomatic. Today in developed countries LGV is predominantly associated with rectal infection and the classical findings of inguinal lymphadenopathy are increasingly uncommon. The diagnosis is confirmed by the detection of serovar L of *C. trachomatis* from the site of infection (ulcer base exudate, rectal mucosa, or bubo aspirates). The diagnostic method of choice is detecting *C. trachomatis* nucleic acid using nucleic acid amplification tests (NAATs) and confirmation by real-time polymerase chain reaction assays for LGV-specific DNA.

MANAGEMENT STRATEGY

Treatment should not be delayed pending laboratory confirmation, so that progression to chronic phase is prevented. Prolonged courses of antibiotics (at least 3 weeks) are required.

The treatment of choice is *doxycycline* 100 mg twice daily for 3 weeks. Fluoroquinolones and tetracyclines are contraindicated in pregnant and lactating women. These women should be treated with *erythromycin* 500 mg four times daily for 3 weeks. Children with LGV should be treated with erythromycin. *Azithromycin* 1 g once a week for 3 weeks has been used successfully as an alternative to erythromycin. *Moxifloxacin* (400 mg once daily for 3 weeks), *minocycline* (300 mg loading dose, followed by 200 mg twice daily for 3 weeks), and *rifampicin* (600 mg once daily for 3 weeks) are mentioned as escape treatments in the current European guidelines.

If alternative treatment regimens are used, a test of cure must be performed 4–6 weeks after end of treatment.

HIV-positive patients are treated with the same regimens; however, these patients may require prolonged treatment and they must be closely monitored for treatment failure and relapse.

Fluctuant buboes may require aspiration through healthy adjacent skin; surgical incision is usually contraindicated due to risk of complications such as sinus formation.

All patients with LGV should also be tested for other sexually transmitted infections (STIs; at a minimum syphilis and gonorrhea) including HIV, hepatitis B, and hepatitis C before starting therapy.

Intensive and repeated safe-sex counseling is necessary because most patients continue to engage in high-risk behaviors. Sex partners within the last 3 months should be offered testing for LGV from all exposed sites and empirical treatment with doxycycline.

Specific Investigations

- NAAT swab test (nucleic acid amplification test)

2019 European guideline on the management of lymphogranuloma venereum. De Vries HJ, De Barbeyrac B, De Vrieze NH, et al. *J Eur Acad Dermatol Venereol* 2019; 33(10): 1821–8.

Assessment of alternative diagnostic methods (e.g., *Chlamydia* serology) can be found in this review. However, they are generally considered to be unreliable.

Lymphogranuloma venereum 2015: clinical presentation, diagnosis, and treatment. Stoner BP, Cohen SE. *Clin Infect Dis* 2015; 61(Suppl 8): S865–73.

Proctitis and proctocolitis are now the most common clinical manifestations of LGV. The classic inguinal presentation with buboes is becoming increasingly uncommon.

Lymphogranuloma venereum among men who have sex with men. An epidemiologic and clinical review. De Vrieze NH, de Vries HJ. *Expert Rev Anti Infect Ther* 2014; 12: 697–704.

MSM who have had receptive anal intercourse in the past 6 months should be screened. Asymptomatic carriers are a reservoir of infection, and these persons should be treated.

Lymphogranuloma venereum presenting as perianal ulceration: an emerging clinical presentation? Singhrao T, Higham E, French P. *Sex Transm Infect* 2011; 87: 123–4.

LGV, along with herpes simplex, chancroid, and syphilis, must be included in the differential diagnosis of anal ulcers, particularly in MSM. Herpes simplex remains the most common cause.

The association between lymphogranuloma venereum and HIV among men who have sex with men: systematic review and meta-analysis. Rönn MM, Ward H. *BMC Infect Dis* 2011; 11: 70.

In 13 studies the prevalence of HIV among MSM with LGV ranged from 67% to 100%. HIV-positive MSM are disproportionately affected by LGV.

Persistent high-risk sexual behavior in men who have sex with men after symptomatic lymphogranuloma venereum proctitis. Van den Bos RR, van der Meijden WI. *Int J STD AIDS* 2007; 18: 715–6.

After treatment of LGV proctitis, 17 of 26 patients (65%) were subsequently treated for another STI within 3 years. Health education and counseling efforts must be intensified because patients continue to engage in high-risk sexual activities.

First-Line Therapy

- Doxycycline 100mg orally twice daily for 21 days **B**

2019 European guideline on the management of lymphogranuloma venereum. De Vries HJ, De Barbeyrac B, De Vrieze NH, et al. *J Eur Acad Dermatol Venereol* 2019; 33(10): 1821–8.

Second-Line Therapies

- Erythromycin base 500mg orally four times daily for 21 days (first choice in pregnant women and children) **B**
- Azithromycin 1.0g orally once weekly for 3 weeks **C**
- Moxifloxacin 400mg daily for 10 days **E**

Treatment of lymphogranuloma venereum. McLean CA, Stoner BP, Workowski KA. *Clin Infect Dis* 2007; 44: 147–52.

Doxycycline 100mg twice daily for 3 weeks is recommended as first-line treatment for LGV. Azithromycin 1.0g orally once weekly for 3 weeks appears to be effective against LGV. Erythromycin base 500mg four times a day orally is the preferred treatment for pregnant women with LGV.

Doxycycline failure in lymphogranuloma venereum. Méchaï E, de Barbeyrac B, Aoun O, et al. *Sex Transm Infect* 2010; 86: 278–9.

The authors report a patient with LGV proctitis who failed a full 3-week course of doxycycline. The patient achieved rapid clinical cure with a 10-day course of moxifloxacin 400mg daily. Failure of doxycycline is unusual.

An audit on the management of lymphogranuloma venereum in a sexual health clinic in London, UK. Hill SC, Hodson L, Smith A. *Int J STD AIDS* 2010; 21: 772–6.

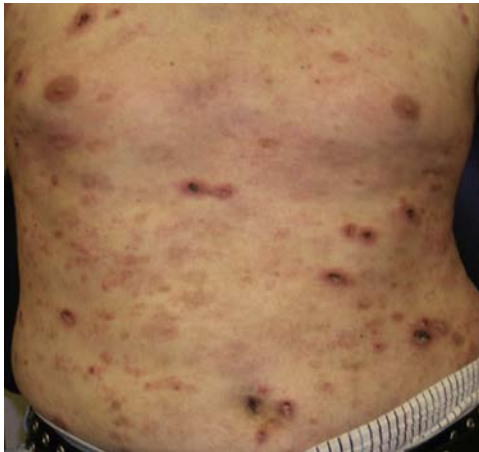
Fifty-five patients were treated with doxycycline, and seven patients were treated with azithromycin 1g per week for 3 weeks. All patients treated with azithromycin achieved clinical cure, and microbiological cure was proven in six. Half of the treated patients returned for follow-up within 3 months; a notable proportion tested positive for newly acquired STIs. Patients continue to engage in high-risk behaviors after treatment, and safe-sex counseling efforts need to be intensified.

Approach to lymphogranuloma venereum. O’Byrne P, MacPherson P, DeLaplante S, et al. *Can Fam Physician* 2016; 62: 554–8

For partner follow-up, the Canadian guidelines recommend that sexual contacts from the preceding 60 days should be tested for chlamydia and standard LGV treatment should be started for both confirmed and probable cases, in the absence of LGV-specific NAATs.

Lymphomatoid papulosis

Daniel J. Lewis, Alain H. Rook, Ellen J. Kim



Lymphomatoid papulosis (LyP) is a chronic papulonodular disorder that consists of recurrent, self-healing crops of papulonodules characterized by a variable infiltrate of CD30+ lymphocytes on histopathology. In the World Health Organization/European Organization for the Research and Treatment of Cancer (WHO/EORTC) classification of cutaneous lymphomas, the disorder is defined as a benign clonal proliferation of T lymphocytes and is a distinct entity in the spectrum of cutaneous CD30+ lymphoproliferative disorders, which also includes primary cutaneous anaplastic large-cell lymphoma (pcALCL). Patients with LyP may present with very few or with multiple lesions, which may evolve into a crusted or necrotic stage, often healing with scarring. Less common presentations include regional, isolated acral, and oral disease. The lesions may cause pruritus. LyP affects adults and children as young as 11 months of age and may persist for years to decades. Approximately 5–25% of patients with LyP may present with or develop a hematologic malignancy, including systemic anaplastic large-cell lymphoma (ALCL), Hodgkin lymphoma, or a cutaneous T-cell lymphoma (CTCL) such as mycosis fungoides (MF). There may also be a slightly increased risk of a non-hematologic neoplasm. The same T-cell clone has been identified in some patients with LyP and the associated lymphoma (including MF and primary cutaneous anaplastic large-cell lymphoma [pcALCL]), supporting the concept that LyP lies within the spectrum of CTCL. Clinical and histologic features may overlap with arthropod bites, pityriasis lichenoides, and folliculitis.

MANAGEMENT STRATEGY

Management of LyP must take into consideration the natural history of the disease. LyP is defined as a recurrent, self-healing (remission of every individual lesion), papulonodular eruption, with histology suggestive of CTCL. There are six histologic variants, including type A (wedge-shaped infiltrate containing eosinophils

and histiocytes), type B (epidermotropism, resembles MF), type C (cohesive sheets of CD30+ cells, resembles ALCL), type D (CD8/CD30+, resembles primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma), type E (CD30+ with angioinvasion), and type F (CD30+, follicular). A minor subset of LyP patients may have chromosomal rearrangements involving the DUSP22-IRF4 locus on 6p25.3, which has been observed in some pcALCL patients. Recognition of these different subtypes is essential to avoid misdiagnosis of other, more aggressive, forms of CTCL.

Clinical evaluation should include a complete history and examination assessing for atypical findings, including previous lymphoid neoplasms, constitutional symptoms, lymphadenopathy, or laboratory abnormalities in peripheral blood counts, blood chemistry, and lactate dehydrogenase. Patients with abnormal findings should undergo computed tomography (CT) or positron emission tomography (PET)/CT scanning to exclude a systemic lymphoma. Distinguishing LyP from pcALCL is important though somewhat challenging because of their clinical and histologic overlap. Persistent lesions greater than 2–3 cm in diameter are more consistent with pcALCL; however, some patients do not fit well into either category. Such 'borderline' cases exhibit similar biologic behavior to LyP and can be managed as such.

Treatment of LyP should be tailored to disease burden, as treatment has not been proven to alter the natural course of LyP, nor does it prevent the development of associated lymphomas. Treatment should be reserved for symptomatic or cosmetically bothersome cases. First-line therapies include topical corticosteroids, phototherapy, and low-dose methotrexate. A response may be seen within the first few weeks of treatment, yielding fewer lesions, quicker resolution of individual lesions, and occasionally complete remission. Large or borderline lesions may be treated with local radiation or excision. Therapies effective for MF may be used for LyP, including topical agents such as carmustine (BCNU), mechlorethamine (nitrogen mustard), bexarotene (retinoid X receptor agonist), and imiquimod. Systemic biologic agents such as interferon- α and oral bexarotene are also effective for suppressing lesions. The anti-CD30 antibody-drug conjugate brentuximab vedotin is highly effective; however, use of this agent may produce peripheral neuropathy and is only warranted in severe, refractory cases. Multiagent chemotherapy is not indicated, despite histologic features that may suggest ALCL. LyP can recur for decades, requiring careful consideration of treatment side effects and continued monitoring for the development of lymphoma.

Specific Investigations

- Biopsy and histologic review to confirm the diagnosis
- Exclusion of constitutional ('B') symptoms, hepatosplenomegaly, lymphadenopathy, or laboratory abnormalities
- Ongoing surveillance for a lymphoproliferative neoplasm

EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Kempf W, Pfaltz K, Vermeer M, et al. *Blood* 2011; 118: 4024–35.

These consensus guidelines provide recommendations for managing the spectrum of CD30+ cutaneous lymphoproliferative disorders. LyP does not require staging procedures if history and

examination are unremarkable. Long-term follow-up is required for all subtypes.

Lymphomatoid papulosis. Reappraisal of clinicopathologic presentation and classification into subtypes A, B, and C. El Shabrawi-Caelen L, Kerl H, Cerroni L. Arch Dermatol 2004; 140: 441–7.

A retrospective review of 85 patients with LyP identified histologic overlap among subtypes A, B, and C, and between type B and MF. Eight percent of patients had more than one histologic subtype of LyP. The authors also stress the tight overlap between LyP and CD30+ CTCL such as pcALCL and MF with large-cell transformation. A variety of clinicohistopathologic presentations, including those with histology showing follicular mucinosis, syringotropism, vesicle formation, MF-like bandlike infiltrates, and associated keratoacanthoma, are discussed.

A variant of lymphomatoid papulosis simulating primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. Description of 9 cases. Saggini A, Gulia A, Argenyi Z, et al. Am J Surg Pathol 2010; 34: 1168–75.

A variant of LyP, termed *LyP type D*, is described in nine patients with clinical aspects of LyP but with histopathological features resembling primary cutaneous aggressive epidermotropic CD8+ cytotoxic lymphoma. LyP type D features medium-sized CD8+CD30+ pleomorphic cells with prominent, pagetoid reticulis-like epidermotropism. None of the patients developed a lymphoproliferative malignancy during 84 months of mean follow-up.

Accurate clinicopathologic correlation is necessary to diagnose LyP type D and avoid a misdiagnosis of primary cutaneous aggressive epidermotropic CD8+ cytotoxic lymphoma.

Angioinvasive lymphomatoid papulosis: a new variant simulating aggressive lymphomas. Kempf W, Kazakov DV, Schärer L, et al. Am J Surg Pathol 2013; 37(1): 1–13.

Another variant of LyP, termed type E LyP, is described retrospectively in 16 patients with oligolesional papules that ulcerated with histopathology showing CD30+CD8+ angioinvasive medium-to-large anaplastic cells in the dermis and subcutaneous tissue. Such histology can overlap with cytotoxic cutaneous lymphomas such as extranodal natural killer/T-cell lymphoma (nasal type) or gamma/delta T-cell lymphoma. Despite the aggressive features, none of the patients developed extracutaneous disease.

Follicular lymphomatoid papulosis revisited: a study of 11 cases, with new histopathological findings. Kempf W, Kazakov DV, Baumgartner HP, et al. J Am Acad Dermatol 2013; 68(5): 809–16.

Follicular LyP is a variant of LyP with involvement of hair follicles, manifesting as a perifollicular infiltrate with variable degree of folliculotropism. Other changes, including hyperplasia of the follicular epithelium, hair follicle rupture, and follicular mucinosis, are less common. Rarely, intrafollicular pustules can be seen in the follicular epithelium; such lesions manifest clinically as pustules.

Some propose that follicular LyP should be termed LyP type F, whereas others categorize it as a subtype of types A and C.

Primary and secondary cutaneous CD30+ lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Bekkenk MW, Geelen FAMJ, van Voorst Vader PC, et al. Blood 2000; 95: 3653–61.

Guidelines are proposed for the diagnosis and treatment of patients with CD30+ lymphoproliferative disorders based on long-term follow-up of 219 patients, 118 of whom had LyP. Fifty-two of 118 patients were not treated, whereas others received various standard therapies, none of which were associated with complete, sustained remission. Staging of patients with type C LyP failed to reveal extracutaneous disease. Nineteen percent developed an associated lymphoma. Inducing remission of the secondary lymphoma had no effect on the natural course of LyP. The risk of extracutaneous disease was 4% at 10 years.

Lymphomatoid papulosis: treatment response and associated lymphomas in a study of 180 patients. Wieser I, Oh CW, Talpur R, et al. J Am Acad Dermatol 2016; 74(1): 59–67.

In this retrospective chart review of 180 patients diagnosed with LyP between 1995 and 2015 at a specialty cancer clinic, histologic type A was the most common (47.2%), followed by type C (22.8%), type B (17.2%), type D (7.8%), and type E (0.6%), as well as mixed type (4.4%). One hundred fourteen other lymphomas were observed in 93 patients (51.6%), of which the most common were MF (61.4%) and ALCL (26.3%). Risk factors for lymphoma included male sex and types B and C; patients with type D were less likely to have lymphoma. Number of lesions, symptom severity, and T-cell clonality were not associated with an increased risk of lymphoma. Treatment provided symptomatic relief but did not prevent progression to lymphoma.

The higher association (40%) with lymphoma compared with other studies may represent a referral bias.

CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. Liu HL, Hoppe RT, Kohler S, et al. J Am Acad Dermatol 2003; 49: 1049–58.

In 19 of 31 cases with LyP, a higher than previously reported association with hematolymphoid malignancy (61%) was observed. Most patients had MF, which occurred before, during, or after the diagnosis of LyP. Some patients had two hematolymphoid malignancies. No association between LyP type and malignancy was noted. Three patients had their disease progress to pcALCL after 77 to 152 months. The overall 5- and 10-year survival of patients with LyP was 100% and 92%, respectively, and none died from LyP. Those with pcALCL had a favorable course.

The higher association with hematolymphoid malignancy (61%) may represent selection bias.

Lymphomatoid papulosis in children: a series of 25 cases. Miquel J, Fraitag S, Hamel-Taillac D, et al. Br J Dermatol 2014; 171(5): 1138–46.

This retrospective analysis studied 25 children with LyP up to 15 years of age diagnosed with LyP, of which 82% had type A and 18% had type C. Marked eosinophilic infiltrate was common (44%). No associated lymphomas were observed during median follow-up of 10 years. Pityriasis lichenoides chronica (PLC) was observed in 36% of patients and atopic dermatitis in 28%.

In children, PLC may be a predisposing factor for LyP.

Lymphomatoid papulosis in children and adolescents: a systematic review. Wieser I, Wohlmuth C, Nunez CA, et al. 2016; 17(4): 319–27.

In this systemic review, a total of 251 children and adolescents with LyP were studied. The mean age at diagnosis was 9.3 years. The most common subtype was type A in 106 patients. Of 14 children with associated lymphomas, two developed ALCL and one had MF.

LyP presents similarly in children and adults with no clear differences in prognosis, disease extent, or disease duration. Children with LyP require lifelong monitoring given the risk of an associated lymphoma, which may develop much later in life. Whereas MF is the most common secondary lymphoma in adults with LyP, ALCL is the most common in children.

Single cell analysis of CD30+ cells in lymphomatoid papulosis demonstrates a common clonal T-cell origin. Steinhoff M, Hummel M, Anagnostopoulos I, et al. *Blood* 2002; 100: 578–84.

The large CD30+ cells in LyP type A represent a single clone in each individual, whereas the majority of CD30– cells are polyclonal. The identical T-cell clone can be identified in separate skin lesions and at different time points, demonstrating the persistence of the T-cell clone in LyP.

Assessing clonality does not help to differentiate borderline cases of LyP from pALCL or MF.

Lymphomatoid papulosis associated with mycosis fungoides: a study of 21 patients including analyses for clonality. Zackheim H, Jones C, LeBoit PE, et al. *J Am Acad Dermatol* 2003; 49: 620–3.

Of 21 patients with LyP, 39% had MF. LyP preceded (67%), followed (19%), or was concurrent with (14%) a diagnosis of MF, and 95% had type A LyP. In seven patients in whom clonality was assessed, all had an identical clone in LyP and MF lesions.

Large cell transformation mimicking regional lymphomatoid papulosis in a patient with mycosis fungoides. Nakahigashi K, Ishida Y, Matsumura Y, et al. *J Dermatol* 2008; 35: 283–8.

A 57-year-old male with stage III MF developed a regional eruption on his chest consistent with transformed MF versus type C LyP. Spontaneous resolution supported a diagnosis of LyP.

The importance of differentiating LyP from MF with large-cell transformation of MF is emphasized. In contrast to the favorable prognosis of LyP, MF with large-cell transformation portends a poorer prognosis.

First-Line Therapies

• Therapy not required	B
• Psoralen ultraviolet A (PUVA)	B
• Low-dose methotrexate	B
• Topical corticosteroids	E

Practical management of CD30+ lymphoproliferative disorders. Hughey LC. *Dermatol Clin* 2015; 33(4): 819–33.

This review discusses current therapies for symptomatic LyP. Given the excellent long-term prognosis, it may be reasonable simply to monitor patients off therapy. The remaining specific treatment options are discussed in further detail.

PUVA-treatment in lymphomatoid papulosis. Wantzin GL, Thompson K. *Br J Dermatol* 1982; 107: 687–90.

Five patients with LyP, including one with tumors, were treated with PUVA (51–124 J/cm² for classic LyP and 481 J/cm² for tumors). Reduced lesion count was observed as well as shortening of the life cycle of each lesion to 1 week from 3–6 weeks. One patient achieved skin clearance.

Methotrexate is effective therapy for lymphomatoid papulosis and other primary cutaneous CD30+ lymphoproliferative

disorders. Vonderheid EC, Sajjadian A, Kadin ME. *J Am Acad Dermatol* 1996; 34: 470–81.

A 20-year experience of methotrexate therapy in 45 patients with LyP, borderline LyP, and CD30+ CTCL was reviewed. Patients responded within 4 weeks of methotrexate 15–20 mg weekly. Maintenance doses were administered at 10- to 14-day intervals (range 7–28 days). Twenty-nine percent had concomitant MF, requiring other therapies (mechlorethamine, carmustine, UVB, and PUVA), which offered some additional benefit but demonstrated lower relative efficacy than methotrexate. LyP and CD30+ CTCL responded similarly. Three patients exhibited diminished responsiveness, suggesting resistance to methotrexate. Severe exacerbations occurred upon abrupt drug discontinuation.

Methotrexate is considered first-line therapy for symptomatic disease as it suppresses new lesions and can lead to disease control, but relapse after discontinuing therapy is common.

Lymphomatoid papulosis: successful weekly pulse super-potent topical corticosteroid therapy in three pediatric patients. Paul MA, Krowchuk DP, Hitchcock MG, et al. *Pediatr Dermatol* 1996; 13: 501–6.

Three children with LyP were treated with halobetasol or clobetasol propionate twice daily for 2–3 weeks, followed by weekly pulsed application, resulting in resolution of nearly all lesions. Adjuvant intralesional triamcinolone was used for three ulcerated lesions.

Although potent topical steroids are unlikely to alter the disease course, they are a reasonable treatment approach given their favorable safety profile.

Second-Line Therapies

• Topical mechlorethamine (nitrogen mustard)	B
• Topical carmustine	C
• Topical bexarotene	C

Long-term efficacy, curative potential, and carcinogenicity of topical mechlorethamine chemotherapy in cutaneous T cell lymphoma. Vonderheid EC, Tan ET, Kantor AE, et al. *J Am Acad Dermatol* 1989; 20: 416–28.

Seven patients with LyP and 17 with concomitant LyP and MF were treated with 10–20 mg of mechlorethamine dissolved in 40–60 mL water applied once daily to the entire skin surface except for the genitalia, until at least 2 weeks after clearance of lesions. Four patients achieved a complete response, with one lasting for more than 8 years during follow-up. A slightly increased risk of squamous and basal cell carcinomas, Hodgkin lymphoma, and colon cancer was reported.

A common side effect of mechlorethamine therapy is an allergic hypersensitivity reaction, which may occur less frequently when mechlorethamine is prepared in an ointment base.

Topical carmustine therapy for lymphomatoid papulosis. Zackheim HS, Epstein EH, Crain WR. *Arch Dermatol* 1985; 121: 1410–14.

Seven patients with LyP were treated with once-daily total skin application of topical carmustine. Total doses ranged from 280 to 1180 mg. Local treatment of individual lesions after the total skin course included twice-daily application of 2–4 mg/mL 95% ethanol. All patients exhibited a rapid reduction in the number and size of lesions. Lesions cleared faster and did not scar with maintenance therapy, but remission was not seen. Rare persistent telangiectasias were noted.

Third-Line Therapies

• Oral bexarotene	C
• Recombinant interferon	C
• Excimer laser	E
• Radiotherapy	E
• Topical methotrexate	E
• Imiquimod cream	E
• Brentuximab vedotin	B

Bexarotene is a new treatment option for lymphomatoid papulosis. Krathen RA, Ward S, Duvic M. *Dermatology* 2003; 206: 142–7.

Oral bexarotene, initiated at 300 mg daily, was associated with more rapid resolution of lesions with decreased necrosis as well as a reduction in new lesions. One of three patients had a complete response. Bexarotene gel used in patients with an affected body surface area of less than 10% yielded a similar benefit.

Oral bexarotene is often used in conjunction with levothyroxine and lipid-lowering agents because of frequently seen central hypothyroidism and hyperlipidemia.

Therapeutic use of interferon-alpha for lymphomatoid papulosis. Schmuth M, Topar G, Illersperger B, et al. *Cancer* 2000; 89: 1603–10.

Five patients were treated with subcutaneous interferon- α 3–15 million IU three times per week. Three patients were treated for 12–13 months and achieved a complete response lasting for at least 1 year after therapy was completed. Two patients were treated for 5–7 months, with one complete response and one partial response, neither of which was durable after discontinuation of therapy. Only one of six controls achieved spontaneous remission.

308-nm excimer laser for the treatment of lymphomatoid papulosis and stage IA mycosis fungoides. Kontos AP, Kerr HA, Malick F, et al. *Photodermatol Photoimmunol Photomed* 2006; 22: 168–71.

A patient with LyP who had failed PUVA and methotrexate was treated with 308 nm excimer pulse laser three times weekly for a total of 13 treatments, with a maximum fluence of 500 mJ/cm². This regimen resulted in 75% clearance, with minimal recurrence and postinflammatory hyperpigmentation.

This handheld device allows delivery of higher fluences with a lower risk of carcinogenesis.

Persistent agmination of lymphomatoid papulosis: an equivalent of limited plaque mycosis fungoides type of cutaneous T-cell lymphoma. Heald P, Subtil A, Breneman D, et al. *J Am Acad Dermatol* 2007; 57: 1005–11.

Seven cases of regional LyP were treated as if they were localized MF, with 30–46 Gy local radiation in fractionated doses, resulting in durable remissions. One patient was also treated with bexarotene gel and localized electron beam therapy. At follow-up (2–6 years), six of the seven remained free of recurrence. One patient with disease relapse subsequently achieved complete remission with interferon- α and PUVA.

Treatment of regional LyP with localized radiation therapy as if it were MF may yield prolonged remission of LyP, but these patients may still develop an associated lymphoma. Long-term follow-up is critical.

Treatment of lymphomatoid papulosis with imiquimod 5% cream. Hughes PH. *J Am Acad Dermatol* 2006; 54: 546–7.

A 13-year-old boy with LyP was reported to have a complete response within 2 weeks with lesional application of imiquimod 5% cream three times per week.

Responses to imiquimod are variable, and patients should be warned of possible inflammation. The utility of imiquimod is limited by its cost.

Brentuximab vedotin for patients with refractory lymphomatoid papulosis: an analysis of phase 2 results. Lewis DJ, Talpur R, Huen AO, et al. *JAMA Dermatol* 2017; 153(12): 1302–6.

Brentuximab vedotin is an antibody–drug conjugate that consists of an anti-CD30 monoclonal antibody conjugated to the tubulin toxin monomethyl auristatin E. The drug was approved in 2017 by the Food and Drug Administration for refractory CD30+ CTCL. In this study, 12 patients with extensive or refractory LyP received intravenous brentuximab vedotin 1.8 mg/kg every 21 days. Nine patients had been enrolled in a previous open-label, single-center, phase II clinical trial of brentuximab vedotin for CD30+ CTCL. All 12 patients responded, and seven exhibited a complete response. Time to response was 3 weeks in all patients, and median duration of response was 20 weeks (range, 6–103 weeks). The most common adverse event was grade 1–2 peripheral neuropathy in 10 patients (83%), which can persist after therapy.

Brentuximab vedotin exhibits superb efficacy for LyP and can control extensive, refractory disease with few infusions and potentially can provide sustained responses. However, it likely does not alter the risk of lymphoma, and its efficacy must be balanced against the risk of adverse effects, particularly peripheral neuropathy. In rare cases, it may result in progressive multifocal leukoencephalopathy in immunosuppressed patients. Given the overall favorable prognosis of LyP, brentuximab vedotin should be reserved for only severe, refractory cases.

Malignant atrophic papulosis

Kiran Motaparthy



Atrophic papulosis, also known as Köhlmeier-Degos disease or Degos disease, is a rare occlusive vasculopathy for which treatment is challenging. Atrophic papulosis occurs in three distinct clinical contexts: malignant atrophic papulosis (MAP); benign atrophic papulosis (BAP); and atrophic papulosis in the context of autoimmune connective tissue disease.

MAP is associated with significant gastrointestinal (GI) and neurologic disease. GI involvement occurs in half of patients with MAP and can manifest as abdominal pain, indigestion, constipation, or diarrhea. Central nervous system involvement manifests as headaches, dizziness, paresthesias, and seizures. Ocular, hepatorenal, and cardiopulmonary systems may also be involved. BAP is a skin-limited disease without systemic symptoms and is a retrospective diagnosis that requires long-term follow-up, as the cutaneous findings usually precede systemic manifestations. The probability of only having BAP at onset is approximately 70% but increases to 97% after 7 years of skin-limited disease. Systemic disease in MAP has a median onset of 1 year after cutaneous findings. The 5-year survival rate of MAP is 55%, and the most common cause of death is peritonitis secondary to intestinal perforation. Lastly, atrophic papulosis may be observed in patients with systemic lupus erythematosus, antiphospholipid syndrome, dermatomyositis, or systemic sclerosis, without the potentially catastrophic neurologic or GI disease associated with MAP.

Early, fully developed, and late papules demonstrate a spectrum of overlapping phase-dependent changes. Early papules are skin colored with a lymphocytic infiltrate. Established papules demonstrate porcelain-white centers and erythematous peripheral rims. Dermoscopy demonstrates white stellate structureless areas surrounded by telangiectasia, hyperpigmentation, and follicular plugs. Fully developed lesions demonstrate vasculitis and superficial changes of lichen sclerosus. Late papules feature atrophy without erythema, corresponding to the classic histopathology: wedge-shaped dermal necrosis and thrombotic vasculopathy.

MAP has been reported in association with factor V Leiden, antiphospholipid and anticardiolipin antibodies, and parvovirus B19 infection. In the past decade, evidence of high expression of

interferon- α and excessive deposition of late-stage complement components C5b-9 in diseased vessels provided deeper insight into the pathogenesis of this vasculopathy and identified the most effective therapy, *eculizumab*.

MANAGEMENT STRATEGY

Differentiation of MAP, BAP, and atrophic papulosis in the context of autoimmune connective tissue disease influences prognosis and therapy and requires review of symptoms, clinical context, serology, and long-term follow-up. Imaging and laboratory evaluation may identify early findings MAP, permitting prompt institution of therapy with first-line agents. While stool guaiac tests and endoscopy permit noninvasive evaluation of GI involvement, laparoscopy is more sensitive in early MAP.

Specific Investigations

- Physical examination
- Tissue biopsy (skin, intestines, and other internal organs)
- Complete blood count
- Stool guaiac
- Antinuclear antibody titer
- Protein C, protein S, and factor V Leiden; antithrombin III; and homocysteine levels
- Anticardiolipin antibody titer
- Antiphospholipid antibody titer
- Endoscopy of the GI tract
- Laparoscopy of the intestine
- Clinical integration of the aforementioned data

Malignant atrophic papulosis. Scheinfeld N. Clin Exp Dermatol 2007; 32: 483–7.

Benign atrophic papulosis (Degos disease) with lymphocytic vasculitis and lichen sclerosus-like features. Kim E, Motaparthy K. Am J Dermatopathol 2018; 40: 272–4.

Malignant and benign forms of atrophic papulosis (Köhlmeier-Degos disease): systemic involvement determines the prognosis. Theodoridis A, Konstantinidou A, Makrantonaki E, et al. Br J Dermatol 2014; 170: 110–5.

Degos-like lesions associated with systemic lupus erythematosus. Jang MS, Park JB, Yang MH, et al. Ann Dermatol 2017; 29: 215–8.

Systemic lupus erythematosus, following prodromal idiopathic thrombocytopenic purpura, presenting with skin lesions resembling malignant atrophic papulosis. Wallace MP, Thomas JM, Meligoni G, et al. Clin Exp Dermatol 2017; 42: 774–6.

Systemic lupus erythematosus with Degos disease: role of dermatoscopy in diagnosis. Vinay K, Sawatkar G, Dogra S, et al. Int J Dermatol 2017; 56: 770–2.

A fatal case of malignant atrophic papulosis (Degos' disease) in a man with factor V Leiden mutation and lupus anticoagulant. Hohwy T, Jensen MG, Tøttrup A, et al. Acta Derm Venereol 2006; 86: 245–7.

Degos disease: a C5b-9/interferon- α -mediated endotheliopathy syndrome. Magro CM, Poe JC, Kim C, et al. Am J Clin Pathol 2011; 135: 599–610.

Laparoscopy shows superiority over endoscopy for early detection of malignant atrophic papulosis gastrointestinal complications: a case report and review of literature. Toledo AE, Shapiro LS, Farrell JF, et al. BMC Gastroenterol 2015; 15: 156.

First-Line Therapies

• Eculizumab	D
• Treprostinil	D
• Aspirin	D

Eculizumab is a monoclonal antibody directed against the complement protein C5.

Chronic pleuritis leading to severe pulmonary restriction: a rare complication of Degos disease. Saha BK, Beegle S. BMJ Case Rep 2019; 12: e232759.

A 23-year-old man with MAP associated with intestinal perforation, chronic pleuritis, and restrictive lung disease was treated with eculizumab and treprostinil, surviving for 9 years.

Malignant atrophic papulosis. Mareschal A, Razanamahery J, Aubin F. JAMA Dermatol 2019; 10.1001/jamadermatol.2019.3726.

A man in his 30s with MAP was treated with eculizumab with prompt improvement in GI and neurologic symptoms and no thrombotic sequelae at 6 months.

Kohlmeier–Degos disease with constrictive pericarditis and atrial fibrillation. Wang SC, Patel H, Shapiro LS, et al. J Echocardiogr 2018; 16: 192–3.

A 17-year-old with MAP and bowel obstruction, restrictive lung disease and pleural effusions, pulmonary hypertension, pericarditis, and heart failure was alive 9 years after diagnosis while undergoing treatment with eculizumab and treprostinil.

Pediatric malignant atrophic papulosis. Huang YC, Wang JD, Lee FY, et al. Pediatrics 2018; 141: S481–4.

Treatment with eculizumab and enoxaparin for 18 months produced near, but temporary, resolution of neurologic sequelae in a 4-year-old girl.

Degos disease, not just a scar: lethal outcome in spite of immunomodulatory therapy. Calderón-Castrat X, Yuste-Chaves M, Hernández A, et al. E. J Eur Acad Dermatol Venereol 2017; 31: e435–8.

In a 4-year-old boy with MAP, eculizumab and treprostinil stabilized the disease course for 4 months until progression ensued again.

Vision loss, rash, and abnormal brain magnetic resonance imaging in a 17 year old. Tooley AA, Eckel LJ, Salomão DR, et al. J Neuroophthalmol 2017; 37: 303–8.

Eculizumab, treprostinil, aspirin, and pentoxifylline initially stabilized the disease course in a 17-year-old male patient with multiple acute cerebral infarctions and optic neuritis.

Diffuse atrophic papules and plaques, intermittent abdominal pain, paresthesias, and cardiac abnormalities in a 55-year-old woman. Oliver B, Boehm M, Rosing DR, et al. J Am Acad Dermatol 2016; 75: 1274–7.

Therapy with eculizumab, apixaban, and aspirin resolved GI symptoms and stabilized cardiac, neurologic, and cutaneous disease in a 55-year-old woman with MAP with a 5-year clinical follow-up.

The effects of eculizumab on the pathology of malignant atrophic papulosis. Magro CM, Wang X, Garrett-Bakelman F, et al. Orphanet J Rare Dis 2013; 8: 185.

Effective treatment of malignant atrophic papulosis (Köhlmeier-Degos disease) with treprostinil — early experience. Shapiro LS, Toledo-Garcia AE, Farrell JF. Orphanet J Rare Dis 2013; 8: 52.

Commentary on Degos disease: a C5b-9/interferon-α-mediated endotheliopathy syndrome by Magro et al: a reconsideration of Degos disease as hematologic or endothelial genetic disease. Scheinfeld N. Dermatol Online J 2011; 17: 6.

Congenital Degos disease: case report and dermoscopic findings. Calderón-Castrat X, Castro R, Peceros-Escalante J, et al. Pediatr Dermatol 2017; 34: e109–15.

Aspirin and dipyridamole were effective for congenital BAP with 14-month follow-up.

New onset of few atrophic white papules of the trunk and limbs. Pinho A, Cardoso JC, Vieira R, et al. Clin Exp Dermatol 2016; 41: 948–50.

Pentoxifylline and aspirin prevented halted cutaneous disease in a 26-year-old man with BAP, based on 18-month follow-up.

A case of malignant atrophic papulosis with cranial nerve and peripheral nerve impairment. Liu F, Liu H, Zhang M, et al. An Bras Dermatol 2015; 90: 19–21.

After 9 months, dipyridamole and aspirin halted cutaneous and ocular findings in a 47-year-old woman who eventually died of GI hemorrhage.

Central nervous system involvement in systemic malignant atrophic papulosis (Degos disease): a case report. Su Z, Lu Y, Ge Y, et al. Int J Dermatol 2015; 54: 699–703.

In a 41-year-old woman, GI and cutaneous disease initially responded for several years to aspirin, dipyridamole, and systemic corticosteroids.

Degos disease with an intestinal perforation: a case report. Zhu M, Jiang Z, Jiang R, et al. J. Int J Dermatol 2014; 53: 631–4.

Pentoxifylline, dipyridamole, and aspirin – followed by aspirin monotherapy – were effective for cutaneous and GI disease in a patient alive after 7 years.

Successful treatment of neurological malignant atrophic papulosis in child by corticosteroid combined with intravenous immunoglobulin. Guo YF, Pan WH, Cheng RH, et al. CNS Neurosci Ther 2014; 20: 88–91.

Aspirin, systemic corticosteroids, and intravenous immunoglobulin (IVIG) for 6 months were effective for cutaneous and neurologic disease in a 9-year-old boy with a 4-year history of MAP.

Malignant atrophic papulosis in an infant. Torrelo A, Sevilla J, Mediero I, et al. Br J Dermatol 2002; 146: 916–8.

A 7-month-old female with GI disease was treated successfully with aspirin and dipyridamole.

Malignant atrophic papulosis: treatment with aspirin and dipyridamole. Stahl D, Thomsen K, Hou-Jensen K. Arch Dermatol 1978; 114: 1687–9.

Aspirin and dipyridamole arrested the development of both cutaneous and systemic disease, without relapse.

Ecilizumab has demonstrated efficacy in multiple reports of MAP, particularly for early disease and when administered in combination with treprostinil, a synthetic analog of prostacyclin (PGI₂). As ecilizumab is a very expensive, complex treatment, its use is not recommended for BAP. The efficacy of ecilizumab for MAP is still variable and anecdotal, and multiple treatment failures have been recorded, particularly when utilized as monotherapy and in late disease. Similarly, aspirin can be also effective in combination with other treatments.

Second-Line Therapies

• Dipyridamole	D
• Pentoxifylline	D

Benign atrophic papulosis (Köhlmeier-Degos disease): the wedge-shaped dermal necrosis can resolve with time. Zouboulis CC, Theodoridis A, Brunner M, et al. *J Eur Acad Dermatol Venereol* 2017; 31: 1753–6.

In a 54-year-old woman with BAP, clinicopathologic findings demonstrated improvement following pentoxifylline and apixaban over a 16-year clinical follow-up.

The platelet inhibitor dipyridamole and the xanthine derivative and phosphodiesterase pentoxifylline have both demonstrated anecdotal efficacy in MAP, although less frequently than ecilizumab, treprostinil, or aspirin.

Third-Line Therapies

• Intravenous immunoglobulin	E
• Systemic corticosteroids	E
• Apixaban	E
• Enoxaparin	E
• Phenformin	E
• Ethylestrenol	E
• Ciclosporin	E
• Nicotine patches	E

Successful treatment of neurological malignant atrophic papulosis in child by corticosteroid combined with intravenous immunoglobulin. Guo YF, Pan WH, et al. *CNS Neurosci Ther* 2014; 20: 88–91.

Aspirin, systemic corticosteroids, and IVIG for 6 months were effective for cutaneous and neurologic disease in a 9-year-old boy.

The use of intravenous immunoglobulin in cutaneous and recurrent perforating intestinal Degos disease (malignant atrophic papulosis). Zhu KJ, Zhou Q, Lin AH, et al. *Br J Dermatol* 2007; 157: 206–7.

A 38-year-old Chinese woman was treated with one cycle of high-dose IVIG therapy, with subsequent dramatic and sustained improvement.

Effect of fibrinolytic treatment in malignant atrophic papulosis. Delaney TJ, Black MM. *Br Med J* 1975; 3: 415.

Cutaneous disease was halted in a 42-year-old female patient treated with phenformin and ethylestrenol.

Penile ulceration in fatal malignant atrophic papulosis (Degos disease). Thompson KE, Hight AS. *Br J Dermatol* 2000; 143: 1320–2.

Ciclosporin resulted in clinical improvement in a patient with penile ulceration.

A case of malignant atrophic papulosis successfully treated with nicotine patches. Kanekura T, Uchino Y, Kanzaki T. *Br J Dermatol* 2003; 149: 660–2.

Applied daily, nicotine patches resulted in clearance in a patient with BAP.

Intravenous immunoglobulin and systemic corticosteroids have been used but with limited success. Other treatments for MAP and BAP include anticoagulation with either apixaban or enoxaparin, and agents with fibrinolytic activity, including phenformin and ethylestrenol. Single reports of efficacy with ciclosporin or nicotine patches are also available.

Insufficient descriptions of efficacy to recommend use

• Heparin	E
• Cyclophosphamide	E
• Clopidogrel	E
• Alprostadil	E
• Dalteparin	E
• Tocilizumab	E

Early failure of ecilizumab in a patient with malignant atrophic papulosis: is it time for initial combination therapy of ecilizumab and treprostinil? Razanamahery J, Payet-Revest C, Mareschal A, et al. *J Dermatol* 2020; 47: e22–3.

Anticoagulation with heparin and low-dose aspirin, systemic corticosteroids, and subsequent treatment with ecilizumab were ineffective in a 31-year-old man with MAP.

Severe neurologic involvement of Degos disease in a pediatric patient. Karaoğlu P, Topçu Y, Bayram E, et al. *J Child Neurol* 2014; 29: 550–4.

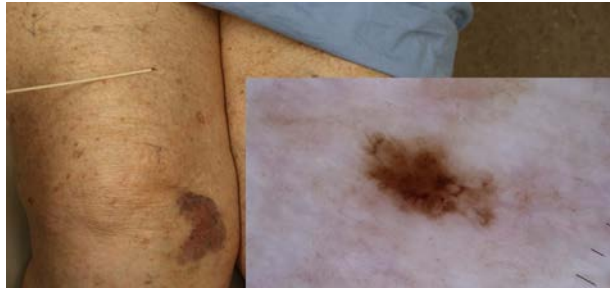
IVIG followed by enoxaparin, systemic corticosteroids, and cyclophosphamide were ineffective in a 14-year-old boy with catastrophic neurologic disease.

Malignant atrophic papulosis with motor aphasia and intestinal perforation: a case report and review of published works. Hu P, Mao Z, Liu C, et al. *J Dermatol* 2018; 45: 723–6.

Despite treatment with aspirin, dalteparin, systemic corticosteroids, alprostadil, and IVIG, a 30-year-old patient died from rapidly progressive neurologic and GI disease.

Malignant melanoma

Faezeh Talebi-Liasi, Cynthia Chan, Orit Markowitz



Melanoma remains the leading cause of mortality among all cutaneous diseases in the United States. The national incidence of melanoma continues to increase, now to 1 per 4500 adults per year, with 96,480 new cases in 2019, according to the National Institutes of Health and National Cancer Institute (NCI). Approximately 2.3% of adults will be diagnosed with cutaneous melanoma during their lifetime, according to the NCI.

MANAGEMENT STRATEGY

While incidence of melanoma has been increasing, mortality has decreased, likely as a result of improved diagnosis, staging, and treatment, according to a retrospective 10-year analysis from the 8th edition of the American Joint Commission on Cancer (AJCC).

Specific Investigations

- Dermoscopy
- Biopsy of primary site: excisional preferred, incisional acceptable if excision impractical
- SLNB
- Laboratory and imaging studies: chest radiograph, CT, PET
- Reflectance confocal microscopy

Early detection, a method of secondary prevention, is critical because treatment is most curative at early stages. A lesion is often clinically suspicious to patients and primary care physicians for having the 'ABCDE' signs of Asymmetry, Border irregularity, Color variation, Diameter greater than 6 mm, and/or Evolution, or for being an 'ugly duckling' compared with other lesions on the same individual. For specialists, detection is further aided by non-invasive cutaneous imaging tools, including *dermoscopy* and *reflectance confocal microscopy* (RCM), which can identify lesions prior to the development of the ABCDE signs.

Dermoscopy allows the detection of melanomas that may not otherwise look suspicious to the naked eye. For example, in the figure, dermoscopy reveals atypical pigment networks and irregular globules, as well as regression structures at the periphery, that raise suspicion for melanoma. A meta-analysis of nine prospective

studies found that dermoscopy was nine times more accurate than naked-eye examination in the detection of melanoma.

In addition to dermoscopy, RCM has emerged as a non-invasive, real-time tool that provides cellular level information to specialists with expert knowledge in this area. A Cochrane meta-analysis of 18 publications found that RCM was more accurate than dermoscopy in the detection of melanoma, particularly in difficult to diagnose cases. At a sensitivity of 90%, specificity was 82% for RCM and 42% for dermoscopy. RCM is approved by the Federal Drug Administration for skin imaging and diagnosis and was granted new reimbursement codes by the Center for Medicare and Medicaid Services (CMS) in 2016.

The gold standard for diagnosis and staging remains biopsy and histopathology, as described in the American Academy of Dermatology (AAD) 2019 Melanoma Working Group guidelines. Appropriate biopsy technique helps establish accurate Breslow depth for staging, which affects management. A *diagnostic excisional biopsy* can be performed in one of three ways: 1) elliptical or fusiform excision with 1–3-mm clinically negative margins; 2) punch excision around a smaller lesion when clear clinical margins can be achieved; or 3) deep shave or saucerization to a sufficient depth usually extending to the reticular dermis. Full-thickness incisional biopsy is an inferior alternative that may be more practical in some cases, such as very large lesions.

Final version of 2017 American Joint Committee on Cancer (AJCC) 8th edition of melanoma staging and classification. Gershenwald JE, Scolyer RA, Hess KR, et al. CA Cancer J Clin 2017; 67: 472–92.

This paper provides the most recent staging and management recommendations for melanoma since the 7th edition was published in 2009. The updates are based on a multivariate analysis of over 46,000 patients from 10 locations worldwide. Tumor thickness is now recorded to the nearest 0.1 mm instead of 0.01 mm. Stage T1a is now defined as less than 0.8 mm thick without ulceration, and T1b is now defined as less than 0.8 mm thick with ulceration, or 0.8–1 mm thick. Discussion of SLNB is now recommended for stage T1a–b with high-risk features, and both discussion and offering of SLNB for stage T2a or higher, where T2a corresponds to a thickness of at least 1 mm. Pathological stage Ia now includes T1b N0 M0. 'Macroscopic' and 'microscopic' descriptors for the N category are now defined as 'clinically apparent' and 'clinically occult' metastasis. Stage III is now defined by both N and T categories and expanded to include substages a–d. Presence of satellites, microsatellites, or in-transit metastasis constitutes new categories of N1c, N2c or N3c, respectively, depending on the number of regional lymph nodes involved. The M category now includes designation for involvement of the nervous system and presence of lactate dehydrogenase level, a significant prognostic factor. Management recommendations for stage IV melanoma did not change.

Evidence-based clinical practice guidelines for the management of patients with lentigo maligna. Robinson M, Primiero C, Guitera P, et al. Dermatology 2019; 22: 1–6.

This systemic review by the Melanoma Working Group established by the Cancer Council of Australia evaluated management strategies for LM. Surgical excision with 5- to 10-mm margins remains the first-line therapy. While the use of perioperative RCM to assess margins shows promise, there is currently a lack of high-quality evidence for this. Radiotherapy appears more effective than topical imiquimod and is recommended as second-line therapy. When surgery or radiotherapy is not possible, topical imiquimod is recommended.

Atlas of dermoscopy. Marghoob AA, Braun R, Kopf AW, eds. London: Parthenon Publishing, 2005.

Dermoscopy increases the diagnostic sensitivity of melanoma for appropriately trained clinicians. In high-risk patients, the availability of baseline dermoscopic images for comparison permits the detection of melanomas that are growing or changing. The use of 3-month-interval digital dermoscopic nevus monitoring has demonstrated 93% diagnostic sensitivity for LM and MIS, and 96% sensitivity for invasive melanoma. This clinician-oriented atlas is an up-to-date multicolored text reviewing almost every aspect of dermoscopy.

Reflectance confocal microscopy for diagnosing cutaneous melanoma in adults. Dinnes J, Deeks JJ, Saleh D, et al. Cochrane Database of Systematic Reviews 2018, Issue 12. Art. No.: CD013190.

This Cochrane review of 18 publications contained 19 study cohorts, 2838 lesions (including 658 melanomas), 67 datasets for RCM, and seven datasets for dermoscopy. Meta-analysis found RCM to be more accurate than dermoscopy in diagnosing melanoma, in particular in difficult to diagnose cases. At a sensitivity of 90%, specificities were 82% for RCM and 42% for dermoscopy for any lesion suspicious for melanoma.

First-Line Therapies

- Local surgical wide excision of primary melanoma **A**
- SLNB **B**
- Selective completion lymphadenectomy **C**
- Elective completion lymphadenectomy **C**

MIS to Clinical Stage IIC

Wide local excision (WLE) remains the main treatment for melanoma in situ (MIS) to clinical stage IIC melanoma. AJCC 8th edition recommends margins based on Breslow depth: 0.5–1 cm for MIS, 1 cm for shallower than 1 mm, 1–2 cm for 1–2 mm, and 2 cm for deeper than 2 mm (Table 150.1). A discussion of *sentinel lymph node biopsy* (SLNB) should be offered for Breslow depth greater than 0.8 mm, and for shallower lesions with negative prognostic features such as ulceration. If SLNB is positive, a *completion lymphadenectomy* of all involved nodal basins should be considered. Presence of any clinically palpable lymph nodes is another indication for SLNB using fine needle aspiration, core biopsy, or excisional biopsy.

Table 150.1 Surgical margin recommendations for primary cutaneous melanoma

Tumor thickness	Surgical margin*
In situ	0.5–1 cm (1 cm for LM type)
≤1.0 mm	1 cm
>1.0–2.0 mm	1–2 cm
>2.0 mm	2 cm

*Recommended surgical excision margins are clinically measured from the edge of the lesion or prior biopsy at the time of surgery; they are not histologic margins as measured by the pathologist. Margins may be modified for functional considerations or anatomic location.

Surgical margins for melanoma in situ. Kunishige JH, Brodland DG, Zitelli JA. J Am Acad Dermatol 2012; 66: 438–44.

The previously accepted 5-mm margin for surgical excision of MIS was shown to be inadequate in several studies. This prospective series of 1072 patients with 1120 melanomas in situ investigated the minimal surgical margins required to remove 97% of tumors. The researchers determined that 86% of melanomas in situ were completely excised with 6-mm margins, and the minimum surgical margin required to remove 98.9% of melanoma in situ was 9 mm. The 9-mm margin was found to be statistically superior to the 6-mm margin.

Elective lymph node dissection in patients with melanoma: systematic review and meta-analysis of randomized controlled trials. Lens MB, Dawes M, Goodacre T. Arch Surg 2002;137: 458–61.

This is a large systematic review and meta-analysis of randomized controlled trials comparing elective lymph node dissection with surgery delayed until the time of clinical recurrence. Elective lymphadenectomy shows no significant OS benefit for patients undergoing elective lymph node dissection.

Completion dissection or observation for sentinel-node metastasis in melanoma. Faries MB, Cochran AJ, Elashoff RM, Thompson JF. N Engl J Med 2017; 376:2211–22.

MSLT-I is a prospective study of over 1600 patients with intermediate (defined as 1.2–3.5 mm thick) to thick melanomas (defined as thicker than 3.5 mm) randomized to SLNB versus observation with 10-year follow-up. This study demonstrated that SLNB provides important prognostic data about risk of recurrence and staging information for management. SLNB-based surgical intervention prolonged DFS survival for all patients and distant DFS and melanoma-specific survival in node-positive patients with intermediate thickness melanomas. MSLT-II is an international multicenter prospective study of over 3000 patients that investigated the value of completion lymphadenectomy. It found that while completion lymphadenectomy increased the rate of regional disease control, it did not increase melanoma-specific survival.

For patients with lentigo maligna (LM) type MIS, which tends to be a larger lesion in sun-exposed areas of the head and neck in older patients with comorbidities who may not be amenable to surgical excision, second-line therapies may be offered based on the AAD 2019 guidelines. Several phase II and III trials have shown complete clinical response rates of 35–78% using 5% *topical imiquimod cream*, with or without *topical tazarotene 0.1% gel*, for an average duration of 12 weeks. Primary *radiation therapy* is another second-line treatment for LM. Three large retrospective European studies have reported recurrence rates of 0–17% and favorable cosmetic outcomes in patients with LM treated with superficial, ultrasoft X-ray or grenz ray. However, interpretation of these results and evidence quality are affected by variable dosing protocols and follow-up times. Staged surgery, such as *Mohs micrographic surgery* (MMS), has also been used to treat LM. A few retrospective studies and a prospective study found no significant difference in overall survival (OS) between MMS and WLE for lesions on the head and neck only. At present, limited evidence exists for the use of non-invasive imaging in intraoperative margination of LM.

Patients with clinical stage IIB-C melanoma – defined as deeper than 2 mm and up to 4 mm with ulceration, or deeper than 4 mm, without metastasis – who are at higher risk of recurrence are being offered enrollment in clinical trials with *adjuvant immunotherapy* or targeted therapy. In addition, combination medications

are being evaluated in clinical trials with the hopes of enhanced therapeutic effect.

Clinical Stages III–IV Melanoma

Presence of macroscopic or microscopic metastasis in SLNB, or in-transit or satellite metastasis, indicates at least clinical stage III melanoma. As defined by the NCI, satellite metastasis indicates spread within 2 cm from the primary tumor, and in-transit metastasis indicates more than 2 cm. For clinical stage III disease, *surgical excision, with or without adjuvant therapies*, remains the mainstay of therapy, and requires coordination with surgical and medical oncologists for timely management.

Second-Line Therapies	
• Ipilimumab	A
• Nivolumab	A
• Pembrolizumab	A
• Vemurafenib	A
• Trametinib	A
• Nivolumab plus ipilimumab	A
• Dabrafenib plus trametinib	A
• Vemurafenib plus cobimetinib	A
• Radiotherapy for LM	A
• Topical imiquimod for LM	B
• Isolated limb perfusion	E

Third-Line Therapies	
• MMS	B
• IFN- α	A
• Dacarbazine and Bcl-2	A
• IL-2	B

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Cutaneous Melanoma, Version 2.2019. Coit DG, Thompson JA, Albertini MR, et al. J Natl Compr Canc Netw 2019;17: 367–402.

The NCCN practice guidelines for cutaneous melanoma have undergone significant revision in the past few years. Systemic adjuvant therapy is recommended only for advanced resected stage III–IV disease or unresectable disease. IFN- α and biochemotherapy, both previously mainstays of systemic therapy, are no longer recommended as first-line adjuvants, with immunotherapy and targeted molecular therapies in favor instead. High-dose ipilimumab can now be used as an adjuvant only if there is history of anti-PD1 treatment, because anti-PD1 agents are associated with less toxicity.

There are Food and Drug Administration (FDA)-approved adjuvant therapies for clinical stages III and IV melanoma that increase survival. Without treatment, 5-year survival for metastatic and clinical stage III melanoma is around 20% and 60%, respectively. A recent meta-analysis of a large number of trials involving *interferon alpha* (IFN- α) found improvements in 5- and 10-year recurrence-free survival (RFS), but an OS of less than 4%. In contrast, recent trial data showed that *checkpoint inhibitors* may improve 5-year survival by 10–15% for resected clinical stage III and stage IV melanoma. Accordingly, in 2019, the National

Comprehensive Cancer Network (NCCN) discontinued recommending IFN- α and biochemotherapy (cisplatin, vinblastine, dacarbazine, and IL-2) as first-line adjuvant options in light of newer and less toxic immune checkpoint inhibitors with more robust evidence of efficacy in advancing RFS.

Two major classes of systemic agents are now in widespread use as adjuvant therapy for clinical stage IIIA–C melanoma and as sole therapy for clinical stage IV melanoma: immune checkpoint inhibitors and targeted molecular therapies.

Checkpoint inhibitors enhance the endogenous host immune response and have targets including cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed death 1 (PD-1), and programmed death ligand 1 (PD-L1). *Ipilimumab* is a CTLA-4 inhibitor that was first FDA approved in 2011 for clinical stage IV melanoma and later as a first-line adjuvant therapy for resectable clinical stage III melanoma. These approvals were based on evidence that first showed efficacy of ipilimumab in comparison to dacarbazine in extending survival in clinical stage IV melanoma and, later in 2015, compared to placebo in patients with clinical stage IIIA–C disease who had undergone surgery. While ipilimumab's toxicity profile is better than predecessors such as IFN and chemotherapeutics such as dacarbazine, the drug exhibited dose-dependent toxicity in clinical trials, with the most common side effect being morbilliform dermatitis. Recent trials have shown that low-dose ipilimumab may have similar efficacy to high-dose ipilimumab while causing less toxicity. Another checkpoint inhibitor, anti-PD-1 antibodies, including *nivolumab* and *pembrolizumab*, interfere with ligand binding by T-cell receptor PD-1, resulting in a more robust T-cell activation. These agents have shown efficacy as adjuvant treatment for resected melanoma in two phase III trials, CheckMate 238 and Keynote-054. In CheckMate 238, nivolumab, compared with ipilimumab, significantly improved RFS and distant metastasis-free survival (DMFS), and had a significantly lower proportion of high-grade adverse events. In Keynote-054, pembrolizumab, compared with placebo, showed efficacy in disease-free survival (DFS) and DMFS in resected clinical stage III melanoma.

BRAF proto-oncogene inhibitors (BRAFI) such as *vemurafenib* and *dabrafenib*, with or without MAPK inhibitors (MEKI) such as *trametinib* and *cobimetinib*, are a targeted molecular therapy that has shown efficacy in the 40–50% of melanoma patients with BRAF-V600 mutation. BRAFIs can increase the risk of hyperproliferative epidermal cutaneous neoplasms including squamous cell carcinomas and keratoacanthoma. Therefore, dermatologic assessment for actinic keratoses is necessary before initiating BRAFI. Combination therapy with BRAFIs and MEKIs augments the improvements in RFS and OS and reduces the toxicities associated with monotherapy.

A variety of locoregional therapies including *intralesional bacillus Calmette-Guerin* (BCG) or granulocyte-macrophage colony-stimulating factor (G-CSF), topical imiquimod with or without *intralesional interleukin (IL)-2*, *laser*, *electrodessication*, and *radiotherapy* have been used, but evidence of their efficacy is lacking. Radiologic imaging with X-ray, computed tomography (CT), and/or positron emission tomography (PET) is often attempted but has not been shown to affect OS.

Overview and update of the phase III Multicenter Selective Lymphadenectomy Trials (MSLT-I and MSLT-II) in melanoma. Morton DL. Clin Exp Metastasis 2012; 29(7): 699–706.

Adjuvant interferon- α for the treatment of high-risk melanoma: an individual patient data meta-analysis. Ives NJ, Suciu S, Eggermont AMM, et al. Eur J Cancer 2017; 82: 171–83.

This meta-analysis of 15 studies shows that adjuvant IFN- α significantly improves survival and reduces the risk of relapse. The risk is reduced to less than 4% at 5- and 10-years, follow-up. Event-free survival (EFS) and OS were improved by 3.5% and 2.7% for EFS, and 3.0% and 2.8% for OS, at 5- and 10-years, follow-up, respectively. Dose, duration of treatment, age, gender, site of primary tumor, disease stage, Breslow thickness, or presence of clinical nodes did not affect the efficacy of IFN- α .

High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. Atkins MB, Lotze MT, Dutcher JP, et al. *J Clin Oncol* 1999; 17: 2105–16.

In this intention-to-treat analysis, 270 patients with metastatic melanoma were entered into eight clinical trials conducted between 1985 and 1993. These patients received at least one dose of high-dose recombinant IL-2 by IV infusion every 8 hours for up to 14 consecutive doses over 5 days as clinically tolerated, with a second cycle performed after 6–9 days of rest. Additional courses were repeated every 6–12 weeks as tolerated in stable or responding patients. The overall response rate was 16%, with 6% of patients achieving complete responses. The median response duration in partial responders was 5.9 months. Severe toxicities reversed rapidly after therapy was completed.

Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al. *Lancet Oncol* 2015; 16: 522.

This study aimed to address whether ipilimumab could have a role as adjuvant therapy for patients with completely resected stage III melanoma at high risk of recurrence. In a double-blind phase III trial of 951 patients, ipilimumab was found to significantly improve RFS for patients with completely resected, high-risk, stage III melanoma.

Improved survival with ipilimumab in patients with metastatic melanoma. Hodi FS, O'Day SJ, McDermott DF, et al. *N Engl J Med* 2010; 363: 711–23.

The FDA approved ipilimumab based on this randomized phase III trial in which 676 patients with unresectable stage III or IV melanoma were assigned to three groups: ipilimumab plus glycoprotein 100 peptide vaccine (gp100) ($n = 403$), ipilimumab alone ($n = 137$), or gp100 alone ($n = 136$). Ipilimumab, with or without gp100, compared with gp100 alone, significantly improved OS in patients with previously treated metastatic melanoma (10.1 months for ipilimumab alone, 10.0 months for combination therapy, and 6.4 months for gp100 alone).

Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. Eggermont AMM, Chiarion-Sileni V, et al. *N Engl J Med* 2016; 375: 1845–55.

This paper describes the results of the European Organisation for Research and Treatment of Cancer (EORTC) 18071 phase III clinical trial with high-dose ipilimumab (10 mg per kilogram) in stage III patients who had undergone resection. At a median follow-up of 5.3 years, the 5-year rate of RFS was 40.8% in the ipilimumab group, compared with 30.3% in the placebo group (hazard ratio [HR] for recurrence or death, 0.76 (95% confidence interval [CI], 0.64–0.89; $p < 0.001$)).

Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. Weber J, Mandala M, Del Vecchio M, et al. *N Engl J Med* 2017; 377: 1824–35.

This paper describes the results of CheckMate 238, a phase III trial of 906 patients with resected stage III or IV melanoma. At 18-month follow-up, the rate of RFS was significantly different between adjuvant therapy with nivolumab versus ipilimumab. The RFS rate at 12 months was 70.5% (95% CI, 66.1–74.5) in the nivolumab group and 60.8% (95% CI, 56.0–65.2) in the ipilimumab group (HR for disease recurrence or death, 0.65 (97.56% CI, 0.51–0.83; $p < 0.001$)). The nivolumab group had a lower rate of grade 3 and 4 adverse events than the ipilimumab group.

Overall survival with combined nivolumab and ipilimumab in advanced melanoma. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. *N Engl J Med* 2017; 377: 1345–56.

This paper describes the results of 3-year OS data of phase III trial, CheckMate 067, which compared combination therapy with nivolumab and ipilimumab with nivolumab alone and with ipilimumab alone in 945 patients with advanced unresectable stage III and stage IV melanoma. Significantly longer OS was reached with combination therapy than with monotherapy with either nivolumab or ipilimumab alone. At a minimum 36-month follow-up, the median OS had not been reached in the nivolumab-plus-ipilimumab group and was 37.6 months in the nivolumab group, as compared with 19.9 months in the ipilimumab group (HR for death with nivolumab plus ipilimumab versus ipilimumab, 0.55 ($p < 0.001$); HR for death with nivolumab versus ipilimumab, 0.65 ($p < 0.001$)).

Adjuvant pembrolizumab versus placebo in resected stage III melanoma. Eggermont AMM, Blank CU, Mandala M, et al. *N Engl J Med* 2018; 378:1789–801.

This paper describes the results of EORTC 1325 (Keynote054), a phase III trial with 1019 patients with high-risk resected stage III melanoma randomized to adjuvant pembrolizumab or placebo. At a median follow-up of 15 months, the 1-year RFS rate was 75.4% (95% CI, 71.3–78.9) versus 61.0% (95% CI, 56.5–65.1), respectively; HR for recurrence or death, 0.57 (98.4% CI, 0.43–0.74; $p < 0.001$). Subgroup analysis with PD-L1 positive patients showed similar results, demonstrating efficacy regardless of PD-L1 positivity. The rate of grade 3 or 5 adverse events was much lower for pembrolizumab at 14.7%, compared with placebo and previous trials for ipilimumab.

Pembrolizumab versus ipilimumab in advanced melanoma. Robert C, Schachter J, Long GV, et al. *N Engl J Med* 2015; 372: 2521–32.

This study was a phase III trial of 834 patients with stage IV melanoma who were not previously treated with an inhibitor of CTLA-4 or PD-1, who were randomized to treatment with ipilimumab or pembrolizumab. A significant improvement in response rate, 6-month progression-free survival (PFS), and 12-month OS favoring PD-1 inhibitor treatment was observed. The rate of high-grade autoimmune toxicity was lower in the PD-1 group.

Safety and efficacy of vemurafenib in BRAFV600E and BRAFV600K mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomized, open-label study. McArthur GA, Chapman PB, Robert C, et al. *Lancet Oncol* 2014;15: 323–32.

This is a multicenter, open-label, phase III trial of 675 patients randomized to vemurafenib versus dacarbazine. Vemurafenib improved median OS and PFS compared with dacarbazine, regardless of BRAF mutation status.

Improved survival with MEK inhibition in BRAF-mutated melanoma. Flaherty KT, Robert C, Hersey P, et al. *N Engl J Med* 2012;367: 107–14.

The MEKI trametinib showed promise in previous trials. In this phase III open-label trial, trametinib, compared with chemotherapy, significantly improved rates of PFS and OS among patients with metastatic melanoma containing the V600E or V600K BRAF mutation. A total of 322 patients were randomized to receive either oral trametinib daily or chemotherapy in a 2:1 ratio (intravenous dacarbazine or paclitaxel) every 3 weeks. Patients in the chemotherapy cohort who demonstrated disease progression were permitted to cross over to the trametinib cohort. Median PFS was 4.8 months in the trametinib group and 1.5 months in the chemotherapy group. At 6 months, the overall rate of survival was 81% in the trametinib group and 67% in the chemotherapy group despite crossover.

Inhibition of mutated, activated BRAF in metastatic melanoma. Flaherty KT, Puzanov I, Kim KB, et al. *N Engl J Med* 2010; 363: 809–19.

This landmark multicenter, phase I, dose-escalation trial of PLX4032, an oral inhibitor of V600E-mutated BRAF, demonstrated complete or partial tumor regression in the majority of patients with metastatic melanoma. Fifty-five patients (49 had melanoma) were enrolled in the dose-escalation phase, with an additional 32 patients with V600E-mutated BRAF melanomas enrolled in the extension phase, allowing the maximum dose

that could be administered without adverse effects. In the dose-escalation cohort, among the 16 patients with V600E-mutated BRAF melanoma, 10 demonstrated partial response and one had a complete response. In the extension cohort, 24 patients had a partial response and two had a complete response. Median PFS survival for all patients was over 7 months. Responses to PLX4032 were seen as early as 14 days after initiating treatment, as seen on fludeoxyglucose (FDG)-labeled PET imaging.

Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. Larkin al J, Ascierto PA, Dréno B, et al. *N Engl J Med* 2014; 371: 1867–74.

This study randomized 495 patients with previously untreated, unresectable, locally advanced, or metastatic BRAF V600 mutation-positive melanoma to either vemurafenib plus cobimetinib or to vemurafenib plus placebo. Median PFS showed a statistically significant difference of 9.9 months in the former combination group and 6.2 months in the latter control group.

Mohs micrographic surgery for the treatment of melanoma. Hui AM, Jacobson M, Markowitz O, et al. *Dermatol Clin* 2012; 30: 503–15.

The article discusses the current literature on the utility of MMS for the treatment of MIS, with an extensive review of Mohs technique, the latest advances in immunohistochemical staining, and outcomes.

Mastocytoses

Nicholas A. Soter



The mastocytoses are a group of disorders of clonal mast cell proliferation that may exhibit both cutaneous and systemic features. Clinical manifestations result from mast cell activation and from infiltration of various organs. The World Health Organization has classified mastocytosis into disease categories: cutaneous mastocytosis, indolent systemic mastocytosis, systemic mastocytosis with a non-mast-cell clonal hematologic disorder, aggressive systemic mastocytosis, mast cell leukemia, mast cell sarcoma, and extracutaneous mastocytoma. The most frequent site of organ involvement in individuals with mastocytosis is the skin. Cutaneous forms include urticaria pigmentosa (see figure), mastocytoma, diffuse and erythrodermic cutaneous mastocytosis, and telangiectasia macularis eruptiva perstans. An international task force has proposed a revised classification of cutaneous mastocytosis into maculopapular cutaneous mastocytosis with monomorphic and polymorphic variants, diffuse cutaneous mastocytosis, and cutaneous mastocytoma, with the elimination of telangiectasia macularis eruptiva perstans. The cutaneous forms of mastocytosis may be present with or without systemic manifestations. In pediatric patients, the cutaneous lesions usually are not associated with systemic involvement and often have spontaneous resolution around puberty. In adult patients, the cutaneous lesions usually are chronic and are associated with systemic mastocytosis. Adult patients should be classified because the type and stage of systemic mastocytosis has therapeutic and prognostic implications. Only the treatment of the cutaneous features will be discussed.

MANAGEMENT STRATEGY

An important aspect of therapy of the cutaneous lesions of mastocytosis is avoidance of triggering factors, which may include temperature changes, friction, physical exertion, ingestion of alcohol, the use of non-steroidal antiinflammatory agents (NSAIDs) or

opiate analgesics, and emotional stress. Of concern is the possibility of anaphylaxis after stings by *Hymenoptera* spp., which may occur even in patients receiving venom immunotherapy.

A history seeking systemic features should be undertaken, as well as a physical examination to determine the types of skin lesions and to assess for lymphadenopathy and hepatosplenomegaly. The presence of specific systemic manifestations will determine the type of specialty physician to whom a referral should be made for further evaluation.

Patients with systemic mastocytosis require long-term follow-up because associated non-mast-cell clonal hematologic disorders, such as myelodysplastic or myeloproliferative syndromes and lymphoproliferative disorders, may develop.

A skin biopsy should be obtained in all individuals with cutaneous lesions. A complete blood count with differential analysis, a blood chemistry profile that includes liver function tests, and a blood tryptase level should be obtained in all patients with cutaneous lesions, except those with mastocytomas.

In many cases cutaneous mastocytomas may involute spontaneously; they rarely are described in adults. Childhood urticaria pigmentosa regresses spontaneously in approximately 50% of cases and urticaria pigmentosa in adults in 10%. Diffuse and erythrodermic cutaneous mastocytosis usually resolves spontaneously during childhood. Telangiectasia macularis eruptiva perstans tends to be a chronic condition.

Most of the therapeutic reports have been in patients with urticaria pigmentosa and, to a lesser extent, in diffuse and erythrodermic cutaneous mastocytosis. The major therapeutic measure is the administration of oral H_1 antihistamines to alleviate pruritus and whealing. Oral disodium cromoglycate has been efficacious in some individuals. The role and efficacy of topical high potency glucocorticoid preparations with plastic-film occlusion, of narrowband ultraviolet B (NB-UVB) phototherapy, of psoralens and ultraviolet A (PUVA) photochemotherapy, and UVA1 phototherapy have not been subjected to controlled clinical trials or remain anecdotal.

The use of tyrosine kinase inhibitors and cyto-reductive therapy to reduce mast cell proliferation is not recommended in patients with only cutaneous manifestations. There is no therapy that will eradicate the mast cells in the cutaneous lesions.

Specific Investigation

- Skin biopsy

Cutaneous manifestations in patients with mastocytosis: consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology. Hartmann K, Escribano L, Grattan C, et al. *J Allergy Clin Immunol* 2016; 37: 35–45.

The major criterion for cutaneous involvement in patients with mastocytosis is typical skin lesions that are associated with Darier sign. Minor criteria include increased numbers of mast cells in biopsy specimens of lesional skin and an activating KIT mutation in lesional skin tissue. In lesional skin biopsy specimens, the number of mast cells is increased four to eightfold, which is about 40 mast cells/mm². The use of an antibody against tryptase should be the standard histochemical marker to detect and quantitate mast cells. No specific, aberrantly expressed marker of clonal cutaneous mast cells has been identified.

First-Line Therapies

- H₁ antihistamines **A**
- H₂ antihistamines **A**
- Disodium cromoglycate **A**

Comparison of azelastine and chlorpheniramine in the treatment of mastocytosis. Friedman BS, Santiago ML, Berkebile C, et al. J Allergy Clin Immunol 1993; 92: 520–6.

In a double-blind, randomized, crossover trial in 13 subjects with urticaria pigmentosa and systemic mastocytosis, the administration of both azelastine and chlorpheniramine for 4 weeks was associated with a reduction in pruritus.

Rupatadine improves quality of life in mastocytosis: a randomized, double-blind, placebo controlled trial. Siebenhaar F, Förtsch A, Krause K, et al. Allergy 2013; 68: 949–52.

In a double-blind, randomized, placebo-controlled, crossover trial in seven patients with cutaneous mastocytosis and in 23 with indolent systemic mastocytosis, the administration of rupatadine for 28 days was associated with a 16.1% reduction ($p=0.004$) in the mean ItchyQoL total score and 30.3% reduction ($p=0.001$) in pruritus.

Comparison of the therapeutic efficacy of cromolyn sodium with that of combined chlorpheniramine and cimetidine in systemic mastocytosis: results of a double-blind clinical trial. Frieri M, Alling DW, Metcalfe DD. Am J Med 1985; 78: 9–14.

Five of six patients with systemic mastocytosis had less pruritus and four of six had less urticaria while receiving chlorpheniramine and cimetidine. There was no beneficial effect in those receiving disodium cromoglycate.

Oral disodium cromoglycate in the treatment of systemic mastocytosis. Soter NA, Austen KF, Wasserman SI. N Engl J Med 1979; 301: 465–9.

In a double-blind, crossover study in five patients with systemic mastocytosis and urticaria pigmentosa, in 15 of 18 trials oral disodium cromoglycate ameliorated pruritus and whealing.

Urticaria pigmentosa: clinical picture and response to oral disodium cromoglycate. Czarnetzki BM, Behrendt H. Br J Dermatol 1981; 105: 563–7.

In a blind, crossover trial, three children and 10 adults with urticaria pigmentosa were treated with oral disodium cromoglycate or placebo for 1 month, respectively. Relief of pruritus was observed in 67.7% of children and in 70% of adults.

Second-Line Therapies

- Topical glucocorticoid with plastic-film occlusion **C**
- NB-UVB phototherapy **D**
- Oral PUVA photochemotherapy **D**
- Psoralen baths plus UVA photochemotherapy **D**
- UVA1 phototherapy **D**

Urticaria pigmentosa: systemic evaluation and successful treatment with topical steroids. Guzzo C, Lavker R, Roberts LJ II, et al. Arch Dermatol 1991; 127: 191–6.

In seven of nine adult patients with urticaria pigmentosa, the topical application of betamethasone dipropionate ointment

0.05% under occlusion overnight to half of the body for 6 weeks was associated with resolution of the lesions, with a maximum response within 3–12 weeks after the cessation of treatment. Lesions began to recur between 6 and 9 months after completing therapy. Retreatment for 6 months followed by once-weekly application of betamethasone dipropionate ointment under occlusion kept the patients clear of lesions, with the longest follow-up time being 2.5 years.

The appropriate method for using topical glucocorticoids in patients with urticaria pigmentosa needs to be determined in controlled trials.

Topical corticosteroids versus ‘wait and see’ in the management of solitary mastocytoma in pediatric patients: a long-term follow-up. Patrizi A, Tabanelli M, Neri I, et al. Dermatol Ther 2015; 28: 57–61.

In 130 patients with mastocytomas, 62 were treated with clobetasol cream, and 68 were untreated. A retrospective analysis showed no statistical differences between the two groups in the number of resolved or partially improved subjects. Complete remission occurred in an average of 16.4 months with treatment and 37.5 months without treatment. Average follow-up time was 56.3 months, with a range of 4 to 142 months.

Although the resolution of mastocytomas may occur with or without treatment, the time to resolution is faster with treatment using topical glucocorticoids, which are effective and safe considering the long time for resolution.

Narrow-band UVB phototherapy and psoralen ultraviolet A photochemotherapy in the treatment of cutaneous mastocytosis: a study of 20 patients. Brazelli V, Grassi S, Merante S, et al. Photodermatol Photoimmunol Photomed 2016; 32: 238–46.

In a retrospective, observational study, eight patients with urticaria pigmentosa and two with indolent systemic mastocytosis (ISM) were treated with narrowband ultraviolet B phototherapy (NB-UVB), and two with urticaria pigmentosa and eight with ISM were treated with psoralen ultraviolet A photochemotherapy (PUVA photochemotherapy). A mean reduction in pruritus was observed in both groups ($p<0.01$). The mean cutaneous score (number of macules and papules and the extent of body surface area) in those treated with NB-UVB decreased from 2.4 ± 0.8 to 1.8 ± 0.6 ($p=0.08$) and in those treated with PUVA photochemotherapy decreased from 1.9 ± 0.5 to 1.0 ± 0.8 ($p=0.01$). The number of treatments in those treated with PUVA photochemotherapy (20.7 ± 11.7) was lower when compared with those treated with NB-UVB (40.9 ± 18.6) ($p=0.00095$). The mean cumulative dose in those treated with PUVA photochemotherapy (100.3 ± 63.2 J/cm²) was higher when compared to those treated with NB-UVB (50.9 ± 37.5 J/cm²) ($p=0.047$).

Due to its excellent safety profile, NB-UVB phototherapy is preferred to PUVA photochemotherapy or UVA1 phototherapy.

Short- and long-term effectiveness of oral and bath PUVA therapy in urticaria pigmentosa and systemic mastocytosis. Godt O, Proksch E, Streit V, et al. Dermatology 1997; 195: 35–9.

In 20 patients with urticaria pigmentosa treated with PUVA photochemotherapy, improvement in pruritus was seen in eight of 15 patients. Darier sign was suppressed in seven and reduced in eight patients. There was follow-up for 18 years; 25% showed improvement for more than 5 years. Bath PUVA photochemotherapy with 8-methoxypsoralen was without effect. The success of PUVA photochemotherapy lasted from only a few weeks to more than 10 years.

Photochemotherapy of dominant, diffuse, cutaneous mastocytosis. Smith ML, Orton PW, Chu H, et al. *Pediatr Dermatol* 1990; 7: 251–5.

In three infants and one child with diffuse cutaneous mastocytosis treated with oral PUVA photochemotherapy twice weekly for 3–5 months, there was reduced pruritus, reduced blister formation, and a less thick skin, with persistence of dermatographism.

Medium- versus high-dose ultraviolet A1 therapy for urticaria pigmentosa: a pilot study. Gobello T, Mazzanti C, Sordi D, et al. *J Am Acad Dermatol* 2003; 49: 679–84.

In 12 patients with urticaria pigmentosa, treatment with both medium-dose UVA1 (60 J/cm²) for 15 days and high-dose UVA1 (130 J/cm²) for 10 days was associated with less pruritus, with a decrease in the number of mast cells, and a change in the number of lesions over a 6-month period.

The appropriate method and schedules or the use of oral PUVA photochemotherapy, UVA phototherapy, and even NB-UVB phototherapy need to be determined by controlled trials.

Third-Line Therapies

• Interferon- α	D
• Topical calcineurin inhibitors	D
• Leukotriene-receptor inhibitors	E
• Thalidomide	C
• Surgical excision	E
• Flashlamp-pumped pulsed dye and Nd:YAG lasers	E
• Tyrosine kinase inhibitors	A
• Cyto-reductive therapy	B
• Omalizumab	E

Treatment of urticaria pigmentosa using interferon alpha. Kolde G, Sunderkotter C, Luger TA. *Br J Dermatol* 1995; 133: 91–4.

Six adult patients with urticaria pigmentosa were treated with subcutaneous interferon- α started at a daily dose of 0.5×10^6 U, increasing to 5×10^6 U within 10 days. This dose was given five times a week for 6–20 weeks and then reduced to three injections a week for 6–38 weeks. There was marked improvement of pruritus and whealing and Darier sign became negative. There was no reduction in the number or appearance of the macular and papular skin lesions or in the number or structural organization of the lesional mast cells in light or electron microscopic studies.

Topical pimecrolimus for paediatric cutaneous mastocytosis. Mashiah J, Harel A, Bodemer C, et al. *Clin Exp Dermatol* 2018; 43: 559–65.

In 18 patients with a mastocytoma or urticaria pigmentosa, 11 boys and seven girls with an average age of 16.9 months, who were treated with 1% pimecrolimus cream twice daily, 11 (61.2%) achieved a good response, 5 (27.7%) a partial response, and 2 (11.1%) a poor response. Of the total number of lesions treated, 26.7% disappeared and 67% started fading or developed postinflammatory hyperpigmentation. Papular lesions became macular in 47%, and 16.4% showed partial flattening. Darier sign became negative in 82%.

Leukotriene-receptor inhibition for the treatment of systemic mastocytosis. Tolar J, Tope WD, Neglia JP. *N Engl J Med* 2004; 350: 735–6.

In a 2-month-old boy with systemic mastocytosis and skin lesions, wheezing, and hepatomegaly, when montelukast 0.25 mg/

kg twice daily was not given, wheezing and cutaneous vesicles reappeared and subsided when the drug was readministered.

The leukotriene-receptor inhibitors should be evaluated in mastocytosis in a controlled trial.

Thalidomide in systemic mastocytosis: results from an open-label, multicenter, phase II study. Gruson B, Lortholary O, Canioni D, et al. *Br J Haematol* 2013; 161: 434–42.

In a prospective, open-label, multicenter study on 19 patients with systemic mastocytosis, 14 of whom had urticaria pigmentosa and one of whom had diffuse cutaneous mastocytosis, thalidomide was used for 6 months. Of the patients with skin lesions or symptoms, the overall response rate was 61%, with improvement or disappearance of pruritus in 64%.

Solitary mastocytoma in an adult: treatment by excision. Ashinoff R, Soter NA, Freedberg IM. *J Dermatol Surg Oncol* 1993; 19: 487–8.

In a 33-year-old woman, a solitary mastocytoma was excised.

Treatment of an unusual solitary mast cell lesion with the pulsed dye laser resulting in cosmetic improvement and reduction in the degree of urticarial reaction. Rose RF, Daly BM, Sheehan-Dave R. *Dermatol Surg* 2007; 31: 851–3.

In a 12-year-old girl with a solitary mast cell lesion with features of solitary mastocytoma and telangiectasia macularis eruptiva perstans treated with a 585-nm pulsed dye laser, there were cosmetic improvement and reduction in the severity of wheals after six treatments.

The treatment of urticaria pigmentosa with the frequency-doubled Q-switch Nd:YAG laser. Bedlow AJ, Gharrie S, Harland CC. *J Cutan Laser Tuer* 2000; 2: 45–7.

In a 30-year-old woman with urticaria pigmentosa treated with a frequency-doubled Q switch Nd:YAG laser, there was initial improvement in the clinical appearance, but the lesions recurred after 9 months.

The cosmetic treatment of urticaria pigmentosa with Nd:YAG laser at 532 nanometers. Resh B, Jones E, Glaser DA. *Cosmet Dermatol* 2005; 4: 78–82.

In a 19-year-old man with urticaria pigmentosa treated with a 532-nm diode-pumped Nd:YAG laser, there was a reduction in the number of lesions.

The efficacy of lasers in the treatment of various forms of cutaneous skin lesions of mastocytosis remains unknown.

Imatinib mesylate in the treatment of diffuse cutaneous mastocytosis. Morren M-A, Hoppé A, Renard M, et al. *J Pediatr* 2013; 162: 205–7.

In a 3-month-old girl and in an 11-month-old girl with diffuse cutaneous mastocytosis and an activating KIT mutation in exon 8 (p. Asp 419 del) in the skin lesions, with the administration of imatinib mesylate for 9 months and 1 year, respectively, there were no relapses with a 2-year and 6-month follow-up, respectively.

Imatinib in systemic mastocytosis: a phase IV clinical trial in patients lacking exon 17 KIT mutations and review of the literature. Alvarez-Twose L, Matito A, Morgado JM, et al. *Oncotarget* 2017; 8: 68950–63.

In a clinical trial in 10 patients with systemic mastocytosis treated with imatinib for 12 months, a complete response was observed in three patients with diffuse cutaneous skin lesions

that resolved and with exon 9 (K509I) KIT mutations. A partial response was observed in one patient with maculopapular skin lesions (urticaria pigmentosa). There was no response in four other patients with urticaria pigmentosa and in one with a solitary mastocytoma.

Masitinib for treatment of severely symptomatic indolent systemic mastocytosis: a randomised, placebo-controlled, phase 3 study. Lortholary O, Chandesris MO, Livideanu CB, et al. *Lancet* 2017; 389: 612–20.

In a randomized, double-blind, placebo-controlled study in 135 patients with ISM, masitinib was administered to 71 patients and placebo to 64 patients for 24 weeks.

Urticaria pigmentosa decreased in average body surface area of 12.3% with masitinib and increased in 15.9% with placebo. The abolition of Darier sign occurred in 18.9% with masitinib and 2.7% with placebo.

Cladribine therapy for systemic mastocytosis. Kluin-Nelemans HC, Oldhoff JM, van Doormaal JJ, et al. *Blood* 2003; 102: 4270–6.

In each of seven patients with systemic mastocytosis and urticaria pigmentosa treated with cladribine, which is a synthetic purine analog cytoreductive agent, there was a reduction in the number of skin lesions to near disappearance and a reduction in mast cells in skin biopsy specimens.

Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis. Barete S, Lortholary O, Damaj G, et al. *Blood* 2015; 126: 1009–16.

In a nationwide retrospective study in France over one decade in 68 adult patients with various types of systemic mastocytosis who were treated with cladribine, those with urticaria pigmentosa

showed improvement in the skin with a decrease in the number of mast cells in skin biopsy specimens.

The efficacy of omalizumab in cutaneous mastocytosis: a case series. Hinojosa T, Lewis DJ, Vangipuram R, et al. *Dermatol Ther* 2019; 32: e12848.

Two patients were treated with omalizumab 300mg every 4 weeks for a median of 24 weeks. One patient experienced improvement in pruritus and a 50% reduction in cutaneous lesions. One patient experienced resolution of pruritus and a 90% reduction in cutaneous lesions.

Cutaneous and gastrointestinal symptoms in two patients with systemic mastocytosis successfully treated with omalizumab. Lieberoth S, Thomsen SF. *Case Rep Med* 2015; 2015: 903541.

In a 48-year-old woman and in a 57-year-old man with systemic mastocytosis and severe pruritus, the administration of omalizumab was associated with a reduction in pruritus.

Efficacy of omalizumab in indolent systemic mastocytosis. Slapnicar C, Trinkaus M, Hicks L, et al. *Case Rep Hematol* 2019 Sep 16; Article ID 3787586. <https://doi.org/10.1155/2019/3787586>.

Four patients with ISM were treated with omalizumab 300mg every 4 weeks. In one patient with telangiectasia macularis eruptiva perstans and in one with urticarial pigmentosa, there was a decrease in the number of lesions. In two patients with urticaria pigmentosa, there was no change.

Tyrosine kinase inhibitors, cytoreductive agents, and omalizumab have been used in patients with systemic mastocytosis, with improvement of the skin symptoms in some patients. The use of these therapeutic agents in extensive cutaneous mastocytosis without systemic disease warrants further investigation.

Melasma

Pearl E. Grimes



Melasma is an acquired hypermelanosis that most commonly affects females of childbearing age, although males may also be affected. The condition can be classified according to the pattern of facial involvement, which includes centrofacial (forehead, cheeks, chin, and upper lip), malar, and mandibular. Less frequently the neck, arms, and chest may be affected. Melasma is more prevalent in individuals with Fitzpatrick skin types III and above and can have a significant psychosocial impact.

Three histologic subtypes of melasma exist – epidermal, dermal, and mixed – which may be differentiated by the use of a Wood lamp, where epidermal melasma shows enhanced contrast and dermal melasma less contrast. More recently, in vivo reflectance confocal microscopy has been studied as a non-invasive method of evaluating melasma. Histologic features of melasma include increased epidermal and dermal melanin, solar elastosis, damage to the basement membrane, increased vascularity, and increased numbers of dermal mast cells and CD4+ T cells. Epidermal melasma is the most responsive to treatment.

The pathogenesis of melasma is not fully understood; however, a genetic predisposition, hormonal factors, pregnancy, and the use of oral contraceptives are the most common precipitants. Exposure to ultraviolet (UV) radiation both precipitates and exacerbates. Other etiologic factors include phototoxic medications, genetic predisposition, and thyroid disease. Patients should be queried regarding symptoms suggestive of thyroid abnormalities.

MANAGEMENT STRATEGY

Melasma is often difficult to treat due to the recalcitrant and recurrent nature of the condition and the risk of postinflammatory hyperpigmentation associated with some treatments, particularly in individuals with darker skin. Pregnancy-induced melasma may sometimes resolve spontaneously postpartum, and females taking the oral contraceptive pill may be advised to change to an alternative form of contraception.

Sun exposure increases melanin production and may exacerbate melasma; therefore, all patients should receive sun protection advice and use a *high-factor broad-spectrum sunscreen with good protection against ultraviolet A (UVA)*. Recent evidence suggests that *sunscreens with protection against visible light* may provide additional benefit. Patients may also wish to use *camouflage makeup, which may also provide significant visible light protection*.

Current treatment options include *topical lightening agents, chemical peels, laser therapies, tranexamic acid, and oral antioxidants*. The response to monotherapy is often limited, and therefore a combination of treatments may optimize outcome. Commonly used treatments include 2%–5% hydroquinone, tretinoin, triple combination creams (containing hydroquinone, tretinoin, and fluocinolone), kojic acid, niacinamide, and azelaic acid. Glycolic acid is the most commonly reported peeling agent and may be used as an adjunct to topical depigmenting agents. Other commonly used peeling agents include salicylic acid, Jessner peel, trichloroacetic acid, and tretinoin. The results of laser therapies are mixed, and treatment carries a significant risk of relapse and postinflammatory hyperpigmentation depending on the type of laser used and skin type of the patient.

First-Line Therapies

• Triple combination cream	A
• Hydroquinone	A
• Tretinoin	A
• Sunscreen	A

Systematic review of randomized controlled trials on interventions for melasma: an abridged Cochrane Review. Jutley GS, Rajaratnam R, Halpern J, et al. *J Am Acad Dermatol* 2014; 70: 369–73.

This review included 20 studies and concluded that triple combination cream was more effective than hydroquinone or any agent in dual combination. Azelaic acid (20%) was superior to 2% hydroquinone in lightening melasma, and tretinoin led to greater objective improvement in melasma than placebo.

Melasma treatment: an evidence based review. McKesey J, Tovar-Garza A, Pandya AG. *Am J Clin Dermatol* 2020; 21(2): 173–225.

This review included randomized, controlled trials or controlled clinical trials of melasma. Triple combination cream was the most effective treatment for melasma, as well as hydroquinone alone. Chemical peels and laser light-based therapies had mixed results and a higher rate of complications.

Efficacy and safety of a new triple-combination agent for the treatment of facial melasma. Taylor SC, Torok H, Jones T. *Cutis* 2003; 72: 67–72.

Two multicenter, randomized studies compared a formulation containing tretinoin 0.05%, hydroquinone 4%, and fluocinolone acetonide 0.01% with the three possible dual

combinations of the three agents in 641 patients with melasma (Fitzpatrick skin types I–IV). At week 8, the triple combination formulation was significantly more effective than any of the dual combinations.

Commonly reported adverse effects with triple combination cream include mild erythema, burning, and peeling.

A histologic examination for skin atrophy after 6 months of treatment with fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05% cream. Bhawan J, Grimes P, Pandya AG, et al. *Am J Dermatopathol* 2009; 31: 794–8.

This study found no evidence of clinical or histologic atrophy in 30 melasma patients after daily use of triple combination cream for 24 weeks.

Topical tretinoin (retinoic acid) improves melasma. A vehicle-controlled, clinical trial. Griffiths CEM, Finkel LJ, Ditre CM, et al. *Br J Dermatol* 1993; 129: 415–21.

A study of 0.1% tretinoin once daily in 38 Caucasian women for 40 weeks found that 68% of tretinoin-treated patients were improved or much improved, compared with only 5% in the vehicle-treated group. Erythema and desquamation were more common in the tretinoin group.

The efficacy of a broad spectrum sunscreen in the treatment of melasma. Vasquez M, Sanchez JL. *Cutis* 1983; 92: 95–6.

Broad-spectrum sunscreen compared with vehicle used alongside hydroquinone led to improvement in 96% of subjects compared with 81% of those using vehicle.

Role of broad-spectrum sunscreen alone in the improvement of Melasma Area Severity Index (MASI) and Melasma Quality of Life Index in melasma. Sarkar R, Ghunawat S, Narang I, et al. *J Cosmet Dermatol* 2019; 18(4): 1066–73.

One hundred patients with melasma were included in this study. A broad-spectrum sunscreen was applied thrice daily for 12 weeks. No lightening agents were otherwise used. There was significant improvement in melasma at 12 weeks as assessed by reduction in MASI scoring.

Near-visible light and UV photoprotection in the treatment of melasma: a double-blind randomized trial. Castaneda-Cazares JP, Hernandez-Blanco D, Carlos-Ortega B, et al. *Photodermatol Photoimmunol Photomed* 2014; 30: 35–42.

A randomized study of 68 patients with melasma treated with 4% hydroquinone and sunscreen with either broad-spectrum UV protection alone or with iron oxide as a visible light-absorbing pigment. Patients using sunscreen with additional protection against visible light experienced significantly greater improvement in melasma.

The vast majority of recent clinical trials for melasma treatments include regular use of a high-factor sunscreen as part of the regimen.

Prevention of melasma relapses with sunscreen combining protection against UV and short wavelengths of visible light: a prospective randomized comparative trial. Boukari F, Jourdan E, Fontas E, et al. *J Am Acad Dermatol* 2015; 72(1): 189–90.e1.

This was a randomized 6-month trial of 40 patients. Two sunscreen formulations were assessed. Formula A contained UV and visible light protection with iron oxide and formula B only contained UV protective ingredients. There was a statistically greater reduction in MASI scores and overall improvement in the subjects using the UV plus visible light protection with iron oxide.

Second-Line Therapies

• Azelaic acid	A
• Glycolic acid peels	A
• Adapalene	A

The treatment of melasma: 20% azelaic acid versus 4% hydroquinone cream. Balina LM, Graupe K. *Int J Dermatol* 1991; 30: 893–5.

A double-blind, randomized study of over 300 women. After the 24-week treatment period, 65% of azelaic acid-treated patients had good or excellent results. No significant treatment differences were observed between azelaic acid- and hydroquinone-treated patients.

Glycolic acid peels/azelaic acid 20% cream combination and low potency triple combination lead to similar reduction in melasma severity in ethnic skin: results of a randomized controlled study. Mahajan R, Kanwar AJ, Parsad D, et al. *Indian J Dermatol* 2015; 60: 147–52.

A 12-week, randomized study of 40 patients treated with either low-potency triple combination cream (hydroquinone 2%, tretinoin 0.05%, fluocinolone 0.01%) or glycolic acid peels (starting at 20% and gradually increasing to 70% repeated at 2-week intervals) in combination with 20% azelaic acid cream at night (apart from 2 days before and after peels).

Chemical peels for melasma in dark-skinned patients. Sarkar R, Bansal S, Garg VK. *J Cutan Aesthet Surg* 2012; 5(4): 247–53.

In a review of 14 studies assessing levels of evidence and strength of recommendations for various peeling agents in ethnic skin, glycolic acid peels provided the best outcomes.

Comparative evaluation of efficacy and tolerability of glycolic acid, salicylic/mandelic acid, and phytic acid combination peels in melasma. Sarkar R, Garg V, Bansal S, et al. *Dermatol Surg* 2016; 42(3): 384–91.

In this 20-week study, 40 patients were randomly assigned to one of three groups: Group A received glycolic acid peels 35%, Group B received salicylic acid/mandelic peels, and Group C received phytic acid combination peels. All groups were primed with hydroquinone 4% and tretinoin 0.05%. Peeling was performed every 2 weeks. Glycolic acid 35% and salicylic acid were equally effective in significantly improving melasma severity.

Adapalene in the treatment of melasma: a preliminary report. Dogra S, Kanwar AJ, Parasad D. *J Dermatol* 2002; 29: 539–40.

A randomized, split-face study of 30 women comparing adapalene 0.1% and tretinoin 0.05% for 14 weeks. Both retinoids produced a similar significant improvement in melasma. Adapalene was better tolerated.

Third-Line Therapies

• Niacinamide	A
• Kojic acid	A
• Cysteamine	A
• Topical tranexamic acid	A
• Laser and intense pulsed light (IPL)	B
• Oral tranexamic acid	B

A double-blind, randomized clinical trial of niacinamide 4% versus hydroquinone 4% in the treatment of melasma. Navarrete-Solis J, Castaneda-Cazares J, Torres-Alvarez B, et al. *Dermatol Res Pract* 2011; 2011: 379173.

Twenty-seven patients with Fitzpatrick skin types IV or V were enrolled in this 8-week study. The MASI scores improved from 4 to 1.2 in the hydroquinone-treated skin and from 3.7 to 1.4 in the niacinamide-treated skin.

Kojic acid vis-à-vis its combinations with hydroquinone and betamethasone valerate in melasma: a randomized, single blind, comparative study of efficacy and safety. Deo KS, Dash KN, Sharma YK, et al. *Indian J Dermatol* 2013; 58: 281–5.

A single-blind, randomized study of 80 patients treated with either kojic acid 1% cream; kojic acid 1% and hydroquinone 2% cream; kojic acid 1% and betamethasone valerate 0.1% cream; or kojic acid 1%, hydroquinone 2%, and betamethasone valerate 0.1% cream. All groups demonstrated improvement in MASI score; however, the greatest response was seen with kojic acid used in combination with hydroquinone.

Kojic acid is derived from fungi and is considered to have high sensitizing potential.

Evaluation of the efficacy of cysteamine 5% cream in the treatment of epidermal melasma: a randomized double-blind placebo-controlled trial. Mansouri P, Farshi S, Hashemi Z, et al. *Br J Dermatol* 2015; 173(1): 209–17.

The authors report on 50 patients who were enrolled in this 16-week randomized, double-blinded trial: 25 subjects received cysteamine and the other 25 received placebo applied once a day. Cysteamine showed significant efficacy compared with placebo at 8 and 16 weeks.

Cysteamine is the degradation product of the amino acid L-cysteine. It is a tyrosinase and peroxidase inhibitor.

A comparative study of topical 5% tranexamic acid and triple combination therapy for the treatment of melasma in Indian population. Khuraiya S, Kachhawa D, Chouhan B, et al. *Pigment Int* 2019; 6: 18–23.

This was a 12-week split-face study of 23 patients with melasma. Tranexamic acid 5% was applied to one side of the face and triple combination to the opposite side. The mean MASI decreased significantly on both sides with equal efficacy. In addition, tranexamic acid (TA) 5% had less erythema irritation and telangiectasias.

Randomized, placebo-controlled, double-blind study of oral tranexamic acid in the treatment of moderate-to-severe melasma. Del Rosario E, Florez-Pollack S, Zapata L Jr, et al. *J Am Acad Dermatol* 2018; 78(2): 363–9.

A total of 39 patients completed this 6-month placebo-controlled, double-blinded study. At 3 months, there was a 49% reduction in mMASI (modified MASI) score in the TA group versus 18% in the control group. Patients with severe melasma

improved more than those with moderate melasma. Three months after treatment was stopped, there was a 26% reduction in mMASI score in the TA group compared with the baseline visit vs. a 19% reduction in the placebo arm. No serious adverse events were noted in either group.

TA is thought to reduce melanin synthesis through inhibition of the plasminogen/plasmin pathway. It is contraindicated in individuals with a history of thromboembolic disease. Further controlled studies are required to determine the short- and long-term safety, efficacy, and optimal dosing regimens.

Laser and laser compound therapy for melasma: a meta-analysis. Zhang Y, Zheng X, Chen Z, et al. *J Dermatolog Treat* 2020; 31(1): 77–83.

A total of 346 patients were enrolled in nine randomized clinical trials. The types of lasers used were Q-switched, non-ablative, 550-nm fractional laser, non-ablative 1927-nm laser, IPL, and fractional erbium:YAG lasers. Intervention ranged from 3 to 6 weeks. Lasers and light therapies improved the severity of melasma during the follow-up period.

A meta-analysis-based assessment of intense pulsed light for treatment of melasma. Yi J, Hong T, Zeng H, et al. *Aesth Plast Surg* 2020; 44: 947–52.

Eight studies involving 215 patients. IPL was effective in decreasing the MASI score in all studies. Seven of the included studies were in Asian patients who are often skin type III. One study included an American cohort of 58 patients.

IPL should not be performed in skin types V and VI due to a substantially greater risk of postinflammatory hyperpigmentation.

Pulsed dye laser versus intense pulsed light in melasma: a split-face comparative study. Hassan AM, Elfar NN, Rizk OM, et al. *J Dermatolog Treat* 2018; 29(7): 725–32.

Twenty-eight Egyptian females were treated with pulsed-dye laser on the right hemiface (Group A) and with IPL on the left hemiface (Group B). The hemifacial mMASI was significantly reduced in both groups. Both modalities significantly impacted the vascular component of melasma.

Nonablative 1550-nm fractional laser therapy versus triple topical therapy for the treatment of melasma: a randomized controlled pilot study. Kroon MW, Wind BS, Beek JF, et al. *J Am Acad Dermatol* 2011; 64: 516–23.

This observer-blinded study of 20 women with melasma compared triple combination cream with four sessions of non-ablative 1550-nm fractional laser therapy over an 8-week period. Both treatments resulted in a significant improvement in melasma, although there was evidence of recurrence in half the patients in each group at 6-month follow-up.

The results of open-label studies of fractional photothermolysis for melasma are variable. A number of uncontrolled studies have reported a significant incidence of postinflammatory hyperpigmentation.

Merkel cell carcinoma

Heather Layher, Henry Heaton, Naomi Lawrence



INTRODUCTION

First described by Toker in 1972, Merkel cell carcinoma (MCC) is a rare, aggressive cutaneous malignancy of neuroendocrine origin with 2000–2500 cases diagnosed annually. MCC is most common in fair-skinned individuals over 70 years old. Lesions are rapidly growing erythematous-violaceous nodules on sun-exposed areas of primarily the head and neck, although trunk and extremity involvement occurs. Immunosuppression is associated with an increased risk of developing MCC; links with solid organ transplantation, human immunodeficiency virus, and lymphoproliferative diseases have been described. Merkel cell polyomavirus (MCPyV) and ultraviolet radiation also contribute to tumorigenesis. MCPyV has been detected in 75–80% of MCCs. The remaining 20–25% of MCPyV-negative tumors demonstrate a higher frequency of UV-characteristic mutations relative to MCPyV-positive tumors. Correlation between overall survival and MCPyV positivity has yet to be determined. At time of diagnosis, 25–33% of patients have lymph node involvement and up to 15% have distant metastasis. Recurrence rates range between 25% and 50%, and overall survival at 5 years is 50–75% for local disease and less than 15–25% for metastatic disease.

MANAGEMENT STRATEGY

The National Comprehensive Cancer Network (NCCN) developed clinical practice guidelines for MCC. There is a paucity of randomized controlled trials regarding therapy for MCC and, as such, much of the data behind these guidelines comes from retrospective analyses and case series.

Thorough skin examination and lymph node evaluation are required. Imaging can assist in confirming lymph node involvement and distant metastasis if clinically suspected. However, no imaging method has demonstrated conclusive efficacy in detecting

nodal spread in the absence of clinical lymph node involvement. Imaging is not recommended without clinical concern for disease spread. Computed tomography (CT), magnetic resonance imaging, and positron emission tomography (PET) imaging have been utilized, with FDG-PET/CT being the most well studied in MCC. Sentinel lymph node biopsy (SLNB) is useful in clinically node-negative disease for accurate staging and management planning and is recommended prior to primary tumor excision. If nodal enlargement is detected clinically, confirmation by fine-needle aspiration or core biopsy is indicated. PET/CT and full nodal dissection with or without radiation therapy are generally indicated for pathologically confirmed nodal positivity.

Treatment requires *excisional clearance through Mohs micrographic surgery or wide local excision using 1–2-cm margins*. Due to the high recurrence rate even with pathologically clear margins, adjuvant therapies are indicated. Similar to other small cell neuroendocrine carcinomas, such as those of the lung, breast, and gastrointestinal tract, MCCs are radiosensitive. *Radiation* may be utilized as monotherapy in patients who are not surgical candidates, or as adjuvant therapy following surgical removal. Radiation delivered solely to the primary site is indicated if SLNB is negative, and to the primary site plus nodal basin if SLNB is positive or if there are other high-risk features, like concomitant immunosuppression or aggressive tumor characteristics.

For metastatic disease, systemic therapy may be indicated. Traditional cytotoxic chemotherapy does not produce a durable response and is limited by significant toxicity. For in-transit metastasis, *isolated limb perfusion or isolated limb infusion* may be used to avoid amputation. Newer targeted therapies have shown greater and more durable response rates, including *checkpoint inhibitors avelumab* (anti-PD-L1 monoclonal antibody) and *pembrolizumab* (PD-1 to PD-L1 and PD-L2 inhibitor), and the genetically modified herpes simplex virus *talimogene laherparepvec*.

Specific Investigations

- Sentinel lymph node biopsy
- Diagnostic imaging
- Prognostic serology

Relationships among primary tumor size, number of involved nodes, and survival for 8044 cases of Merkel cell carcinoma. Iyer JG, Storer BE, Paulson KG, et al. *J Am Acad Dermatol* 2014; 70: 637–43.

Retrospective analysis of 8044 cases of MCC showed increased risk of nodal involvement with increasing tumor size, and poorer prognosis with increasing number of involved nodes. Lymph node involvement was 14% for 0.5-cm tumors, 25% for 1.7-cm tumors, and 36% for tumors larger than 6 cm; 5-year survival was 76% with 0 nodes involved, 50% with 1 node involved, 47% with 2 nodes involved, 42% with 3–5 nodes involved, and 24% with 6 or more involved nodes. This study confirms that level of nodal involvement correlates with overall prognosis and management.

Sentinel lymph node biopsy in Merkel cell carcinoma: predictors of sentinel lymph node positivity and association with overall survival. Conic RRZ, Ko J, Saridakis S, et al. *J Am Acad Dermatol* 2019; 81: 364–72.

Retrospective review of 3048 cases of MCC showed SLN positivity in 30.8%. Nodal involvement correlated more highly with truncal location, tumor-infiltrating lymphocytes, and lymphovascular invasion (LVI), with LVI having the strongest association. Poorer survival correlated with age over 75, male gender,

immunosuppression, and SLN positivity. This study reconfirms the importance of SLNB even for clinically node-negative patients.

This study differs from smaller studies and previous editions of this text that showed no association between SLN status and disease-specific survival.

Positron emission tomography/computed tomography imaging in Merkel cell carcinoma: a study of 270 scans in 97 patients at the Dana-Farber/Brigham and Women's Cancer Center. Hawryluk EB, O'Regan KN, Sheehy N, et al. *J Am Acad Dermatol* 2012; 68: 592–9.

Retrospective review of 97 patients who underwent 270 FDG-PET/CT scans: 61 scans were done during initial management in 61 patients and 209 scans were done during subsequent management in 79 patients. FDG-PET/CT upstaged 16% of patients on baseline scan, particularly in advanced disease. FDG-PET/CT showed the greatest utility in patients with known lymph node involvement with unknown primary, confirming both regional nodal involvement and distant metastases in 50% of patients. When used in subsequent management, FDG-PET/CT identified more bone and bone marrow metastases compared to CT. This study shows that while FDG-PET/CT should not be used in place of SLNB for detection of micrometastatic disease, it is useful in staging and restaging MCC.

This study differs from smaller studies and previous editions of this text, which show no difference between conventional CT and FDG-PET/CT in initial and subsequent management of MCCs.

Absolute lymphocyte count: a potential prognostic factor for Merkel cell carcinoma. Johnson ME, Zhu F, Li T, et al. *J Am Acad Dermatol* 2014; 70: 1028–35.

Retrospective review of 64 patients with MCC with baseline complete blood count within 1 month prior to treatment. Absolute lymphocyte count (ALC) $<1.1 \text{ k/mm}^3$ correlated with median overall survival of 18.8 months compared with 110.1 months with ALC $>1.1 \text{ k/mm}^3$ ($p = 0.002$). Thirty-six-month disease-free survival with ALC $<1.1 \text{ k/mm}^3$ was 26.9% versus 64.4% with ALC $>1.1 \text{ k/mm}^3$ ($p = 0.01$). Overall, ALC $<1.1 \text{ k/mm}^3$ is a useful prognostic factor in overall survival but is not a significant predictor of disease-free survival ($p = 0.12$).

Prognostic value of antibodies to Merkel cell polyomavirus T antigens and VP1 protein in patients with Merkel cell carcinoma. Samimi M, Molet L, Fleury M, et al. *Br J Dermatol* 2016; 174: 813–22.

Review of 143 patients with MCPyV-positive MCC for detection of antibodies to MCPyV capsid protein (VP1) and oncoproteins (T-antigens). At baseline, VP1 antibody titers inversely correlated with risk of recurrence and death, and showed a favorable prognostic value when detected at high levels. VP1 antibody titers did not significantly correlate with disease status during follow-up.

Baseline titers of antibodies to T-antigens (TAG) did not correlate with overall risk of recurrence or death. However, in the follow-up period, TAG antibody titers cleared in remission and rose in both recurrence and in disease progression when detected >12 months after diagnosis.

VP1 antibodies can be useful as prognostic indicators at baseline, while TAG antibodies can be used during follow-up as indicators of recurrence and progression.

First-Line Therapies

• Mohs micrographic surgery	C/D
• Wide local excision	C

Demographics and outcomes of stage I and II Merkel cell carcinoma treated with Mohs micrographic surgery compared with wide local excision in the National Cancer Database. Singh B, Qureshi MM, Truong MT, et al. *J Am Acad Dermatol* 2018; 79: 126–34.

Retrospective study comparing survival outcomes between wide local excision (WLE) with greater than 1-cm margins versus Mohs micrographic surgery (MMS) for 1795 patients with early-stage MCC. The study demonstrated comparable effectiveness for MMS and WLE in treating early-stage MCC with no significant difference in surgical margin negativity or overall survival rates at 3 years.

Recurrence and survival in patients with Merkel cell carcinoma undergoing surgery without adjuvant radiation therapy to the primary site. Frohm ML, Griffith KA, Harms KL, et al. *JAMA Dermatol* 2016; 152: 1001–7.

The study evaluated 104 patients with 105 primary MCCs, assessing local, regional and distant recurrence rates following excision of low-risk tumors smaller than 2 cm with 1–2-cm margins without adjuvant radiation. Nineteen patients developed recurrence with average time to recurrence of 10.7 months. Two of the 104 patients (1.9%) developed true local and satellite recurrences. This study demonstrated what the authors argue is a relatively low rate of local recurrence in low-risk tumors less than 2 cm treated with surgery without adjuvant radiation.

Second-Line Therapies

• Radiation therapy	C
• Chemotherapy	C
• Checkpoint inhibitors, immune therapy	B/E

Identifying an optimal adjuvant radiotherapy dose for extremity and trunk Merkel cell carcinoma following resection: an analysis of the National Cancer Database. Patel SA, Qureshi MM, Sahni D, et al. *JAMA Dermatol* 2017; 153: 1007–14.

Retrospective review of 2093 patients with stage I–III MCC of the trunk or extremities treated with excision and radiation. Three-year overall survival was 41.8% with 30–39.9 Gy radiation, 69% with 40–49.9 Gy, 69.2% with 50–54.9 Gy, and 66% with 55–70 Gy. In conjunction with excision for MCCs on the trunk and extremities, an adjuvant radiotherapy dosage of 40–49.9 Gy was sufficient and survival was not significantly increased with higher dosages.

In-transit Merkel cell carcinoma treated with isolated limb perfusion or isolated limb infusion: a case series of 12 patients. Zeitouni NC, Giordano CN, Kane JM. *Dermatol Surg* 2011; 37: 357–64.

Case series of 12 patients with in-transit extremity MCC. Nine were treated with isolated limb perfusion (ILP) and three with isolated limb infusion (ILI). All were treated with melphalan and six also received tumor necrosis factor- α , actinomycin D, interferon gamma, nitrogen mustard, or a combination of these agents. ILP and ILI, achieved through tourniquet occlusion, allow high-dose chemotherapy to the involved extremity with minimal systemic side effects. Eleven (92%) had complete clinical response and one (8%) had partial clinical response. Mean duration of response was 21.8 months with mean follow-up of 25.3 months. Four (33.3%) developed regional recurrence and two (16.7%) developed distant metastases resulting in death. Adverse event rates were low. ILP and ILI demonstrate

efficacy and safety in treating in-transit extremity MCC without the need for amputation.

ILI is less invasive than ILP. The article suggests ILI is a more reasonable first-line treatment in loco-regionally advanced extremity MCC.

Systematic literature review of efficacy, safety and tolerability outcomes of chemotherapy regimens in patients with metastatic Merkel cell carcinoma. Nghiem P, Kaufman HL, Bharmal M, et al. *Future Oncol* 2017; 13: 1263–79.

Systematic review of 35 studies showed response rates to chemotherapy of 20–61%; 53–61% to first-line therapies, 23–45% to second-line therapies, and 20% to further-line therapies. Duration of response was less than 8 months for first- and second-line therapies. Most commonly used chemotherapeutic agents were platinum-based with or without etoposide (74% of studies), and cyclophosphamide with doxorubicin and vincristine (31% of studies). Chemotherapy showed a lack of durable response with significant toxicity and adverse events.

This article reaffirms that overall outcomes and durable responses with chemotherapy for metastatic MCC are poor. Due to insufficient literature on its utility, routine use cannot be recommended based on current evidence.

Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Kaufman HL, Russell J, Hamid O, et al. *Lancet Oncol* 2016; 17: 1374–85.

Prospective, open-label, phase 2 trial of avelumab, an anti-PD-L1 monoclonal antibody, in 88 patients with stage IV chemotherapy-refractory MCC. Avelumab was administered intravenously at 10 mg/kg every 2 weeks. The end point was confirmed objective response. Median number of doses was seven and median duration was 17 weeks: 28 patients (32%) achieved an objective response, with eight complete responses and 20 partial responses. Continued response was noted in 23 of the 28 patients (82%) at a median follow-up of 10.4 months. Additionally, nine of the 88 patients (10%) achieved stable disease. Treatment-related adverse events developed in 70% of patients, most commonly fatigue

(24%) and infusion-related reactions (17%). Grade 3 adverse events developed in 5%, including lymphopenia and elevated creatine phosphokinase, cholesterol, and aminotransferases. No grade 4 adverse-events occurred.

Compared with chemotherapy, immune checkpoint inhibition with avelumab shows a longer duration of response with better tolerability.

Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. Nghiem P, Bhatia S, Lipson EJ, et al. *J Clin Oncol* 2019; 37: 693–702.

Phase II trial of 50 patients with advanced MCC who received pembrolizumab 2 mg/kg every 3 weeks for up to 2 years. Pembrolizumab is a checkpoint inhibitor and blocks binding of PD-1 to PD-L1 and PD-L2. Objective response was achieved in 56%, with 24% achieving complete response and 32% achieving partial response. Objective response rates were 59% in virus-positive MCC and 53% in virus-negative MCC. Median progression-free survival was 16.8 months, and the 24-month progression-free survival rate was 48.3%. An overall survival rate of 24 months was 68.7%; 28% developed grade 3 or higher adverse events; 14% discontinued treatment with one death.

This study demonstrates the longest observation to date of patients with advanced MCC receiving anti-PD-1 therapy. Pembrolizumab showed more durable tumor control and more favorable overall survival than traditional chemotherapy, but with a higher rate of adverse events than avelumab.

Talimogene laherparepvec induces durable response of regionally advanced Merkel cell carcinoma in 4 consecutive patients. Westbrook BC, Norwood TG, Terry NLJ, et al. *JAAD Case Reports* 2019; 5: 782–6.

Case report of four patients with regionally advanced MCC treated with intratumoral injection of talimogene laherparepvec (TVEC), a genetically modified herpes simplex 1 virus that increases tumor-antigen presentation by dendritic cells. All patients achieved durable complete response for greater than 16 months with minimal adverse events.

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Dirk M. Elston



Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria have developed resistance to β -lactam antibiotics, such as methicillin, dicloxacillin, nafcillin, and oxacillin, and the cephalosporins, through horizontal gene transfer and natural selection. Although not necessarily more virulent than sensitive strains, infection caused by them is more difficult to treat due to their resistance to standard antibiotics.

MANAGEMENT STRATEGY

Healthcare-type strains of MRSA are associated with sepsis and are common colonists of chronic wounds, where debridement is typically the best strategy. Community-type MRSA infections typically present as an abscess or furunculosis. The most important intervention for an abscess remains *surgical drainage*. Purulent material can reform rapidly, so a punch or cruciate incision is advised, as it tends to remain open longer to allow adequate drainage. A curette is used to probe the wound and ensure that all pockets of purulent material have been adequately drained. Irrigation can be helpful, but packing is discouraged as purulent material often reforms behind the packing material. Evidence suggests that antibiotics can be beneficial even when an abscess is adequately drained.

Patients with significant surrounding cellulitis, refractory infection, or systemic manifestations require *antibiotic therapy*. Most community-associated (CA) MRSA strains are sensitive to *trimethoprim-sulfamethoxazole*. Most strains are also sensitive to *doxycycline* and *minocycline*, but doxycycline does not penetrate well into the nares. Clindamycin resistance is emerging in many communities. For serious infections, therapy should be guided by culture and sensitivity. *Vancomycin*, *linezolid*, *dalbavancin*, *telavancin*, and *daptomycin* are often effective. *Rifampin* improves intracellular

killing of bacteria by vancomycin. Daptomycin may not penetrate reliably into pulmonary tissue, and tigecycline has a significant incidence of nausea. Ceftobiprole appears promising.

Spread occurs through skin-to-skin contact and via fomites. *Decolonization* may be indicated for prevention of recurrence or prevention of serious invasive disease in close contacts, but there is a high incidence of recurrence if the entire family unit is not treated. The most effective decolonization regimens address the nares and intertriginous and anogenital sites, as well as eczematous skin. In some patients, gut colonization may also be an issue. Widespread use of agents for decolonization is associated with emergence of resistance and alternative regimens are needed.

SPECIFIC INVESTIGATIONS

Cultures should be obtained from the contents of purulent infections and resistant infections. New molecular diagnostic tests are being developed to screen for MRSA and identify genes associated with resistance.

Role of nasal swab culture in guiding antimicrobial therapy for acute cellulitis in the era of community-acquired methicillin-resistant *Staphylococcus aureus*: a prospective study of 89 patients. Hsu MS, Liao CH, Fang CT. *J Microbiol Immunol Infect* 2019; 52: 494–7.

In a prospective study of 89 patients with acute cellulitis, nasal swab culture had high specificity (95%) in predicting MRSA cellulitis among the 24 patients whose cellulitis became purulent. Sensitivity is only 20%.

Cellulitis associated with an abscess or purulence is more likely to be staphylococcal. Most other cellulitis is streptococcal. Nasal culture may be of some value in predicting staphylococcal cases, but sensitivity is low.

Existence of multiple SCCmec elements in clinical isolates of methicillin-resistant *Staphylococcus aureus*. Nagasundaram N, Sistla S. *J Med Microbiol* 2019; 68: 720–7.

MRSA can be classified into hospital-acquired and community-associated strains based on SCCmec types. In this report, 118 of 200 isolates carried multiple SCCmec types and three were non-typable.

Community strains are now common in the hospital setting and hospital strains colonize wounds when patients are discharged. This report suggests that even lab typing shows considerable overlap.

***Staphylococcus aureus* and methicillin resistance detection directly from pediatric samples using PCR assays with differential cycle threshold values for corroboration of methicillin resistance.** *J Microbiol Methods* 2019; 159: 167–73.

Two polymerase chain reaction (PCR) assays were evaluated: (1) a singleplex assay targeting the *nucA* gene; and (2) a multiplex PCR assay (*mecA*/SCC-*orf* PCRs) that detects the *mecA* gene and the conjunction region where SCCmec elements insert into the genome. The *nucA* PCR compared well with culture with an overall agreement of 93.1% and sensitivity and specificity of 93.5% and 93.0%, respectively.

Molecular tests are being used more frequently to replace conventional culture and sensitivity techniques.

Epidemiology

Interactions between atopic dermatitis and *Staphylococcus aureus* infection: clinical implications. Kim J, Kim BE, Ahn K, et al. *Allergy Asthma Immunol Res* 2019; 11: 593–603.

Multiple factors predispose to colonization of atopic skin including corneocyte adhesion, deficiency of antimicrobial peptides, microbial dysbiosis, decreased levels of flaggrin and flaggrin degradation products, overexpressed Th2/Th17 cytokines, and altered lipid profiles.

Strategies being evaluated to combat MRSA colonization include microbiome transplant, monoclonal antibodies against staphylococcal toxins, vaccines, and recombinant phage endolysin.

Multidrug and mupirocin resistance in environmental methicillin-resistant *Staphylococcus aureus* (MRSA) isolates from homes of people diagnosed with community-onset MRSA infection. Shahbazian JH, Hahn PD, Ludwig S, et al. Appl Environ Microbiol 2017; 31: 83.

MRSA was isolated from the household environment at the baseline and 3 months later. Patients and household members were randomized to receive mupirocin-based decolonization therapy or education. MRSA isolates were found in 68% (65/95) of homes at baseline and 51% (33/65) of homes 3 months later. The rates of multidrug resistance were 61% at baseline and 55% 3 months later. At the baseline, 100% (14/14) of MRSA isolates from rural homes demonstrated multidrug resistance.

Use of antimicrobial drugs, except clindamycin, was associated with multidrug resistance. Animal reservoirs are an important source of drug-resistant strains in rural settings.

Prognosis

Methicillin-resistant *Staphylococcus aureus*: an overview of basic and clinical research. Turner NA, Sharma-Kuinkel BK, Maskarinec SA, et al. Nat Rev Microbiol 2019; 17(4): 203–18.

The epidemiology of MRSA is characterized by the serial emergence of epidemic strains with varying virulence. Although its incidence has recently declined in some regions, MRSA is still associated with high morbidity and mortality. MRSA is genetically diverse with varying virulence factors among different strains.

Adherence to antibiotic guidelines for erysipelas or cellulitis is associated with a favorable outcome. Klotz C, Courjon J, Michelangeli C, et al. Eur J Clin Microbiol Infect Dis 2019; 38: 703–9.

The authors studied adherence to 28 parameters for all admitted patients with community-acquired erysipelas and cellulitis. Exclusion criteria were abscesses at admission; ear, nose, throat, or dental cellulitis; pyomyositis; and length of stay ≤ 2 days. Adherence to guidelines was defined by the use of amoxicillin, amoxicillin/clavulanic acid, clindamycin, or pristinamycin, alone or in combination or successively.

Even in the age of MRSA, erysipelas and cellulitis unassociated with abscess are largely caused by streptococci. Sulfa drugs are commonly used to treat MRSA infections, but have poor streptococcal coverage. Adherence to guidelines that recommended β -lactam drugs or clindamycin was associated with a favorable outcome.

Pathogenesis

View point: gaps in the current guidelines for the prevention of Methicillin-resistant *Staphylococcus aureus* surgical site infections. Kavanagh KT, Abusaleem S, Calderon LE. Antimicrob Resist Infect Control 2018; 18(7): 112.

The carriage rate of *Staphylococcus aureus* in the general population is about 33% and the rate for MRSA is approximately 2%. In healthcare workers, the rate of MRSA carriage is 5%. The authors suggest preoperative screening of surgical patients and healthcare workers.

MRSA decolonization of healthcare workers can be achieved in 90% and should be part of an overall program to reduce the incidence of surgical infections.

Increased usage of antiseptics is associated with reduced susceptibility in clinical isolates of *Staphylococcus aureus*. Hardy K, Sunnucks K, Gil H, et al. MBio 2018; 29: 9.

Hospital-acquired MRSA has evolved with emergence of resistance to chlorhexidine in isolates from periods of high usage of chlorhexidine. Resistance to octenidine rapidly emerged after the agent was introduced with no cross-resistance between the two.

Decolonization with antiseptics is common practice, but data suggest that MRSA strains become resistant to these antiseptics.

Prevalence of mupirocin and chlorhexidine resistance among methicillin-resistant coagulase-negative staphylococci isolated during methicillin-resistant *Staphylococcus aureus* decolonization strategies. Eed EM, Ghonaim MM, et al. Am J Infect Control 2019 June 13 [Epub ahead of print].

MRSA decolonization strategies using mupirocin on the nasal mucosa only had less effect on resistance patterns than chlorhexidine used over wide areas of the body.

Both strategies may reduce the recurrence of MRSA infection but the widespread of decolonization aimed at MRSA may lead to an increase in the prevalence of multiresistant coagulase-negative staphylococci.

First-Line Therapies

Treatment of MRSA abscesses

• Surgical drainage alone for small lesions	B
• Surgical drainage plus trimethoprim-sulfamethoxazole	B
• Minocycline	B
• Doxycycline	B
• Clindamycin	B

Eradication of colonization: nares

• Mupirocin	B
• Tea tree oil	B

Eradication of colonization: skin

• Bleach baths	D
• Chlorhexidine	B
• Triclosan	B
• Tea tree oil soap	B
• Undecylenamidopropyltrimonium methosulfate/phenoxylethanol	C
• Octenidine dihydrochloride	C

While drainage alone may be adequate therapy for smaller abscesses and furuncles, emerging data suggest the risk of complications is less if an MRSA antibiotic is also prescribed. For erysipelas and cellulitis unassociated with abscess, β -lactam drugs remain first-line therapy because of superior streptococcal coverage. Resistance rates to systemic and topical agents vary widely and physicians should be familiar with local antibiograms.

Bleach baths do not kill staphylococci but reduce itch and exco-riation and may thus have benefits.

Impact of decolonization protocols and recurrence in pedi-atric MRSA skin and soft-tissue infections. Papastefan ST, Buonpane C, Ares G, et al. J Surg Res 2019; 242: 70–7 [Epub ahead of print].

This single-institution, retrospective review of children with MRSA culture-positive abscesses who underwent incision and drainage with or without MRSA decolonization found that decolonized patients did not have lower rates of recurrence. Recurrence was more likely in patients with previous abscesses, family history of abscesses, family history of MRSA infection, previous MRSA infection, Hispanic ethnicity, and those with fever.

MRSA decolonization can increase rates of resistance and did not decrease the rate of recurrence of MRSA abscesses in this study. There were many confounders, including the high prevalence of colonization of family members.

Decolonization to reduce postdischarge infection risk among MRSA carriers. Huang SS, Singh R, McKinnell JA, et al.; Project CLEAR Trial. N Engl J Med 2019; 380: 638–50.

This was a multicenter, randomized, controlled trial of post-discharge hygiene education compared with education plus decolonization in patients colonized with MRSA. The decolonization procedure involved chlorhexidine mouthwash, baths, or showers with chlorhexidine, and nasal mupirocin for 5 days twice per month for 6 months. MRSA infection occurred in 9.2% of patients in the education group vs. 6.3% in the decolonization group, and 84.8% of the infections led to hospitalization.

MRSA decolonization with chlorhexidine and mupirocin correlated with a 30% lower risk of MRSA infection and a lower rate of hospitalization.

A review on mechanism of action, resistance, synergism, and clinical implications of mupirocin against *Staphylococcus aureus*. Khoshnood S, Heidary M, Asadi A, et al. Biomed Pharmacother 2019; 109: 1809–18.

Mupirocin is a natural crotonic acid derivative produced by *Pseudomonas fluorescens* that inhibits protein synthesis by binding to bacterial isoleucyl-tRNA synthetase. Widespread use is associated with emergence of resistance.

Rates of resistance vary across the globe and correlate with how widely the agent has been used.

Tolerance of MRSA ST239-TW to chlorhexidine-based decolonization: evidence for keratinocyte invasion as a mechanism of biocide evasion. Marbach H, Vizcay-Barrena G, Memarzadeh K, et al. J Infect 2019; 78: 119–26.

Strains tolerant to chlorhexidine showed greater binding to fibrinogen and fibronectin, adhesion and intracellular uptake within keratinocytes, and intracellular survival in keratinocytes.

Cellular adhesion and intracellular uptake into keratinocytes help MRSA strains evade infection control measures.

Molecular characterization of nasal methicillin-resistant *Staphylococcus aureus* isolates showing increasing prevalence of mupirocin resistance and associated multidrug resistance following attempted decolonization. Poovelikunnel TT, Budri PE, Shore AC, et al. Antimicrob Agents Chemother 2018; 27: 62.

Sequential MRSA isolates following attempted mupirocin nasal decolonization showed an increase in resistance from 6.6% to 20%.

Patients who failed decolonization carried multiple antimicrobial and antiseptic resistance genes, which complicate treatment regimens.

Control of healthcare- and community-associated MRSA: recent progress and persisting challenges. Henderson A, Nimmo GR. Br Med Bull 2018; 125(1): 25–41.

Morbidity and mortality associated with MRSA infection remains high and its control remains challenging.

British guidelines favor the use of targeted screening and decolonization, hand hygiene, and antimicrobial stewardship. Controversial areas lacking consensus include universal screening, universal decolonization, and contact precautions.

Strategies for prevention of methicillin resistant *Staphylococcus aureus* (MRSA) infections and decolonization. Kaushik A, Wagner C, Consoer H. S D Med 2016; 69: 535–9.

MRSA invasive infections in the pediatric population are associated with high morbidity and mortality.

Decolonization strategies may be particularly important in pediatric patients.

Methodologic considerations of household-level methicillin-resistant *Staphylococcus aureus* decolonization among persons living with HIV. Farley JE, Starbird LE, Anderson J, et al. Am J Infect Control 2017; 45: 1074–80.

Patients with HIV have a higher prevalence of MRSA colonization and greater likelihood of recurrent infection than the general population. This pilot trial examined testing household-level MRSA decolonization. MRSA colonization at 6 months was the primary outcome.

This study measured colonization rates rather than clinical outcomes, which has become the new gold standard. The study remains important in that it identified stigma and confidentiality concerns as well as dynamic living situations that may complicate efforts to treat this group of patients.

Second-Line Therapies

• Vancomycin ± rifampin	B
• Linezolid and newer oxazolidinones	A
• Lipoglycopeptides (dalbavancin, oritavancin, and telavancin)	B
• Daptomycin	B
• Eradication of colonization: nares	
• Retapamulin	D
• Triple antibiotic ointment	D
• Silver sulfadiazine cream	D
• Eradication of colonization: skin	D
• Benzoyl peroxide soap	E
• Zinc pyrithione soap	E

On- and off-label utilization of dalbavancin and oritavancin for gram-positive infections. Morrisette T, Miller MA, Montague BT, et al. J Antimicrob Chemother 2019; 74: 2405–16.

Long-acting lipoglycopeptides are Food and Drug Administration (FDA)-approved for acute bacterial skin and skin structure infections. This study also examined off-label uses including osteomyelitis (27%) and endocarditis (9%). Failure rate was about 15% overall.

These agents have potential for treatment of Gram-positive infections without the need for infusions.

Tedizolid phosphate for the treatment of acute bacterial skin and skin-structure infections: an evidence-based review of its place in therapy. Bassetti M, Castaldo N, Carnelutti A, et al. *Core Evid* 2019; 14: 31–40.

Tedizolid phosphate is a newer oxazolidinone approved for the treatment of acute bacterial skin and skin-structure infections including MRSA. Approval was based on two phase-III randomized, controlled non-inferiority trials comparing 6-day once-daily tedizolid vs. 10-day twice-daily linezolid.

Tedizolid offers once-daily administration, shorter duration, and lower risk of myelotoxicity.

Antibacterial activity of tedizolid, a novel oxazolidinone against methicillin-resistant *Staphylococcus aureus*: a systematic review and meta-analysis. Hasannejad-Bibalan M, Mojtabedi A, Biglari H, et al. *Microb Drug Resist* 2019 October 31. <https://doi.org/10.1089/mdr.2018.0457>.

The overall antibacterial activity of tedizolid on 10,119 MRSA isolates was estimated at 0.25 and 0.5 mcg/mL for MIC₅₀ and MIC₉₀, but only four of 18 included publications reported antibacterial activity against linezolid-resistant isolates, of which the MIC range of tedizolid was 0.25–16 mcg/mL. All of the linezolid-resistant isolates were susceptible to tedizolid in one study, and in the other studies, the susceptibility rates were <50%.

Future studies need to delve further into activity against linezolid-resistant strains.

Third-Line Therapies	
• Tigecycline and omadacycline	B
• Ceftobiprole, ceftaroline	C
• Honey and bee venom	B
• Topical ozenoxacin	B
• Omadacycline	A
• Sugar and povidone-iodine	E

Randomized controlled trial of honey versus mupirocin to decolonize patients with nasal colonization of methicillin-resistant *Staphylococcus aureus*. Poovelikunnel TT, Gethin G, Solanki D, et al. *J Hosp Infect*. 2018; 98: 141–8.

A randomized, controlled trial comparing medical-grade honey with mupirocin 2% for the eradication of nasal MRSA. The proportion of patients who were decolonized after one or two courses of treatment was 42.8% vs. 56.8%. Non-nasal MRSA colonization was associated with persistent nasal colonization (odds ratio: 5.186; 95% CI: 1.736–5.489; $p=0.003$), and the rate of new acquisition of mupirocin resistance was 9.75%.

Mupirocin resistance and non-nasal colonization complicate the analysis, but this report adds support to the use of medical-grade honey for the treatment of MRSA colonization.

In vitro evaluation of methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* susceptibility to Saudi honeys. Hussain MB, Kamel YM, et al. *BMC Complement Altern Med* 2019; 19: 185.

Ten Saudi honeys collected from different geographical locations were evaluated for their antibacterial potential against MRSA by the agar well diffusion method. The honey that exhibited the greatest antibacterial activity in the agar well diffusion assay was evaluated for its minimum inhibitory concentration (MIC) against 10 MRSA clinical isolates and three American

Type Culture Collection (ATCC) reference strains by the micro-broth dilution method. Locally produced honeys were unable to exhibit antibacterial activity against methicillin-sensitive *S. aureus* (MSSA) and MRSA at 25% dilutions but two showed a zone of inhibition at 50% dilutions (w/v) in catalase solution.

Honey may have therapeutic benefits but is prone to dilutional effects.

Omadacycline for acute bacterial skin and skin structure infections. Abrahamian FM, Sakoulas G, Tzanis E, et al. *Clin Infect Dis* 2019; 69(Suppl1): S23–32.

Two randomized, controlled studies examined omadacycline, a novel aminomethylcycline, and linezolid for the treatment of acute bacterial skin and skin structure infections. A total of 691 patients received omadacycline and 689 patients received linezolid. Infection types included wound infection, cellulitis/erysipelas, and major abscess in comparable proportions. *S. aureus* was isolated in 74.7% and MRSA in 32.4% of patients in whom a pathogen was identified. Omadacycline was non-inferior to linezolid (86.2% vs. 83.9%; difference 2.3, 95% confidence interval –1.5–6.2) using the primary end point of investigator-assessed clinical response. Treatment-emergent adverse events, mostly described as mild or moderate, were reported by 51.1% of patients receiving omadacycline and 41.2% of those receiving linezolid.

Omadacycline is a new entry to the market that compares favorably to linezolid.

Ceftobiprole: experience in staphylococcal bacteremia. Soriano A, Morata L. *Rev Esp Quimioter* 2019; 32 (Suppl 3): 24–8.

Ceftobiprole in combination with daptomycin has demonstrated potent activity against MRSA in animal models of endocarditis. It is a fifth generation parenteral cephalosporin active against both MRSA and *Pseudomonas aeruginosa*. It presents a low risk of infection due to *Clostridium difficile*; in comparison with ceftaroline, neutropenia is less of an issue. While not a first- or second-line agent in skin infections, ceftobiprole has a unique role owing to activity against both Gram-positive organisms such as *S. aureus* and Gram-negative organisms such as *P. aeruginosa*.

Topical ozenoxacin cream 1% for impetigo: a review. Schachner L, Andriessen A, Bhatia N, et al. *J Drugs Dermatol* 2019; 18: 655–61.

Ozenoxacin 1% cream can be used to treat impetigo and has shown to be active against MRSA isolates.

A 5-day regimen of topical ozenoxacin provides another treatment option for impetigo with a low probability of selecting resistant mutants in quinolone-susceptible or quinolone-resistant bacterial strains.

Enhanced topical delivery of non-complexed molecular iodine for Methicillin-resistant *Staphylococcus aureus* decolonization. Uchiyama S, Dahesh S, Nizet V, et al. *Int J Pharm* 2019; 554: 81–6.

An iodophor formulation of povidone-iodine in a novel non-staining formulation in glycerin delivers high local concentrations with minimal evaporative loss, and exhibits activity at ≈1 part per million against MRSA.

This formulation was associated with fewer treatment failures compared to traditional iodine in a murine model of MRSA nasal decontamination.

Miliaria

Joshua Schimmel, Warren R. Heymann



Miliaria is a benign, transient disorder caused by occlusion and resultant injury in the eccrine duct or, rarely, by a primary dysfunction of the eccrine duct. It is subdivided into miliaria crystallina, miliaria rubra, and miliaria profunda, based on the level of obliteration. Miliaria crystallina (sudamina), the most superficial form, occurs with occlusion of the sweat duct in the stratum corneum. It is self-limiting and typically appears as clear vesicles without significant erythema. Miliaria rubra ('prickly heat') is the most common, presenting as numerous pruritic non-follicular papules or vesicles with surrounding erythema. The obstruction occurs within the eccrine duct in the stratum malpighii. Typically, it occurs on the trunk, neck, or back but can affect other areas and has been reported to occur under splints, braces, and military uniforms because of the warm occlusive environment. It may also be rarely observed in cases of hypoaldosteronism and pseudohypoaldosteronism secondary to inflammation caused by elevated sodium chloride in sweat. Miliaria profunda is uncommon, classically occurring at the dermoepidermal junction or dermis; however, advances in imaging have begun to cause physicians to question this understanding, raising the possibility of acrosyringial involvement. Miliaria profunda is typically seen after repeated cases of miliaria rubra in tropical settings. These patients can also have associated systemic symptoms related to overheating.

MANAGEMENT STRATEGY

Miliaria most typically occurs as a result of excessive sweating in hot, humid conditions, with prolonged perspiration, or after an extended febrile illness. Sweat-inducing medications such as cholinergic agents, catecholamines, β -blockers, and opiates are linked to the development of miliaria. Few case reports suggest a potential association with anthracyclines, namely doxorubicin and idarubicin. There are less common reports of congenital miliaria in association with pseudohypoaldosteronism (PHA), hypothyroidism, and hypernatremia. In a few cases, miliaria crystallina has developed secondary to Stevens-Johnson syndrome/

toxic epidermal necrolysis. Miliaria is often exacerbated by tight clothing and high humidity. Management begins with *removal of the inciting factors*. There is no strong evidence for the various treatment options.

Adults often develop miliaria during travel in the tropics, military service, or with heavy exercise. *Gradual exposure* helps to acclimatize to a hot and humid environment, but this may take a few months. *Loose-fitting clothing, fans, and cool showers* may minimize the symptoms. With the use of any topical lotion or cream, care must be taken to ensure that the product applied does not occlude the skin, further exacerbating the condition. In the case of severe itching, antihistamines, cold packs, and topical corticosteroids may be used. Oatmeal baths have been anecdotally reported to provide relief. However, all these measures will prove ineffective if the sweating is not reduced. All cases will respond to air conditioning, exposure of the involved skin, and the use of antipyretics in appropriate circumstances. Miliaria profunda has been reported to respond to oral retinoids and anhydrous lanolin.

Miliaria may be complicated by superinfection; it should be treated with *systemic antibiotics or anti-yeast agents*, aimed at *staphylococci*, or *Candida* sp. as the likely pathogens, respectively. Clinicians should make patients aware that anhidrosis in the area of the eruption may occur and persist for up to 3 weeks (or sometimes even longer) after the onset of lesions, and increased heat retention may occur if a large surface area was initially affected. Thus, patients at risk of heat exhaustion or heat stroke should take precautions to remain in air-conditioned environments during hot weather. A biopsy may be helpful in atypical cases of miliaria.

Specific Investigations

- None usually required

In atypical cases

- Microbiology – swab for bacteria and yeasts
- Histology
- Advanced imaging – high-definition optical coherence tomography (HD-OCT)
- Thyroid function tests

Nonneoplastic disorders of the eccrine glands. Wenzel FG, Horn TD. J Am Acad Dermatol 1998; 38: 1–7.

The histology and pathophysiology of eccrine sweat ducts are reviewed. The erythematous macule or papule of miliaria rubra occurs with an obstruction of the sweat duct at the stratum malpighii. In the case of miliaria crystallina, the disruption is in the stratum corneum and, with miliaria profunda, at or beneath the dermoepidermal junction. The pathogenesis of miliaria is reviewed, describing the role of resident bacteria and periodic acid-Schiff (PAS)-positive extracellular polysaccharide substance blocking eccrine ducts.

The role of extracellular polysaccharide substance produced by *Staphylococcus epidermidis* in miliaria. Mowad CM, McGinley KJ, Foglia A, et al. J Am Acad Dermatol 1995; 33: 729–33.

The ability of various strains of coagulase-negative staphylococci to induce miliaria under an occlusive dressing was evaluated. *Staphylococcus epidermidis* was the only strain that induced miliaria. The authors conclude that PAS-positive extracellular polysaccharide substance produced by *S. epidermidis* plays a central role in the pathogenesis of miliaria by obstructing sweat delivery.

Miliaria crystallina in an intensive care setting. Haas N, Martens F, Henz BM. Clin Exp Dermatol 2004; 29: 32–4.

Two cases of miliaria crystallina occurring in an intensive care setting are presented. The authors hypothesize that the mechanism is secondary to transient poral closure due to the drugs used in the intensive care setting that may have stimulated sweating.

Pruritus, papules and perspiration. LaShell M, Tankersley M, Guerra A. Ann Allergy Asthma Immunol 2007; 98: 299–302.

This article reviews common exercise-induced eruptions, with miliaria rubra being discussed as the cause of the patient's recurring, self-limited eruption occurring with indoor exercise or hot tub exposure. An exercise challenge recreated the clinical picture and confirmed the diagnosis.

Miliaria-rash after neutropenic fever and induction chemotherapy for acute myelogenous leukemia. Nguyen TA, Stevens MP. An Bras Dermatol 2011; 86: 104–6.

A 40-year-old female developed miliaria crystallina after developing neutropenic fevers while on treatment with idarubicin and cytarabine. Treatment of the underlying fever led to resolution of cutaneous lesions. A review of miliaria and excessive perspiration associated with medications, including doxorubicin, bethanechol, salbutamol, and clonidine is discussed.

Pegylated liposomal doxorubicin-induced miliaria crystallina and lichenoid follicular eruption. Seghers AC, Tey HL, Tee SI, et al. Indian J Dermatol Venereol Leprol 2018; 84: 121.

A 24-year-old woman developed miliaria crystallina after the treatment of primary peritoneal carcinoma with pegylated liposomal doxorubicin. The authors propose that liposomal doxorubicin elimination via eccrine glands induced local necrosis and subsequent blockade of the acrosyringium in their patient.

Miliaria rubra and thrombocytosis in pseudohypoaldosteronism: case report. Onal H, Erdal A, Ersenb A, et al. Platelets 2012; 23: 645–7.

The authors report a case of miliaria rubra and thrombocytosis in a 6-month-old girl with PHA. They hypothesize that sympathetic activation provides vascular tonus during sodium excretion in sweat, and salt depletion crisis may play a role in the development of skin lesions and thrombocytosis in patients with pseudohypoaldosteronism.

Widespread miliaria crystallina in a newborn with hypernatremic dehydration. Engür D, Türkmen MK, Savk E. Pediatr Dermatol 2013; 30: e234–5.

The authors present a case of extensive, widespread miliaria crystallina that developed in a newborn with severe hypernatremic dehydration. They propose the destruction of sweat ducts with excretion of sweat with high levels of sodium as a possible mechanism.

Miliaria crystallina secondary to herbal remedies-induced toxic epidermal necrolysis: a case report. Pang C, Chen W, Lu J, et al. Dermatol Ther 2019; 32: e12995.

The specific herbal remedies causing the toxic epidermal necrolysis (TEN) were not mentioned. The subsequent miliaria crystallina resolved within 3 days.

In vivo imaging of miliaria profunda using high-definition optical coherence tomography: diagnosis, pathogenesis, and treatment. Tey HL, Tay EY, Cao T. JAMA Dermatol 2015; 151: 346–8.

Two cases of miliaria profunda were evaluated using HD-OCT. In the epidermis, the authors identified dilated spiraling acrosyringium and an adjacent hyperrefractile substance, which they believed to be keratin. As a result of their finding, the authors challenge our prior understanding of the location of the obstruction.

Granulomatous variant of giant centrifugal miliaria profunda in a hypothyroid infant: a case report. Chadha AA, Mahajan SA, Dongre A, et al. Indian Dermatol Online J 2019; 10: 565–6.

The authors present a case of the granulomatous variant of giant centrifugal miliaria profunda in a 10-month-old infant with congenital hypothyroidism and no history of sweating, occlusion, or fever. The authors hypothesize that the accumulation of PAS-positive material in the eccrine apparatus, the sweat electrolyte changes, and defective keratinization seen in hypothyroidism could have contributed to the development of miliaria in this patient.

Dermal and ophthalmic findings in pseudohypoaldosteronism. Korkut S, Gökalp E, Özdemir A. et al. J Clin Res Pediatr Endocrinol 2015; 7: 155–8.

A good review of the dermatological features of pseudohypoaldosteronism (PHA) based on a case report of a neonate with autosomal recessive PHA type.1.

First-Line Therapies

• Prevention	D
• Frequent showering	E
• Air conditioning	B
• Oatmeal baths	E
• Topical antiseptics	E
• Antipyretics	E

Miliaria rubra of the lower limbs in underground miners. Donoghue AM, Sinclair MJ. Occup Med (Lond) 2000; 50: 430–3.

Case series of 25 miners working in a hot and humid environment who developed miliaria. Symptoms resolved after 4 weeks of sedentary duties in the air-conditioned areas. This report also analyzed coexisting dermatologic conditions in these patients.

Diseases of the eccrine and apocrine sweat glands. Miller JL. In: Bologna JL, Jorizzo JL, Rapini RP, eds. Dermatology. Philadelphia, Mosby, 2018; 633–48.

Preventative measures, such as a cool environment, for days to weeks is the primary goal to prevent excessive sweating and maceration of the stratum corneum.

Goosefleshlike lesions and hypohidrosis. Dimon NS, Fullen DR, Helfrich YR. Arch Dermatol 2007; 43: 1323–8.

Numerous treatments for miliaria are described, including anhydrous lanolin, oral isotretinoin, regular bathing to remove salt and bacteria, and antibiotics.

Congenital miliaria crystallina in a term neonate born to a mother with chorioamnionitis. Babu TA, Sharmila V. Pediatr Dermatol 2012; 29: 306–7.

A case report of a full-term infant, whose birth was complicated by chorioamnionitis, presented at delivery with miliaria crystallina that self-resolved in 3 days. The authors proposed that prolonged rupture of membranes, maternal fever, and warm amniotic fluid may have contributed to fetal sweating and development of miliaria. Conservative and preventative measures are emphasized.

Second-Line Therapies

- Topical corticosteroids **E**
- Systemic antibiotics **E**

Miliaria rubra. Siddiqi A. In: Domino FJ, ed. 5-Minute Clinical Consult (online). Philadelphia, Lippincott Williams & Wilkins, 2012; 1–4.

For relief of pruritus, 0.1% betamethasone twice daily for 3 days may be applied over the affected area. In the event of superimposed infection, an antistaphylococcal agent such as dicloxacillin (flucloxacillin) 250 mg four times daily for 10 days may be used.

Heat illness: prickly heat. Platt M, Vicario S. In: Marx JA, ed. Rosen's Emergency Medicine: Concepts and Clinical Practice, 7th edn. Vol 2. Philadelphia, Mosby, 2009; 1887.

If a case of miliaria rubra becomes diffuse or pustular, oral erythromycin has been shown to be helpful. During the most acute phase of miliaria rubra, chlorhexidine lotion or cream can be used as an antibacterial agent, with salicylic acid 1% three times daily over small areas to aid in desquamation (not to be used in children).

Third-Line Therapies

- Anhydrous lanolin/isotretinoin **E**
- Ascorbic acid **B**
- Intramuscular steroids **E**

Miliaria profunda. Kirk JF, Wilson BB, Chun W, et al. J Am Acad Dermatol 1996; 35: 854–6.

This case report describes a 23-year-old man with miliaria profunda successfully treated with both anhydrous lanolin and isotretinoin after a poor response to topical corticosteroids. The impact of either as an individual treatment is therefore difficult to assess.

The effects of administration of ascorbic acid in experimentally induced miliaria and hypohidrosis in volunteers. Hindson TC, Worsley DE. Br J Dermatol 1969; 81: 226–7.

Miliaria and hypohidrosis were induced in 36 subjects, half of whom were given 1 g daily of ascorbic acid and half a placebo, beginning on the day of wrapping the skin with polythene occlusion. Compared with the placebo group, the ascorbic acid group developed less severe miliaria and hypohidrosis, had quicker healing of visible lesions, and had notable improvement in hypohidrosis at 1 week.

Patients presenting with miliaria while wearing flame resistant clothing in high ambient temperatures: a case series. Carter R, Garcia AM, Souhan BE. J Med Case Reports 2011; 5: 474.

Two cases of miliaria rubra are reported in military personnel wearing flame-resistant army combat uniforms (FRACU) in arid environments. Both patients received 250 mg intramuscular methylprednisolone, and one was continued on triamcinolone acetonide 0.1% cream twice daily for 1 week. Resolution was achieved; however, relapse with repeated FRACU use occurred.

Molluscum contagiosum

Anthony K. Guzman, Steven R. Cohen



Molluscum contagiosum (MC), a DNA poxvirus, is a cutaneous infection predominantly affecting children. Peak occurrence ranges from 2 to 5 years, with an estimated overall prevalence of 2.8% among children. The disease tends to occur in epidemics, characteristically targeting childcare centers, swimming pools, and schools. The characteristic lesions appear as flesh-colored, domed papules with central umbilication that may present anywhere on the body surface, including the genitalia in sexually active individuals. Affected patients are contagious and predisposed to autoinoculation; transmission to close contacts may also occur via fomite spread and skin contact. Severe, diffuse involvement may be seen in patients with immunosuppression, including human immunodeficiency virus (HIV) infection.

MANAGEMENT STRATEGY

There is no targeted antiviral therapy nor established consensus regarding the standard of care for MC. Existing treatment options demonstrate a wide range of efficacy but most are associated with pain and irritation, including destructive modalities, topical therapies, keratolytic agents, and immunomodulators. Moreover, few of these treatments have been subjected to the rigor of a placebo-controlled, randomized clinical trial. Notably, a recent Cochrane systematic review concluded that no single intervention has been shown to be convincingly effective in the treatment of MC; as such, contagion control and anticipation of the natural resolution were advised as the primary management strategy. Nonetheless, intervention may be indicated in cases associated with itch, fear of dissemination, poor cosmesis, or protracted disease. While spontaneous resolution may occur within months, some reported cases have persisted for more than 3 years.

The choice of treatment is dependent on age, immune status, number of lesions, and anatomic distribution. Since contagion control is paramount, the avoidance of communal bathing and the restricted sharing of towels and clothing may prevent the

spread of infection. Immune reconstitution, such as the initiation of antiretroviral therapy in HIV patients, is also critical to MC clearance in the immunocompromised.

In patients with limited disease, it is reasonable to consider *active non-intervention* because MC frequently resolves in months without scarring. Although effective, the utility of first-line interventions, such as *curettage* and *cryotherapy*, are diminished by pain, postinflammatory pigment alteration, and the risk of scarring. *Cantharidin*, a topical vesicant derived from the blister beetle, is frequently used by dermatologists, but there is no commercially available formulation. The efficacy of *podophyllotoxin* is supported by data from a placebo-controlled randomized trial, but its safety in young children is not definitively established.

A multitude of alternative therapeutic options have been described but there is insufficient data to support a consensus recommendation. In particular, the use of *imiquimod* remains controversial; although some small studies have suggested its effectiveness, two unpublished, large, randomized trials were not corroborative. Alternatively, *hydrogen peroxide*, *salicylic acid*, and *topical retinoids* are considered reasonable second-line treatment options.

Among the wide spectrum of third-line agents, energy-based destructive modalities (pulsed dye laser, photodynamic therapy), chemotherapy (intralesional 5-fluorouracil), immunomodulators (topical nitric oxide-releasing gel, intralesional purified protein derivatives, intralesional *Candida* antigen), and natural oils (sandalwood, Australian lemon myrtle, tea tree) have demonstrated some level of efficacy in treating MC, but supportive high-level clinical evidence is lacking. Nonetheless, these options may be considered in recalcitrant disease.

Specific Investigation

- Dermoscopy to confirm the presence of the characteristic amorphous, lobular, yellow central umbilication
 - Methylene blue smear preparation to identify molluscum bodies
 - Histopathology to identify eosinophilic intracellular inclusion bodies (Henderson–Paterson bodies)
- These investigations are only required when the diagnosis is in doubt*

First-Line Therapies

• Await spontaneous resolution	B
• Cryotherapy	B
• Curettage	B
• Topical 0.7% cantharidin	A
• Topical 0.5% podophyllotoxin	A

Time to resolution and effect on quality of life of molluscum in children in the UK: a prospective community cohort study. Olsen JR, Gallacher J, Finlay AY, et al. *Lancet Infect Dis* 2015; 15: 190–5.

In a cohort of 306 children, the mean time to complete resolution was 13.3 months; however, 29.7% of cases had not resolved by 18 months. Although most subjects reported a modest effect on quality of life (QOL), 11.0% reported a severe impact as measured by the Children's Dermatology Life Quality Index.

In immunocompetent patients, most MC lesions self-resolve without scarring.

Comparative study on the efficacy, safety and acceptability of imiquimod 5% cream versus cryotherapy for molluscum contagiosum. Al-Mutairi N, Al-Doukhi A, Al-Farag S, et al. *Pediatr Dermatol* 2010; 27: 388–94.

In a study arm of 37 subjects treated weekly with liquid nitrogen spray alone, all achieved complete cure; a total of 26 (70.3%) patients cleared after 3 weeks, and the remaining cleared after 6 weeks.

Cryotherapy of individual lesions may be performed by spraying for 10–20 seconds in two cycles; this may be repeated weekly until clearing. An alternative technique involves dipping a cotton-tipped swab in liquid nitrogen and applying to each MC lesion for 6–10 seconds. Potential adverse effects include dyschromia (hyper- or hypopigmentation) and infrequent scarring.

A prospective randomized trial comparing the efficacy and adverse effects of four recognized treatments of molluscum contagiosum in children. Hanna D, Hatami A, Powell J, et al. *Pediatr Dermatol* 2006; 23: 574–9.

A prospective randomized study comparing four common treatments in 124 children found curettage to be the most efficacious with the lowest rate of side effects (80.6% required only one treatment). However, this method may be limited by patient resistance due to pain, a significant time commitment, and the occasional requirement of local anesthesia. Potential adverse effects include atrophic scarring.

To treat molluscum contagiosum or not-curettage: an effective, well-accepted treatment modality. Harel A, Kutz AM, Hadj-Rabia S, et al. *Pediatr Dermatol* 2016; 33: 640–5.

In a single-center, retrospective review of 2022 children with MC, 1879 (92.9%) underwent curettage; 70% were cured after one treatment and 26% after two treatments. A 97% satisfaction rate was reported by patients and parents.

Safety and efficacy of topical cantharidin for the treatment of pediatric molluscum contagiosum: a prospective, randomized, double-blind, placebo-controlled pilot trial. Guzman AK, Schairer DO, Garelik JL, et al. *Int J Dermatol* 2018; 57: 1001–6.

In a randomized study of 94 pediatric subjects comparing cantharidin monotherapy, cantharidin with occlusion, placebo only, and placebo with occlusion, a non-statistically significant trend was demonstrated favoring lesion clearance in the intervention arms. Post-hoc analysis demonstrated a superior treatment response to cantharidin over placebo after 6 weeks (36.2% vs. 10.6% achieving complete clearance, respectively).

The use of topical 0.7% cantharidin is restricted to trained clinical providers. A wooden applicator stick may be used to apply approximately 0.01 mL of cantharidin to coat each lesion. After the solution has dried, an adhesive, transparent, water-resistant, perforated, latex-free plastic tape may be applied. Subjects are instructed to wash the treated areas with isopropyl alcohol followed by soap and water at the first sign of blistering or up to 6 hours postapplication. Treatment may be repeated every 2–4 weeks until the lesion(s) have resolved. Potential adverse effects include temporary pruritus, burning, blistering, and postinflammatory pigment alteration.

Topical 0.3% and 0.5% podophyllotoxin cream for self-treatment of molluscum contagiosum in males. A placebo-controlled, double-blind study. Syed TA, Lundin S, Ahmad M. *Dermatology* 1994; 189: 65–8.

A randomized trial of 150 male subjects evaluated 0.5% podophyllotoxin cream, 0.3% podophyllotoxin cream, or placebo

cream twice daily for 3 consecutive days per week for up to 4 weeks. The greatest cure rate (92%) was achieved in subjects receiving the 0.5% cream.

Podophyllotoxin is a topical antimitotic agent, available as a gel, solution, or cream. The safety and efficacy of this therapy has not been confirmed in young children. Potential adverse effects include pruritus, burning, erythema, and erosions.

Second-Line Therapies

• Topical 10% potassium hydroxide	A
• Topical 12% salicylic acid	B
• Topical 0.05% tretinoin	B
• Manual extrusion	D

Efficacy and safety of topical application of 15% and 10% potassium hydroxide for the treatment of Molluscum contagiosum. Teixido C, Diez O, Marsal JR, et al. *Pediatr Dermatol* 2018; 35: 336–42.

A double-blind trial randomized 53 pediatric subjects to receive topical 10% potassium hydroxide (KOH) solution, 15% KOH solution, or placebo applied daily for a maximum of 2 months. Both intervention arms achieved greater rates of complete clearance in comparison to placebo (58.8% and 64.3% vs. 18.8%, respectively). The 10% treatment was better tolerated. Adverse events included burning and stinging.

Topical therapy with salicylic gel as a treatment for molluscum contagiosum in children. Leslie KS, Dootson G, Sterling JC. *J Dermatol Treat* 2005; 16: 336–40.

A total of 114 children with MC were treated with 10% phenol monthly, 12% salicylic acid (SA) gel applied once or twice weekly, or 70% alcohol vehicle monthly. Although no significant difference was seen in the intention-to-treat analysis, among those who completed the study, those treated with SA demonstrated a greater proportion of subjects achieving complete clearance (87.5%). The treatment in all groups was well tolerated or acceptable in 93% of children.

Comparative study of 5% potassium hydroxide solution versus 0.05% tretinoin cream for molluscum contagiosum in children. Rajouria EA, Amatya A, Karn D. *Kathmandu Univ Med J* 2011; 9: 291–4.

In a randomized trial, 50 children were treated with either 5% KOH solution or 0.05% tretinoin cream nightly. Both treatments were effective in reducing the lesion count, but a greater number of lesions resolved within 4 weeks among those treated with KOH.

Limited data suggests the effectiveness of topical retinoids, such as tretinoin and adapalene, for MC. The treatment may be initiated at alternate day dosing and increased to twice daily as tolerated. Adverse effects include erythema, dryness, and irritation.

Molluscum contagiosum in Greek children: a case series. Kakourou T, Zachariades A, Anastasiou T, et al. *Int J Dermatol* 2005; 44: 221–3.

A retrospective review of 110 pediatric subjects demonstrated a 70% cure rate after one session of manual MC extrusion with sterilized tweezers; the remainder cleared within 1–2 additional treatments. No patients experienced secondary infection or scarring.

Alternatively, MC lesions may be extruded with an ear speculum, angled forceps, or by hand.

Third-Line Therapies

Physical destruction

- Pulsed dye laser D
- Photodynamic therapy D
- Intralesional 5-fluorouracil E

Topical therapy

- 5% imiquimod A
- 12% nitric oxide-releasing gel A
- 6–12% glycolic acid D
- East Indian sandalwood oil C
- 1.8% hydrogen peroxide solution B
- 2% povidone-iodine D
- Australian lemon myrtle oil C
- Local hyperthermia B
- 75% tea tree oil with organically bound iodine C

Systemic therapy

- Subcutaneous dupilumab E
- Intralesional *Candida* antigen D
- Intralesional tuberculin purified protein derivatives (PPD) B
- Interferon- α E

Effectiveness of imiquimod cream 5% for treating childhood molluscum contagiosum in a double-blind, randomized pilot trial. Theos AU, Cummins R, Silverberg NB, et al. *Cutis* 2004; 74: 134.

In a small, randomized clinical trial, a greater proportion of pediatric subjects achieved partial clearance after 12 weeks of imiquimod treatment than those receiving placebo (67% vs. 18%, respectively). The mean percentage change in lesion count at week 12 was -46% in the imiquimod group and +27% in the vehicle group.

The use of imiquimod in MC is controversial. Two large, unpublished randomized trials failed to demonstrate improved lesion clearance over placebo. Furthermore, a comparative trial demonstrated no superiority over cryotherapy. Spontaneous resolution may account for the efficacy described in previous uncontrolled studies.

Efficacy and tolerability of an investigational nitric oxide-releasing topical gel in patients with molluscum contagiosum: a randomized clinical trial. Hebert AA, Siegfried EC, Durham T, et al. *J Am Acad Dermatol* 2020; 82(4): 887–94.

A total of 256 pediatric subjects received topical berdazimer sodium gel coadministered with hydrogel (4% twice daily, 8% twice daily, 12% once daily, 12% twice daily) or placebo; total clearance was achieved by 13.2%, 41.0%, 41.9%, 35.1%, and 20.0%, respectively, after 12 weeks. Application site reactions included dryness, erythema, and peeling.

One-year experience with *Candida* antigen immunotherapy for warts and molluscum. Marron M, Salm C, Lyon V, et al. *Pediatr Dermatol* 2008; 25: 189–92.

A retrospective study showed that in 25 patients with MC, treatment with intralesional *Candida* antigen was associated with complete resolution in 56%, partial clearing in 28%, and no improvement in 16%.

A comparative study of topical cantharidin and intralesional PPD to treat molluscum contagiosum. Khattab FM, Nasr MM. *J Dermatolog Treat* 2019; 1–5.

A total of 40 patients were randomized to receive either topical cantharidin 0.7% solution every 2 weeks or an intralesional injection of 10IU (0.1 mL) tuberculin PPD into the largest lesion every 2 weeks. No statistically significant difference in complete clearance was demonstrated after up to 8 weeks of treatment (90% vs. 85%, respectively).

Clearance of molluscum contagiosum virus infection in patients with atopic eczema treated with dupilumab. Storan ER, Woolf RT, Smith CH, et al. *Br J Dermatol* 2019; 181: 385–6.

A case series of four adult patients with MC and concomitant atopic dermatitis demonstrated clearance of lesions within 24 weeks of initiation of dupilumab.

Glycolic acid cream for treatment of molluscum contagiosum. Dave D, Abdelmaksoud A. *Dermatol Ther* 2018; 31: e12630.

Nine patients were treated with glycolic acid cream for a maximum of 3 months or until resolution. The authors favored a 6% cream in patients $\leq$ 2 years or with periorbital involvement. If there was no sufficient response after 2 weeks, the patient was transitioned to the 12% cream. Application was discontinued when MC showed erythema or crusting. Complete resolution was seen in all subjects within 4–12 weeks.

Treatment of molluscum contagiosum with hydrogen peroxide. Schianchi R, Nazzaro G, Veraldi S. *Clin Exp Dermatol* 2018; 43: 66–7.

In an open-label study, 25 immunocompetent children received treatment with topical 1.8% hydrogen peroxide twice daily under occlusion for 3 weeks. A 37.8% reduction in lesion count in the overall cohort was noted. Complete remission was seen in three patients (14.3%) and partial remission in 18 patients (85.7%); however, in the remaining three patients (14.3%), the number of lesions increased.

Clinical evaluation of local hyperthermia at 44°C for molluscum contagiosum: pilot study with 21 patients. Gao YL, Gao XH, Qi RQ, et al. *Br J Dermatol* 2017; 176: 809–12.

In an open-label study, 21 subjects underwent weekly treatments with a patented infrared hyperthermia device, which raised the targeted skin surface to a temperature of 44°C. In total, 12 patients (57.1%) were cured by 12 weeks. Patients reported transient burning or itch.

Intralesional 5-fluorouracil to treat extensive molluscum contagiosum in an immunocompromised patient: a novel therapeutic modality. Bhattacharjee R, Kumaran MS, Vinay K. *Dermatol Ther* 2018; 31: e12658.

In a single patient with HIV infection, the authors instilled intralesional 5-fluorouracil (3–6 mg) into each lesion weekly for 8 weeks; a reduction in lesion count was noted but with residual scarring.

Molluscum contagiosum treated with dilute povidone-iodine: a series of cases. Capriotti K, Stewart K, Pelletier J, et al. *J Clin Aesthet Dermatol* 2017; 10: 41–5.

A retrospective study of 12 pediatric MC cases treated twice daily with 2% povidone-iodine gel showed complete resolution in eight patients (67%). Four patients cleared by 4 weeks and the remainder by 8 weeks. Of 115 lesions treated in the case series, 103 (89.6%) resolved.

Treatment of molluscum contagiosum with an East Indian sandalwood oil product. Haque M, Coury DL. *J Dermatolog Treat* 2018; 29: 531–3.

In an open-label trial involving 10 subjects, an East Indian sandalwood oil product was associated with complete lesion clearance in 90% of subjects within 12 weeks.

Treatment of molluscum contagiosum with the pulsed dye laser over a 28-month period. Hancox JG, Jackson J, McCagh S. *Cutis* 2003; 71: 414–6.

A retrospective study of 43 patients treated with pulsed dye laser in which all the approximately 1250 lesions treated resolved; 35% of patients had no new lesions after two treatments. No complications were associated with the procedure.

Photodynamic therapy for molluscum contagiosum infection in HIV-coinfected patients: review of 6 cases. Moiin A. *J Drugs Dermatol* 2003; 6: 637–9.

Among six adult patients with extensive MC treated with 5-aminolevulinic acid and photodynamic therapy, there was a 60–80% reduction in lesion count after 1–5 sessions.

Essential oil of Australian lemon myrtle (*Backhousia citriodora*) in the treatment of molluscum contagiosum. Burke BE, Baillie JE, Olson RD. *Biomed Pharmacother* 2004; 58: 245–7.

A solution of 10% Australian lemon myrtle oil applied for 21 days to MC resulted in a 90% reduction of lesions in 9 (56.3%) pediatric subjects. No subjects in the placebo arm met the same criteria for improvement.

Combination of essential oil of *Melaleuca alternifolia* and iodine in the treatment of molluscum contagiosum in children. Markum E, Baillie J. *J Drugs Dermatol* 2012; 11: 349–54.

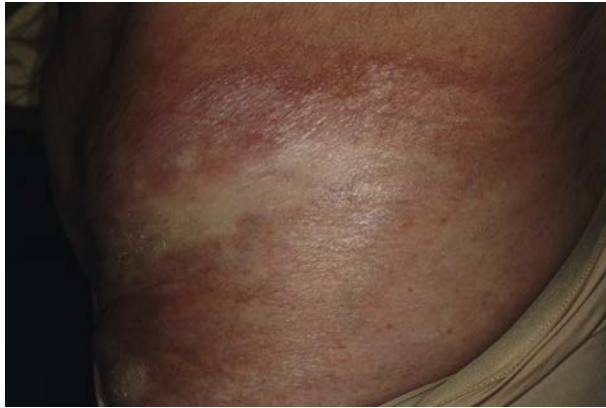
Fifty-three children were treated twice daily with essential oil of *Melaleuca alternifolia* (tea tree) alone (TTO), a combination of *Melaleuca alternifolia* and iodine (TTO-I), or iodine alone. A greater than 90% reduction in lesion count was observed in 16 subjects (84.2%) in the TTO-I arm, a significantly greater proportion than those treated with iodine (6.3%) or TTO (16.7%), respectively.

Interferon-alpha treatment of molluscum contagiosum in a patient with hyperimmunoglobulin E syndrome. Kilic SS, Kilicbay F. *Pediatrics* 2006; 117: e1253–5.

An immunodeficient patient with treatment-resistant MC was successfully treated with 3 million units subcutaneous interferon- α 3 times a week for 6 months.

Morphea

Samantha Black, Jane L. Zhu, Heidi Jacobe



Morphea, or localized scleroderma, is an autoimmune inflammatory disorder that affects the skin and soft tissue. Morphea subtype classification includes linear, generalized, circumscribed (plaque), and mixed morphea. Linear morphea is most common in children while circumscribed and generalized morphea are more common in adults. Evaluation and treatment of patients with morphea is dependent on assessment of lesion activity, damage, depth of involvement, and subtype. The goal of treatment is to abrogate active disease to stabilize and limit damage.

MANAGEMENT STRATEGY

Initial evaluation of a patient with morphea begins with a history and physical examination to determine morphea subtype, lesion activity level, depth of involvement, rate of progression, and presence of extracutaneous manifestations. The following elements of the history are of particular importance. Establishment of a clear timeline of lesion onset and progression aid in determination of activity level. Careful assessment of additional findings such as Raynaud phenomenon or acrosclerosis may distinguish morphea from systemic sclerosis (SSc). Importantly, morphea may occur concurrently with arthritis, fasciitis, and myositis, typically in the context of soft tissue lesions of linear or generalized subtype. Neurological manifestations and ocular complaints occur most often with linear head and neck lesions. Additionally, patients with linear head and neck lesions should be questioned regarding jaw or oropharynx changes. Patients with generalized morphea should be questioned regarding genital/perianal changes.

The aim of the physical exam is to confirm the diagnosis, assess disease activity and extent (body surface area and depth of involvement), and assign subtype. Lesion activity and damage can be determined by the Localized Scleroderma Cutaneous Assessment Tool (LoSCAT), a validated clinical measure for evaluating patients with morphea. Active morphea is defined by erythema, peripheral induration, and presence of new or enlarging lesions, quantified by the LoSCAT activity component. Erythema

and induration are obvious if the superficial levels of the skin and soft tissue are involved. However, deep morphea lesions involving the subcutis are difficult to assess. Palpation of the lesion may help determine depth and extent of sclerotic plaques, but MRI or ultrasound is often needed.

Inactive morphea, the sequelae of active lesions, can be quantified by the damage component of the LoSCAT and is defined by peripheral dyspigmentation, dermal or soft tissue atrophy, telangiectasias, and central sclerosis causing a yellow-white color. Lesion sclerosis is eventually replaced by dermal/subcutaneous atrophy with shiny skin, prominent vessels, and cliff-drop atrophy, or in the case of deep lesions loss of normal body contour. Hair regrowth may occur as lesions become inactive.

Importantly, only active lesions (as seen in the photograph) respond to immunosuppressives or phototherapy. Therefore, patients who exclusively have inactive lesions should receive supportive care and monitoring for reactivation. Determination of activity and damage guide treatment modalities.

SSc and morphea are distinct entities distinguishable by physical exam. Features of SSc including nailfold capillary changes, sclerodactyly, acrosclerosis, Raynaud phenomenon, and salt and pepper skin pigmentation changes are absent in morphea. Morphea patients lack the hallmark antibodies of SSc, including RNA polymerase, topoisomerase, and centromere antibodies. Presence of these physical exam findings and antibodies is concerning for SSc.

Specific Investigations

- Localized Scleroderma Cutaneous Assessment Tool (LoSCAT)
- Serial digital photography
- Ultrasound and Doppler ultrasound
- Magnetic resonance imaging (MRI)

Development of consensus treatment plans for juvenile localized scleroderma. Li SC, Torok KS, Pope E, et al. *Arthritis Care Res (Hoboken)* 2012; 64: 1175–85.

This paper outlines evaluation and treatment consensus for juvenile moderate-to-severe morphea determined by a morphea expert focus group and literature.

The Localized Scleroderma Cutaneous Assessment Tool: responsiveness to change in a pediatric clinical population. Kelsey CE, Torok KS. *J Am Acad Dermatol* 2013; 69: 214–20.

This is a validation study for the LoSCAT demonstrating that the mLoSSI, the activity measure of the LoSCAT, is a valid and responsive measure of disease activity of morphea in children.

The use of Doppler ultrasound to evaluation lesions of localized scleroderma. Li SC, Liebling MS. *Curr Rheumatol Rep* 2009; 11: 205–11.

Disease-related structural changes, such as tissue thickening, atrophy, and architectural alterations, can be readily detected using ultrasound. High spatial resolution enables monitoring of changes in tissue thickness over the course of the disease and treatment.

MRI findings in deep and generalized morphea (localized scleroderma). Horger M, Fierlbeck G, Kuemmerle-Deschner J, et al. *Am J Roentgenol* 2008; 190: 32–9.

This paper describes MRI findings in morphea and provides images. MRI allows for establishment of the depth of involvement and degree of activity based on signal intensity.

First-Line Therapies

Extensive dermal lesions

- Phototherapy: BB-UVA, NB-UVB, UVA1 **A**

Moderate-to-severe morphea/deep involvement

- Methotrexate + IV corticosteroids **A**
- Methotrexate + oral steroids **A**

Limited dermal lesions

- Topical tacrolimus under occlusion **B**
- Intralesional steroids **B**
- High-potency topical steroids **B**

A systematic review of morphea treatments and therapeutic algorithm. Zwischenberger BA, Jacobe HT. *J Am Acad Dermatol* 2011; 65: 925–41.

An evaluation and treatment algorithm are proposed for all types of morphea based on current literature and expert opinion.

A review of treatment options for morphea based on disease activity, damage, depth of involvement, and disease extent. Florez-Pollack S, Kunzler E, Jacobe HT. *Clin Dermatol* 2018; 36(4): 475–86.

The authors of this article outline treatment options for active vs. inactive morphea. They also discuss therapies to improve function limitation caused by disease damage.

Update on morphea part II. Outcome measures and treatment. Fett N, Werth VP. *J Am Acad Dermatol* 2011; 64: 231–42.

The authors discuss outcome measures and treatment options and provide algorithms for treatment of generalized, linear, and limited plaque morphea.

A randomized controlled study of low-dose UVA1, medium-dose UVA1, and narrowband UVB phototherapy in the treatment of localized scleroderma. Kreuter A, Hyun J, Stucker M, et al. *J Am Acad Dermatol* 2006; 54: 440–7.

Low- and medium-dose UVA1 (20 and 50J/cm²) were compared with narrowband (NB) UVB in a randomized trial. All patients showed a significant decrease in skin scores. Medium-dose UVA1 had a significantly greater decrease compared with NB-UVB; there were no differences between low-dose UVA1 and NB-UVB.

Medium-dose is more effective than low-dose ultraviolet A1 phototherapy for localized scleroderma as shown by 20-MHz ultrasound assessment. Sator PG, Radakovic S, Schulmeister K, et al. *J Am Acad Dermatol* 2009; 60: 786–91.

Ultrasound-measured dermal thickness was the primary outcome measure in this randomized controlled trial comparing low dose (20J/cm²) and high dose (70J/cm²). High doses decreased dermal thickness measured by ultrasound without a significant difference in clinical score.

Different low doses of broad-band UVA in treatment of morphea and systemic sclerosis. El-Mofty M, Mostafa W,

El-Darouty M, et al. *Photodermatol Photoimmunol Photomed* 2004; 20: 148–56.

Sixty-three patients with both progressive systemic sclerosis and morphea were treated with various doses of UVA without psoralen. Results were similar between 5, 10, and 20J/cm². This offers a more widely available alternative to UVA1.

Methotrexate treatment in juvenile localized scleroderma: a randomized, double-blinded, placebo-controlled trial. Zulian F, Martini G, Vallongo C, et al. *Arthritis Rheum* 2011; 63: 1998–2006.

Seventy patients were randomized to receive oral methotrexate (15mg/m², maximum 20mg) or placebo once weekly for 12 months. Both groups received oral prednisone (1mg/kg/day, maximum 50mg) for the first 3 months. Using a composite outcome measure, the methotrexate treatment group had a higher rate of remission and less recurrence.

Pulsed high-dose corticosteroids combined with low-dose methotrexate in severe localized scleroderma. Kreuter A, Gambichler T, Breuckmann F, et al. *Arch Dermatol* 2005; 141: 847–52.

Methotrexate 15mg/week plus intravenous methylprednisolone 100mg/day for 3 days per month was administered to 15 adults. Fourteen of 15 improved with no correlation between disease duration and treatment response.

Localized scleroderma: response to occlusive treatment with tacrolimus ointment. Mancoso G, Berdondini RM. *Br J Dermatol* 2005; 152: 180–2.

Tacrolimus 0.1% ointment was applied twice daily to a targeted plaque and occluded. This was compared to petrolatum in seven adults. There was resolution of early inflammatory lesions softening of late sclerotic lesions softened with no improvement of atrophy and scarring.

Efficacy of topical tacrolimus 0.1% in active plaque morphea: randomized, double-blind, emollient-controlled pilot study. Kroft EB, Groeneveld TJ, Seyger MM, et al. *Am J Clin Dermatol* 2009; 10: 181–7.

In this randomized, double-blind, emollient-controlled study of 10 patients with active plaque morphea, the authors concluded that topical tacrolimus applied twice a day for 12 weeks effectively decreases skin thickness, dyspigmentation, erythema, telangiectasia, and atrophy.

Second-Line Therapies

Extensive dermal lesions

- Psoralen and ultraviolet light (PUVA) (bath or cream) **B**

Moderate-to-severe morphea

- Mycophenolate mofetil **B**

Limited dermal lesions

- Imiquimod **C**
- Calcipotriene under occlusion **C**
- Calcipotriol–betamethasone **C**
- Pirfenidone 8% gel **D**

UVA/UVA1 phototherapy and PUVA photochemotherapy in connective tissue disease and related disorders: a research

based review. Breuckmann F, Gambichler T, Altmeyer P, et al. BMC Dermatol 2004; 4: 11.

These authors systematically review the literature on UVA/ UVA1 and PUVA therapy in various skin conditions, including morphea, and conclude that significant softening of the skin occurs with all modalities used.

Successful treatment of severe or methotrexate-resistant juvenile localized scleroderma with mycophenolate mofetil. Martini G, Ramanan AV, Falcini F, et al. Rheumatology (Oxford) 2009; 48: 1410–3.

Ten children with morphea already taking methotrexate and systemic steroids with limited improvement had mycophenolate mofetil added to their treatment. Nine of the 10 patients reported improvement.

Evaluation of the effectiveness and tolerability of mycophenolate mofetil and mycophenolic acid for the treatment of morphea. Arthur M, Fett NM, Latour E, et al. JAMA Dermatol 2020; 156(5): 521–8.

The effectiveness of mycophenolate for the treatment of morphea has recently been studied. In this retrospective cohort study, 77 patients were treated with mycophenolate. Of these patients, 12 received mycophenolate as initial monotherapy or combination therapy while 65 received mycophenolate after their disease was recalcitrant to prior therapy. After 3–6 months of treatment, 66 patients had stable or improved disease. After 9–12 months, 47 patients had stable or improved disease. At the conclusion of the study, 27 patients achieved disease remission.

First case series on the use of calcipotriol-betamethasone dipropionate for morphea. Dytoc MT, Kossintseva I, Ting PT. Br J Dermatol 2007; 157: 615–8.

Calcipotriol in combination with betamethasone dipropionate was reported to have efficacy in the treatment of morphea in a prospective study of six patients with plaque morphea.

Topical calcipotriene for morphea/linear scleroderma. Cunningham BB, Landells ID, Langman C, et al. J Am Acad Dermatol 1998; 39: 211–5.

Uncontrolled trial evaluated topical calcipotriene 0.005% ointment applied under occlusion to active target lesions twice daily. All 12 patients showed significant decrease in subjective/clinical sclerosis scales.

First case series on the use of imiquimod for morphea. Dytoc M, Ting PT, Man J, et al. Br J Dermatol 2005; 153: 815–20.

The authors used 5% imiquimod cream, an inducer of interferon- γ known to inhibit TGF- β , to treat 12 patients.

Dyspigmentation, induration, and erythema improved. The histology of the skin showed a reduction of dermal thickness.

Third-Line Therapies

• Tofacitinib	E
• Abatacept	D

Combining UVA therapy with systemic immunosuppressives to treat progressive diffuse morphoea. Rose RF, Goodfield MJ. Clin Exp Dermatol 2005; 30: 226–8.

The authors discuss the various treatments used in morphea and comment that combination therapies may hold promise. Of note, ciclosporin and mycophenolate should not be used in combination with PUVA due to risk of photocarcinogenesis.

Case reports describe the successful use of tofacitinib in patients with generalized deep morphea that did not respond to first-line therapy. Kim SR, Charos A, Damsky W, et al. JAAD Case Rep 2018.

Multiple case reports have described improvement in cutaneous induration and joint range of motion in patients taking tofacitinib after failing first-line therapies.

Early- and late-stage morphea subtypes with deep tissue involvement is treatable with Abatacept (Orencia). Adeeb F, Anjum S, Hodnett P, et al. Semin Arthritis Rheum 2017; 46(6): 775–81.

Three patients with deep morphea were involved in this open-label study of abatacept. Patients were started on abatacept (10 mg/kg) intravenously along with oral prednisone at a tapered dose for 6 months. All patients had significant improvement in modified Rodnan skin scores and MRI, which showed reduced fibrosis after treatment.

Changes in disease activity and damage over time in patients with morphea. O'Brien J.C, Nymeyer H, Green A, Jacobe HT. JAMA Dermatol 2020; 156(5): 513–520.

This prospective study involved 130 adults and children with morphea who received standard of care treatment. Levels of disease activity and damage were measured by the LoSCAT. This study found that disease activity significantly improved after 6–12 months of standard treatment. Contrastingly, sclerosis improved at a slower rate with significant improvement seen after 2–5 years, often occurring after treatment was discontinued. Skin atrophy increased as presence of sclerosis decreased. The authors concluded that standard-of-care therapy produces improvement in disease activity and sclerosis with stability of additional disease damage features.

Mucocele

Joshua Schimmel, Warren R. Heymann



Oral mucocoeles fall into two categories: the mucous extravasation cyst and the mucous retention cyst. The mucous extravasation cyst describes a false cyst because the mucous extravasation cyst lacks an epithelial lining arising from the partially or totally severed salivary gland duct, resulting in the accumulation of saliva in the adjacent soft tissue. At this point, the mucocoele is cut off by a fibrous connective tissue pseudocapsule. Ductal epithelium lines the mucous retention cyst. The mucous retention cyst develops from partial obstruction of a duct in the presence of the salivary gland's continued mucus secretion. The extravasation mucocoele manifests most commonly, and on the young person's lower lip. The retention mucocoele is more likely to occur on the buccal cheek or soft palate of an older patient. Despite differences in etiology, extravasation mucocoeles and retention mucocoeles tend to respond similarly to treatment.

Mucous extravasation cysts arise from trauma to salivary gland ducts. This trauma leads to the rupture of ducts and leakage of mucin from the minor salivary glands. The mucin subsequently forms pseudocystic aggregations, most commonly on the lower lip. These aggregations are referred to as *mucocele*s. Mucocele manifests with a variety of tones and colors ranging from flesh to red to translucent blue. The shape of mucocele is round or oval, and their surface is smooth. They usually possess a soft, fluctuant, or gel-like consistency. Single or multiple mucocele can manifest and can range from 0.1 to 2 cm in diameter. A variant of a mucocele termed *superficial mucocele* can manifest on the palate, retromolar pad, and posterior buccal mucosa as single or multiple vesicles, which can ulcerate. Despite healing after a few days, superficial mucocele often recur in the same location. A mucocele is termed a *ranula* when on the floor of the mouth, and an *epulis* when on the gums.

MANAGEMENT STRATEGY

The natural history of mucocele can involve their expansion and periodic rupture, and sometimes spontaneous resolution. For small, superficial mucocele clinicians may opt to just observe the lesions, as they often resolve without treatment. There is some morbidity associated with mucocele ranging from discomfort

to suboptimal cosmetic appearance of a nodule with a hardened consistency due to scarring and tissue consolidation.

A clinical diagnosis can be supported, when necessary, by histology, ultrasound imaging, and mucoscopy. Providers should consider human immunodeficiency virus (HIV) testing in at-risk patients as both simple and plunging type ranula are more common in HIV-positive patients.

A range of surgical and other techniques can be employed for the treatment of mucocele. First-line therapies include cryotherapy, intralesional corticosteroids, and sclerotherapy; these procedures are minimally invasive, cause minimal discomfort, and have high clinical success rates. However, these therapies often require multiple treatments to completely clear the lesion. Punch biopsy may be considered as second-line therapy for small mucocele on the buccal mucosa, labial mucosa, floor of the mouth, anterior one-third of the tongue, and gingiva. It has the added benefit of confirming the diagnosis on histology, but there is an increased risk of scarring, swelling, and bleeding. Third-line therapies include CO₂ and non-ablative lasers, surgical excision, marsupialization, and microwave ablation. These therapies have high clinical success rates but are significantly more expensive and result in higher morbidity than first- and second-line therapies. Microwave ablation, micromarsupialization, and laser treatments are less invasive and more efficient than surgical excision, and thus may be more suitable for children or patients who cannot tolerate long procedures. Recurrence rates are similar between surgical excision and laser treatments; however, there is limited data on recurrence among other treatment modalities. Recurrence is higher in younger patients and lesions located on the ventral surface of the tongue – clinicians may consider close follow-up in these cases.

Specific Investigations

- Biopsy
- Doppler ultrasonography
- Color Doppler imaging
- Mucoscopy
- HIV testing

Mucoscopy of mucocele. Kaur I, Jakhar D, Anand P. Indian Dermatol Online J 2019; 10: 358–9.

Dermoscopy of mucocele reveals a shiny surface, with an extensive network of linear and branched vessels and intervening white structureless areas. In comparison, mucoscopy of healthy mucosa reveals linear and serpentine vessels and the absence of white structureless areas.

Oral mucocele/ranula: Another human immunodeficiency virus-related salivary gland disease? Syebele K, Munzhelele T. Laryngoscope 2015; 125: 1130–6.

HIV-positive patients are significantly more likely to present with simple and plunging type ranula compared with uninfected patients.

First-Line Therapies

• Intralesional sclerotherapy	C
• Cryotherapy	C
• Intralesional corticosteroids	C
• Observation	

The efficacy of polidocanol sclerotherapy in mucocele of the minor salivary gland. Liu J, Zhang A, Jiang L, et al. J Oral Pathol Med 2018; 47: 895–9.

In this study, 122 cases of mucocele of the minor salivary gland were treated with polidocanol sclerotherapy. Of these, 102 cases were cured and 10 had partial remission, resulting in a total cure rate of 91.07%. There were no recurrences and no severe side effects during or after treatment. Treatment of mucocèles on the lower lip was more successful than on the inferior surface of the lingual apex.

Nitrous oxide cryotherapy for the management of benign lesions of the oral cavity. Farah C, Koelmeyer N, Kaney A, et al. *J Oral Pathol Med* 2019; 48: 611–8.

This retrospective study of 12 patients with oral mucocèles found a 100% success rate in mucocele resolution using a closed nitrous oxide cryotherapy system. Two of the 12 patients healed with asymptomatic submucosal fibrosis; there were no other complications. Increased lesion diameter corresponded with an increased number of treatments and cumulative freeze time. Recurrence was not evaluated.

Nonsurgical management of oral mucocele by intralesional corticosteroid therapy. Sinha R, Sarkar S, Khaitan T, et al. *Int J Dent* 2016; 2016: 2896748.

Twenty cases of clinically diagnosed oral mucocèles were treated with a 1 mL intralesional injection of betamethasone (4 mg/1 mL) at weekly intervals; 18 cases showed complete regression at 1 month, and the other two cases showed a decrease in size. There were no postprocedural complications besides minimal pain. There were no cases of recurrence at 6 months.

Clinical characteristics, treatment, and evolution of 89 mucocèles in children. Mínguez-Martínez I, Bonet-Coloma C, Ata-Ali-Mahmud J, et al. *J Oral Maxillofac Surg* 2010; 68: 2468–71.

In a series of 89 cases, mucocèles were more commonly located on the lower lip; 43.8% resolved spontaneously, and 8% of the surgically removed mucocèles reappeared.

Second-Line Therapy

- Punch biopsy

E

Practical pearls for oral procedures. Parastoo D, Fazel N. *Clin Dermatol* 2016; 34: 440–8.

Punch biopsy is useful for lesions on the buccal mucosa, labial mucosa, floor of the mouth, anterior one-third of the tongue, and gingiva.

Third-Line Therapies

- CO₂ laser
- Surgical excision
- Micromarsupialization
- Microwave ablation
- Marsupialization
- Non-ablative lasers

B

B

B

C

D

E

Treatment of mucocele of the lower lip with carbon dioxide laser. Huang IY, Chen CM, Kao YH, et al. *J Oral Maxillofac Surg* 2007; 65: 855–8.

Eighty-two patients with biopsy-confirmed mucocele of the lower lip were treated with CO₂ laser vaporization with no bleeding and minimal scar formation. There were two recurrences. Researchers noted mild discomfort and rare complications. At the operative site, one patient felt temporary numbness. Due to the fact that the operative time is shorter than for excision, carbon dioxide laser appears useful for children and for less cooperative patients.

Micro-marsupialization versus surgical excision for the treatment of mucocèles. Giraddi G, Saifi A. *Ann Maxillofac Surg* 2016; 6: 204–9.

Twenty patients with mucocèles were randomly divided into two groups: surgical excision vs. micromarsupialization. There were two cases of recurrence in the group treated with micromarsupialization and one case in the surgical excision group; this difference was not statistically significant. The authors concluded that micromarsupialization appears to be as effective and less invasive than surgical excision for the treatment of oral mucocèles.

Microwave ablation: a novel treatment for the mucocèles of anterior lingual salivary glands. Feng H, Wang S, Liu Y, et al. *J Oral Maxillofac Surg* 2017; 75: 530–5.

Seventy-eight patients with mucocele of the anterior lingual salivary gland were treated with microwave ablation. Sixty-nine (88.5%) patients had complete regression after one treatment and nine developed recurrences that ultimately resolved on their own or after a second treatment. Microwave ablation is minimally invasive, efficient, and economical when compared with surgical excision, making it particularly suitable for children and other patients who cannot tolerate long procedures.

Treating mucocele in pediatric patients using a diode laser: three case reports. Bagher S, Sulimany A, Kaplan M, et al. *Dent J* 2018; 6: 1–6.

Three cases of mucocèles in children treated using a diode laser with a wavelength of 930 nm. In all three cases there was minimal scarring and pain and no evidence of recurrence. Diode lasers are an effective and simple procedure with minimal complications in the treatment of mucocèles and may be particularly useful in the pediatric population.

Identification of predictive variables for the recurrence of oral mucocele. Choi B, Byun J, Choi J, et al. *Med Oral Patol Cir Bucal* 2019; 24: 231–5.

Oral mucocele recurrence was significantly higher in younger patients (<30) and on the ventral mucosa of the tongue compared with the labial/buccal mucosa. There was no difference in recurrence rates between surgical and laser treatments.

Mucous membrane pemphigoid

Catherine Prost



Mucous membrane pemphigoid (MMP), formerly called cicatricial pemphigoid (CP), is a heterogeneous group of chronic, acquired, autoimmune, subepidermal blistering diseases, with autoantibodies targeting different autoantigens. It is characterized by blistering and erosions of one or more mucous membranes (eyes, oral mucosa, esophagus, genitals) and, to a lesser extent, the skin. Disease severity varies, ranging from mild disease with few gingival lesions, to severe disease affecting multiple mucosal surfaces. Mucosal lesions tend to heal with scarring, and may result in severe and life-threatening complications of the affected areas.

MANAGEMENT STRATEGY

MMP is a chronic disease that does not remit spontaneously. The aim of treatment is to stop the inflammation and hereby the progression of scarring, especially of the eyes, larynx, esophagus, and genital mucous membranes. So, the management of MMP requires a multidisciplinary team. Treatment of MMP is not curative. A maintenance treatment with reduced doses is necessary to avoid relapses.

Optimal treatment for MMP is unclear as there is little evidence in the form of randomized control trials. Management strategy in MMP is mainly based on an international consensus of experts, the evidence described in a Cochrane review, and its recent update. However, new insights regarding diagnosis and therapeutic options are emerging.

The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment and prognostic indicators. Chan LS, Ahmed AR, Anhalt GJ, et al. Arch Dermatol 2002; 138: 370–9.

Interventions for mucous membrane pemphigoid and epidermolysis bullosa acquisita. Kirtshig G, Murrell D, Wojnarowska F, Khumalo N. Cochrane Database Syst Rev 2003; CD004056.

World Workshop on Oral Medicine VI: a systematic review of the treatment of mucous membrane pemphigoid. Taylor J, McMillan R, Shephard M, et al. Oral Surg Oral Med Oral Pathol Oral Radiol 2015; 120: 161–71. e20.

Treatment strategy is based on the site, severity, extent, and rate of progression of disease. Disease severity varies, ranging from mild disease with few gingival lesions, to severe disease affecting multiple mucosal surfaces.

Specific Investigations

For diagnosis

- Perilesional mucosa and/or skin biopsy for direct immunofluorescence (IF) and/or immunoelectron microscopy. Serration pattern analysis in any skin biopsy
- Detection of serological autoantibodies by indirect IF microscopy on human/primate salt-split skin, indirect IF microscopy on recombinant laminin 332 or type VII collagen-NC1- expressing human cells (BIOCHIP mosaics), enzyme-linked immunosorbent assays (ELISAs), and/or immunoblotting

For outcome measurements

- Screening by an ophthalmologist and otolaryngologist at baseline, and during follow-up in case of clinical symptoms
- Scoring inflammatory and scarring lesions (e.g., Mucous Membrane Pemphigoid Disease Area Index [MMPDAI])

For treatment

- Glucose 6 phosphate dehydrogenase (G6PD) activity before dapsone use
- Thiopurine methyltransferase (TPMT) before azathioprine use

Pemphigoid diseases. Schmidt E, Zillikens D. Lancet 2013; 381(9863): 320–32.

A sensitive and specific assay for the serological diagnosis of antilaminin 332 mucous membrane pemphigoid. Goletz S, Prost C, Komorowski L, et al. Br J Dermatol 2019; 180: 149–56.

Six different target antigens of autoantibodies in MMP sera have been identified: BP180, BP230, all three laminin 332 subunits, both subunits of integrin $\alpha 6 \beta 4$, and type VII collagen. Currently four assays are commercially available; they allow the detection of autoantibodies against (1) BP180-NC16A epitope; (2) BP230 (C- and N-terminal parts); (3) the laminin 332 heterotrimer; and (4) type VII collagen (NC1 $\pm$ NC2 domains).

Introducing a novel Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) in pemphigus. Pfützte M, Niedermeier A, Hertl M, et al. Eur J Dermatol 2007; 17: 4–11.

Definitions and outcome measures for mucous membrane pemphigoid: recommendations of an international panel of experts. Murrell DF, Marinovic B, Caux F, et al. J Am Acad Dermatol 2015; 72: 168–74.

Validation of a clinical assessment tool for cicatrizing conjunctivitis. Ong HS, Minassian D, Rauz S, et al. Ocul Surf 2020; 18: 121–9.

Validation of an Oral Disease Severity Score (ODSS) tool for use in oral mucous membrane pemphigoid. Ormond M, McParland H, Thakrar P, et al. *Br J Dermatol* 2020; 183: 78–85.

MMPDAI is a disease-specific severity scoring tool; however, ABSIS is not disease specific. ODSS is an oral mucosal disease severity scoring tool. Both MMPDAI and ABSIS have not been globally validated but their oral part and the ODSS have been validated as disease severity scoring tools in oral aspects of MMP. The score of Ong is a clinical assessment tool for cicatrizing conjunctivitis. It has been validated.

First-Line Therapies

• Topical corticosteroids	C
• Dapsone	C
• Methotrexate	C
• Tetracyclines	D
• Cyclophosphamide	C
• Systemic corticosteroids	C

Double-blind clinical trial of 0.05% clobetasol propionate ointment in orabase and 0.05% fluocinonide ointment in orabase in the treatment of patients with oral vesiculoerosive diseases. Lozada-Nur F, Miranda CM, Maliksi R. *Oral Surg Oral Med Oral Pathol* 1994; 77(6): 598–604.

Treatment of severe erosive gingival lesions by topical application of clobetasol propionate in custom trays. Gonzales-Moles MA, Ruiz Avila I, Rodríguez-Archilla A, et al. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodont* 2003; 95: 688–92.

Improvement in all 22 patients with oral MMP treated with topical clobetasol propionate applied via a gingival tray.

Topical corticosteroids alone may be considered as first-line therapy for mild MMP affecting a single site. They can be used as gels, ointments, or lozenges or in mouth-rinses, 1–4 times daily, as long as needed to suppress the disease. Superpotent corticosteroid ointments can be applied directly, mixed with Orabase, or using a gingival tray to allow more prolonged contact with the oral mucosae. Topical corticosteroids are more often used in addition to systemic therapy.

Cicatricial pemphigoid. Foster CS. *Trans Am Ophthalmol Soc* 1986; 84: 527–663.

Report of the author's experience in 130 patients with CP, including two randomized, double-masked clinical trials. The first compared dapsone with cyclophosphamide (CyP) and the second compared CyP with prednisone versus prednisone alone, both in the treatment of severe CP with ocular ± extraocular involvement. Fourteen (70%) of the 20 patients receiving dapsone (2 mg/kg/day) responded to treatment within 4 weeks.

Dapsone therapy of cicatricial pemphigoid. Rogers RS III, Mehregan DA. *Semin Dermatol* 1988; 7: 201–5.

Seventy-seven patients with oral, ocular, or generalized MMP benefited from either 150 mg dapsone per day or 1500–3000 mg sulfapyridine per day for at least 12 weeks.

The management of oral mucous membrane pemphigoid with dapsone and topical corticosteroid. Arash A, Shirin L. *J Oral Pathol Med* 2008; 37: 341–4.

Five patients with mild MMP had a good response to triamcinolone in Orabase while 15 had a significant response to topical corticosteroids and dapsone 25 to 100 mg daily. Ten of these 15 had complete resolution.

Dapsone efficacy and adverse events in the management of mucous membrane pemphigoid. Hegarty AM, Ormond M, Sweeney M, et al. *Eur J Dermatol* 2010; 20: 223–4.

Eight out of 20 patients improved with dapsone. One failed to respond, and 11 developed side effects necessitating cessation.

Sulphamethoxypyridazine for dermatitis herpetiformis, linear IgA disease and cicatricial pemphigoid. McFadden JP, Leonard JN, Powles AV, et al. *Br J Dermatol* 1989; 121: 759–62.

Sulfamethoxypyridazine 500–1500 mg was partially effective in 10 of 15 patients with oral and generalized MMP.

Sulphapyridine—a new agent for the treatment of ocular cicatricial pemphigoid. Elder MJ, Leonard J, Dart JK. *Br J Ophthalmol* 1996; 80: 549–52.

Prospective, single-armed, unmasked clinical trial. Twenty consecutive patients with moderate or marked conjunctival inflammation due to ocular CP (OCP) were treated with oral sulphapyridine 500 mg twice daily. A successful reduction in inflammation was recorded in 10/20 patients (50%), within 1 month in 64%, and in all by 2 months.

Treatment of ocular cicatricial pemphigoid with sulfasalazine. Doan S, Lerouic JF, Robin H, et al. *Ophthalmology* 2001; 108: 1565–68.

Nine patients with OCP and previous dapsone-related adverse effects were treated with oral sulfasalazine (median dosage 3 g, range 1–4). At the initiation of sulfasalazine therapy, ocular inflammation was controlled in all patients but one. Mean follow-up was 12 months (range 2–35). The disease remained controlled with sulfasalazine alone in four patients (45%).

Dapsone, at a dosage of 1–2 mg/kg/day, alone or in combination with topical corticosteroids, is regarded as first-line treatment for mild-to-moderate MMP.

Oral sulphonamides may be considered as first-line agents in mild-to-moderate MMP patients *when dapsone is contraindicated or poorly tolerated*.

Antiepileptic cicatricial pemphigoid of the larynx successfully treated with a combination of tetracycline and niacinamide. Sakamoto K, Mori K, Hashimoto T, et al. *Arch Otolaryngol Head Neck Surg* 2002; 128: 1420–3.

Single case report.

Successful therapy with tetracycline and nicotinamide in cicatricial pemphigoid. Kreyden OP, Borradori L, Trueb RM, et al. *Hautarzt* 2001; 52: 247–50.

Single case report.

Clinical implications of direct immunofluorescence findings in patients with ocular mucous membrane pemphigoid. Labowsky MT, Stinnett SS, Liss J, et al. *Am J Ophthalmol* 2017; 183: 48–55.

In a cohort of 55 patients of whom 74% had a positive direct IE, 73% were prescribed doxycycline.

Tetracycline (1500 mg/day) or doxycycline (100 mg/day) may be considered as a first-line treatment in mild-to-moderate MMP. Note that use of minocycline *has been discontinued due to* severe adverse reactions. Nicotinamide (500–3000 mg/day) may confer additional protection.

Methotrexate therapy for ocular cicatricial pemphigoid. McCluskey P, Chang JH, Singh R, et al. *Ophthalmology* 2004; 111: 796–801.

Methotrexate (MTX) at an initial single weekly dose of 5–15 mg led to complete control and/or suppression of conjunctival inflammation and prevented progression of scarring in 15 of 17 patients, with side effects requiring cessation of MTX therapy in 24% of them.

Efficacy and adverse reactions of methotrexate in the treatment of ocular cicatricial pemphigoid: a case series study. Shi Y, Xie C, He Y, et al. *Medicine (Baltimore)* 2018; 97: e12338.

In a retrospective, non-controlled, case series study involving 11 patients with severe OCP, Shi et al. demonstrated that low-dose MTX improved visual acuity in three patients.

MTX 5–25 mg/week may be considered as the first-line systemic monotherapy agent in the treatment of mild-to-moderate ocular MMP.

Cicatricial pemphigoid. Foster CS. *Trans Am Ophthalmol Soc* 1986; 84: 527–663.

Randomized, double-masked clinical trials in the treatment of severe CP with ocular ± extraocular involvement (see earlier). The first compared dapsone with CyP and the second compared CyP with prednisone vs. prednisone alone. All 20 patients treated by CyP alone (2 mg/kg/day) responded to treatment (abolition of inflammation and no evidence of conjunctival scarring throughout the 6 months of follow-up). The 12 patients treated by CyP (2 mg/kg/day for 6 months) and prednisone (initial dose 1 mg/kg/day gradually reduced until stopping in 3 months) achieved complete remission in 4–8 weeks and none relapsed after stopping prednisone.

Role of cyclophosphamide and high dose steroid in ocular cicatricial pemphigoid. Elder MJ, Lightman S, Dart JK. *Br J Ophthalmol* 1995; 79: 264–6.

Prospective unmasked study. Ten consecutive patients (19 eyes) were treated with oral CyP (initial dose 1.5–2 mg/kg/day – maintenance dose 50–150 mg/day for more than 6 months in all patients but one) and oral prednisolone (initial dose 60–80 mg/day, mean total duration of 4–8 months). The inflammation resolved in 15 eyes in a mean time of 2.4 months but progressive cicatrization occurred in 21%.

Management of ocular mucous membrane pemphigoid with immunosuppressive therapy. Thorne JE, Woreta FA, Jabs JA, et al. *Ophthalmology* 2008; 115: 2146–52.

Retrospective cohort study. Of 44 patients treated with CyP (2 mg/kg/day) and prednisolone (initially 1 mg/kg/day tapering over 1–2 months), 40 achieved remission within 2 years; five subsequently relapsed.

Cyclophosphamide for ocular inflammatory diseases. Pujari SS, Kempen JH, Newcomb CW, et al. *Ophthalmology* 2010; 117: 356–65.

Retrospective cohort study of 98 patients with MMP treated with CyP (75–150 mg/daily) and oral prednisolone. Forty-two patients achieved complete remission within 6 months, increasing to 67 at 1 year.

Oral cyclophosphamide without corticosteroids to treat mucous membrane pemphigoid. Munyangango EM, Le Roux-Villet C, Doan S, et al. *Br J Dermatol* 2013; 168: 381–90.

Retrospective case series of 13 patients with severe refractory MMP. Oral CyP (2 mg/kg/day) without corticosteroids was commenced on a background of previous treatments (dapsone, sulfasalazine, or topicals) in the absence of corticosteroids. Nine of 13 patients responded to treatment, with 7/13 achieving

complete remission, four of whom maintained this at 6 months after the study. Ten of 13 patients suffered lymphopenia, leading to withdrawal of CyP in 6/13.

Analysis of a novel protocol of pulsed intravenous cyclophosphamide for recalcitrant or severe ocular inflammatory disease. Suelves AM, Arcinue CA, González-Martín JM, et al. *Ophthalmology* 2013; 120: 1201–9.

Retrospective case series of 65 patients (110 eyes) of patients with ocular disease treated with pulsed intravenous CyP (starting dose 1 g/m² body surface area) in combination with methylprednisolone (1000 mg). Complete remission was achieved in 54 patients (84%).

Low-dose pulsed intravenous cyclophosphamide for severe ocular cicatricial pemphigoid in elderly patients. Friedman J, Marcovich AL, Kleinmann G, et al. *Cornea* 2014; 33: 1066–70.

Prospective unmasked case series of 13 patients with severe OCP. Monthly pulses of intravenous CyP (500 mg) were administered and adjusted according to response. Median follow-up was 32 (range 6–167) months. Three to 28 pulses were given. Remission of inflammation in both eyes was achieved in 12/13 patients. Vision improved in 5/13 patients, stabilized in another five, and worsened in three. In 4/13 patients, cicatrization progressed.

CyP, administered either orally at an initial dosage of 2 mg/kg/day or intravenously at a pulsed dosage of 500 mg monthly, showed a high rate of efficacy preventing relapses and allowing to taper corticosteroids. It is efficient both as monotherapy and in combination with corticosteroids and may be recommended as first-line treatment in severe MMP.

Cicatricial pemphigoid. Foster CS. *Trans Am Ophthalmol Soc* 1986; 84: 527–663.

Randomized, double-masked clinical trials in the treatment of severe CP with ocular ± extraocular involvement (see earlier). A complete remission was obtained only in five of the 12 patients treated by prednisone alone (initial dose 1 mg/kg/day gradually reduced over 3 months up to a maintenance dose of 0.25 mg every other day maintained for another 3 months). All five patients relapsed after stopping prednisone.

Mucous membrane pemphigoid. Treatment experience at two institutions. Lamey PJ, Rees TD, Binnie WH, et al. *Oral Surg Oral Med Oral Pathol* 1992; 74: 50–3.

Fourteen patients with oral MMP were treated with a combination of systemic and topical steroids: eight became asymptomatic, five improved, and one was unchanged.

Only one study focusing on systemic corticosteroids in monotherapy has been found. Systemic corticosteroids are usually associated in combination with dapsone, CyP (see earlier), mycophenolate mofetil (MMF), or rituximab (see later). Their side effects limit a prolonged use. Oral corticosteroids, i.e., prednisone at an initial dosage of 0.5–1 mg/kg/day tapering over the next 8–12 weeks, may be considered in combination with a steroid-sparing immunosuppressive agent.

Second-Line Therapies

• Mycophenolate mofetil	C
• Rituximab	C
• Azathioprine	C
• Ciclosporin	D

Immunosuppressive therapy for ocular mucous membrane pemphigoid strategies and outcomes. Saw VPJ, Dart JKG, Rauz S, et al. *Ophthalmology* 2008; 115: 253–61.

To evaluate the effectiveness and toxicity of a stepladder immunosuppression strategy in 115 patients, including the use of MMF and combination therapy, in the treatment of ocular MMP. The most successful therapies were based on CyP followed by MMF, azathioprine, dapsone and sulfapyridine. The most prominent side effects were with azathioprine (40%) and the least with MMF (15%).

Mycophenolate mofetil for ocular inflammation. Daniel E, Thorne JE, Newcomb CW, et al. *Am J Ophthalmol* 2010; 149: 423–32.

Retrospective cohort study of 18 patients with ocular MMP treated with MMF in combination with prednisolone. Forty-one percent achieved complete control at 6 months, increasing to 71% at 1 year; most relapsed on discontinuation of prednisolone, but the authors report a steroid-sparing effect. Doses were not specified.

Long-term results of therapy with mycophenolate mofetil in ocular mucous membrane pemphigoid. Doycheva D, Deuter C, Blumenstock G, et al. *Ocul Immunol Inflamm* 2011; 19: 431–8.

Retrospective study of 10 patients (19 eyes) with ocular MMP treated with MMF (1 g/day) with prednisolone (initially 1 mg/kg/day, tapered to 5 mg/day). Control of inflammation achieved in 58% (11/19 eyes). Progression was prevented in 47% (9/19 eyes).

Treatment of mucous membrane pemphigoid with mycophenolate mofetil. Nottage JM, Hammersmith KM, Murchison AP, et al. *Cornea* 2013; 32: 810–5.

Retrospective case series of 23 consecutive patients with ocular MMP. Sixteen patients achieved control with MMF as monotherapy, and a further three in combination with other treatments. Treatment was stopped in five patients; in four this was due to failure to obtain inflammatory control, and the fifth suffered an adverse reaction.

There is evidence that MMF at a dosage of 0.5–1 g twice daily, alone or in combination with topical/oral corticosteroids, tetracycline, or dapsone, is effective for treatment of mild-to-moderate MMP, with minimal side effects. However, the drug cannot always prevent disease progression in severe refractory cases.

Immunosuppressive therapy for ocular mucous membrane pemphigoid strategies and outcomes. Saw VP, Dart JK, Rauz S, et al. *Ophthalmology* 2008; 115: 253–61. e1.

To evaluate the effectiveness and toxicity of a stepladder immunosuppression strategy in 115 patients (see earlier). Azathioprine 1–2.5 mg/kg daily was effective in 47%. Side effects limited treatment in 40%. Control of inflammation does not necessarily prevent progression.

Azathioprine for ocular inflammatory diseases. Pasadhika S, Kempen JH, Newcomb CW, et al. *Am J Ophthalmol* 2009; 148: 500–9.

Retrospective cohort of 33 patients with ocular disease treated with azathioprine and oral prednisolone. Forty-four percent achieved control by 6 months, with 12% off prednisolone treatment. This increased to 67% controlled by 1 year, with 17% off prednisolone. Doses were not specified.

Treatment with azathioprine, at an initial dosage of 1.5–2 mg/kg/day, in combination with topical corticosteroids, tetracyclines, or dapsone, may be considered as a second-line therapy in mild-to-moderate MMP but side effects are frequent.

Cyclosporine for ocular inflammatory diseases. Kaçmaz RO, Kempen JH, Newcomb C, et al. *Ophthalmology* 2010; 117: 576–84.

Ciclosporin was minimally effective even at doses in excess of 3.5 mg/kg/day. All patients remained on corticosteroids.

Ocular autoimmune pemphigoid and cyclosporine. Alonso A, Bignone ML, Brunzini M, et al. *Allergol Immunopathol (Madr)* 2006; 34: 113–5.

Treatment-resistant ocular pemphigoid in 82 patients was treated with ciclosporin 100 mg/day, with an attendant reduction in the dose of steroids.

Ciclosporin 2–4 mg/kg/day is less widely used than other immunosuppressive agents.

Rituximab for treatment-refractory pemphigus and pemphigoid: a case series of 17 patients. Kasperkiewicz M, Shimanovich I, Ludwig RJ, et al. *J Am Acad Dermatol* 2011; 65: 552–8.

Five patients with refractory MMP were treated with rituximab. Complete remission occurred in three patients, and partial remission in the other two. No serious side effects were noted.

Rituximab for patients with refractory mucous membrane pemphigoid. Le Roux-Villet C, Prost-Squarcioni C, Alexandre M, et al. *Arch Dermatol* 2011; 147: 843–9.

Twenty-five patients with severe refractory MMP received one or two cycles of rituximab (375 mg/m² weekly for 4 weeks); complete response occurred in 22 patients and partial response in one. Twenty-one of the patients were receiving concomitant therapy with dapsone and/or sulfasalazine therapy, which was maintained during rituximab cycles. Two patients died from infectious complications; these patients also received high-dose immunosuppression for laryngeal and tracheal edema.

Rituximab combined with conventional therapy versus conventional therapy alone for the treatment of mucous membrane pemphigoid (MMP). Maley A, Warren M, Haberman I, et al. *J Am Acad Dermatol* 2016; 74: 835–40.

Retrospective review of 49 patients comparing outcomes of 24 who received rituximab (four weekly infusions of 375 mg/m² or two infusions of 1000 mg given 15 days apart) and 25 who received conventional immunosuppression. The mean total infusions of rituximab were 5.25 (range 2–16). All patients in the rituximab group achieved disease control with a mean time to disease control of 10.2 months, compared with 10 (40%) of the patients in the conventional immunosuppression group, with a mean time to disease control of 37.7 months.

Rituximab in the treatment of ocular CP: a retrospective cohort study. You C, Lamba N, Lasave AF, et al. *Graefes Arch Clin Exp Ophthalmol* 2017; 255: 1221–8.

You et al. found that 46 eyes (77.0%) in 26 MMP patients treated with rituximab (RTX) alone or in combination with other immunomodulatory treatments achieved clinical remission, with an average sustained remission time of 24.5 months.

Data from three large and several small, retrospective case series suggest that rituximab at an initial dose regimen of 375 mg/m² each week for 4 consecutive weeks or of 1000 mg given 15 days apart, alone or combined with other immunosuppressants or intravenous immunoglobulins, is effective in patients with severe, refractory MMP. The onset of adverse events, particularly severe infections, is a common concern in patients treated with RTX.

Third-Line Therapies

- Intravenous immunoglobulins
- Topical mitomycin
- Etanercept
- Infliximab
- Low-level laser
- Topical tacrolimus

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The role of intravenous immunoglobulin in treatment of mucous membrane pemphigoid: a review of literature. Tavakolpour S. *J Res Med Sci* 2016; 21: 37. doi: 10.4103/1735-1995.183992.

In this review up to September 2015, 13 studies with a total number of 70 patients with MMP who were under treatment with intravenous immunoglobulin (IVIG) were analyzed. Of the patients, 65 responded completely, one did not respond, two partially responded, and the remaining two patients stopped IVIG therapy, which resulted in OCP progression.

Management of ocular cicatricial pemphigoid with intravenous immunoglobulin monotherapy. Ma L, You C, Hernandez M, et al. *Ocul Immunol Inflamm* 2018; 1-7.

Review of all OCP patients seen between 2005 and 2015. IVIG infusion was 2g/kg/cycle administered in 3 consecutive days monthly. Of 512 OCP patients, 17 patients (34 eyes) treated with IVIG monotherapy were identified. The follow-up time ranged from 12 to 140 months. Twenty-six eyes (76.5%) achieved remission. Nine remission eyes received cataract surgeries, and two of them had relapse (22.2%).

Combination of rituximab and intravenous immunoglobulin for recalcitrant ocular cicatricial pemphigoid: a preliminary report. Foster CS, Chang PY, Ahmed AR. *Ophthalmology* 2010; 117: 861-9.

Six patients were treated with a combination of IVIG and rituximab. Disease progression was arrested in all six. A dose of 375 mg/m² of rituximab was given once weekly for 8 consecutive weeks. Thereafter, for the subsequent 4 months, it was given once monthly.

The dose of IVIG was 2 g/kg per cycle. The frequency of the IVIG was monthly until the B-cell level returned to normal. Thereafter, IVIG was continued, and the intervals between infusions were increased to 6, 8, 10, 12, 14, and 16 weeks. The last cycle was given at the 16-week interval.

Combined use of rituximab and intravenous immunoglobulin for severe autoimmune cicatricial conjunctivitis – an interventional case series. Steger B, Madhusudan S, Kaye SB, et al. *Cornea* 2016; 35: 1611-4.

Single-center, retrospective interventional case series with follow-up between 32 and 65 months. Treatment included 1-2 cycles of RTX (1000 mg twice at an interval of 2 weeks apart), and 2-9 monthly courses of IVIG (2g/kg over 3 days). In four presented cases, progression of cicatricial disease was stopped and visual acuity was stabilized in all patients. Conjunctival scarring was stabilized in two cases and continued to progress in two cases. One patient developed septicemia 6 weeks after RTX infusion.

Long-term follow-up intravenous immunoglobulin therapy in patients with severe ocular mucous membrane pemphigoid unresponsive to conventional therapy. Leuci S, Amato M, Calabria E, et al. *J Ophthalmol* 2018; 8372146.

After 9 years, all the eyes enrolled showed a long-lasting remission of ocular and oral symptoms with a significant steroid-sparing effect.

IVIG at doses 0.5-2g/day (over 3-5 days) initially, once monthly, alone or in combination with other treatments, is justified as third-line treatment in rapidly progressive or recalcitrant MMP. They seem to be effective in maintaining the clinical remission over time with limited adverse events (headache and nausea).

Treatment of recalcitrant cicatricial pemphigoid with the tumor necrosis factor alpha antagonist etanercept. Sacher C, Rubbert A, König C, et al. *J Am Acad Dermatol* 2002; 46: 113-5.

These case reports describe eight patients who responded to etanercept 50 mg/week subcutaneously, including five with ocular disease. Two patients maintained remission after cessation of the drug, and another relapsed.

Successful treatment of mucous membrane pemphigoid with infliximab. Heffernan MP, Bentley DD. *Arch Dermatol* 2006; 142: 1268-70.

Case report. Treatment comprised 5 mg/kg in weeks 0, 2, and every 8 weeks IV.

The anti-TNF agent may have a role, but evidence is limited.

Successful treatment of mucous membrane pemphigoid with tacrolimus. Suresh L, Martinex Caixto LE, et al. *Spec Care Dentist* 2006; 26: 66-70.

Case report of oral MMP: patient treated with tacrolimus ointment 0.1% TDS for 6 weeks.

Oral mucous membrane pemphigoid: complete response to topical tacrolimus. Lee HY, Blazek C, Beltraminelli H, et al. *Acta Derm Venereol* 2011; 91: 604-5.

Single case of a complete response to oral suspension of tacrolimus 0.03% in aqueous solution, twice daily as an oral rinse.

Single case reports suggest topical tacrolimus may be of benefit.

Low-level laser therapy (LLLT) for oral mucous membrane pemphigoid. Cafaro A, Brocchetto R, Arduino PG. *Lasers Med Sci* 2012; 27: 1247-50.

Three patients with oral MMP were successfully treated by LLLT (GaAlAs diode laser, 980-nm wavelength, diameter 0.6 cm, spot size 0.28 cm², output power 300 mW, 4 J/cm²) twice weekly until complete resolution of clinical signs.

Laser light may improve the symptoms of oral lesions of cicatricial pemphigoid: a case report. Oliveira PC, Reis Junior JA, Lacerda JA, et al. *Photomed Laser Surg* 2009; 27: 825-8.

Laser phototherapy (GaAlAs diode laser, 660-nm wavelength, 30 mW, continuous wave, diameter approx. 3 mm, 60 J/cm² per session) was used in association with oral prednisolone (40 mg).

Low-level laser therapy in the treatment of mucous membrane pemphigoid: a promising procedure. Yilmaz HG, Kusakci-Seker B, Bayindir H, et al. *J Periodontol* 2010; 81: 1226-30.

Single case report of patient treated with 810-nm diode laser. The lesions were treated by low-light laser therapy over a period of 7 days using a continuous waveform for 40 seconds and an energy density of 5 J/cm².

Five patients with oral disease have received treatment with low-level laser, either as an adjunct or alone, with benefit reported.

Intraoperative mitomycin C in the treatment of cicatricial obliterations of conjunctival fornices. Secchi AG, Tognon MS. Am J Ophthalmol 1996; 122: 728–30.

Intraoperative topical mitomycin (0.4 mg/mL of saline for 3–5 min) was useful in 10 eyes of five patients.

Subconjunctival mitomycin C for the treatment of ocular cicatricial pemphigoid. Donnenfeld ED, Perry HD, Wallerstein A, et al. Ophthalmology 1999; 106: 72–9.

No disease progression occurred in 8/9 eyes treated with subconjunctival mitomycin C (injections of 0.25 mL of 0.2 mg/mL).

Ocular cicatricial pemphigoid review. Foster CS, Sainz De La Maza M. Curr Opin Allergy Clin Immunol 2004; 4: 435–9.

Subconjunctival mitomycin did not prevent progression of scarring.

Intraoperative mitomycin C and amniotic membrane transplantation for fornix reconstruction in severe cicatricial ocular surface diseases. Tseng SC, Di Pascuale MA, Liu DT, et al. Ophthalmology 2005; 112: 896–903.

Intraoperative adjunction of mitomycin C during fornix reconstruction with amniotic membrane resulted in achieving a deeper fornix in 83% of patients with various cicatrizing conjunctivitis.

The benefit of mitomycin is uncertain.

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Mycetoma: eumycetoma and actinomycetoma

Mahreen Ameen, Wanda Sonia Robles



Mycetomas (Madura foot) were added to the World Health Organization list of neglected diseases in 2016 and are endemic in the tropics and subtropics. They are chronic, granulomatous, subcutaneous infections caused by either actinomycetes bacteria or eumycetes fungi, giving rise to actinomycetomas and eumycetomas, respectively. The infectious agents are saprophytes existing in soil or plants, and infection usually results from traumatic inoculation into the skin. Consequently, the disease most commonly affects agriculturalists and those who are barefoot. The disease is characterized by abscesses, draining sinuses, and discharging grains, and it slowly progresses with risks of bone and visceral involvement. The discharging grains represent aggregates of fungal hyphae or bacterial filaments. Actinomycetomas are produced by agents of the genera *Nocardia*, *Actinomadura*, *Streptomyces*, and *Nocardia*. *Nocardia* is the most common agent, particularly in the Americas, but *Streptomyces somaliensis* is more common in Sudan and the Middle East. Eumycetomas are caused by a large number of fungi: *Madurella mycetomatis* is of particular significance as it is the most prevalent causative agent in regions of India and Africa.

MANAGEMENT STRATEGY

Treatment of mycetomas is generally difficult, and management varies from a very conservative approach to chemotherapy and surgery. Effective chemotherapy is available for actinomycetomas; however, eumycetomas are more refractory to drug therapy.

Eumycetomas may sometimes be managed conservatively as they are usually indolent and seldom life-threatening. Treatment is then symptomatic with relief of pain and applications of dressings to affected areas, particularly the sinuses. Any secondary bacterial infection requires treatment. More active management consists of long courses of antifungals, 18–24 months or even longer, together with aggressive surgical excision and debulking. Antifungal therapy is initiated before surgery and continued

afterwards to reduce the risk of recurrence. Small lesions have a more favorable prognosis as they are more easily excised completely. Advanced disease with bony involvement characteristically shows poor therapy response, and often requires surgical amputation. Of all the antifungal drugs, azoles have been most commonly used. Fluconazole has been found to be ineffective but ketoconazole and itraconazole have both demonstrated efficacy, particularly at high doses (200–400 mg daily for ketoconazole and 300–400 mg daily for itraconazole). Itraconazole is preferred as it is better tolerated for longer periods of time and is thought to demonstrate greater efficacy than ketoconazole, although there are no published studies comparing their efficacy. There are reports of the high tolerability and efficacy of the newer broad-spectrum triazoles such as voriconazole and posaconazole against *Madurella* species and *Scedosporium apiospermum* infection. This is supported by in vitro susceptibility testing. However, their high costs are prohibitive for use in most endemic regions. Griseofulvin appears to be ineffective. Amphotericin has shown variable responses in the few cases for which it has been used. High dose terbinafine (500 mg twice daily) has demonstrated limited clinical efficacy, which correlates with in vitro susceptibility testing, which has shown only moderate efficacy of terbinafine against some black grain mycetomas. In vitro studies have not demonstrated any efficacy of echinocandins against *Madurella mycetomatis*.

Actinomycetomas are usually amenable to antibiotic therapy, but cure rates vary widely from 60% to 90%. Combined drug therapy is preferred in order to prevent the development of drug resistance, as well as to eradicate any residual infection. The duration of drug therapy depends on clinical response. Cure is defined by a lack of clinical activity, absence of grains, and negative cultures. Treatment with sulfonamides and sulfonamide combinations such as trimethoprim-sulfamethoxazole (cotrimoxazole) are usually first line. Aminoglycosides, tetracyclines, rifampicin, ciprofloxacin, and amoxicillin-clavulanate have also been successfully used. Parenteral amikacin and oral cotrimoxazole combination therapy is especially advocated for cases at risk of bone or visceral involvement. Actinomycetomas seldom require surgical management.

Specific Investigations

- Direct microscopy
- Culture
- Histopathology

It is imperative to differentiate between eumycetomas, which respond poorly to chemotherapy, and actinomycetomas, which generally respond well. Furthermore, species identification is important as it has treatment and prognostic implications, some species having demonstrated higher efficacy to some chemotherapy regimens than others.

The clinical diagnosis can be confirmed by the demonstration and identification of grains, which can be obtained by direct extraction, fine needle aspiration, or deep tissue biopsy. Direct microscopy of a crushed grain in 10% potassium hydroxide gives an indication of the size and shape of the grain, which provides an initial clue to the causative agent, whether bacterial or fungal. Histopathology of a deep surgical biopsy demonstrates a granulomatous, inflammatory reaction with abscesses containing grains. Culture of grains using Sabouraud or blood agar media permits species identification. However, fungal culture can be particularly difficult,

as morphological differentiation of fungi may be poor or delayed. Molecular tests have therefore been developed for species identification of several black-grained eumycetoma, including species-specific polymerase chain reaction (PCR) analysis. Serological tests, such as enzyme-linked immunosorbent assay (ELISA), are employed by some centers to support diagnosis as well as to assess therapy response. Radiology and ultrasound enable assessment of disease extent and bony involvement. Helical computed tomography can provide detailed assessments of soft tissue and visceral involvement.

Drug therapy for mycetoma. Scolding P, Fahal A, Yotsu RR. Cochrane Database Sys Rev 2018; (7): CD013082.

This review included prospective clinical studies, both randomized and non-randomized trials, and observational cohort data for antibiotic therapies used to treat actinomycetomas and antifungal therapies used to treat eumycetomas.

Hand mycetoma: The Mycetoma Research Centre experience and literature. Omer RE, Seif El Din N, Abdel Rahim FA, et al. PLoS Negl Trop Dis 2016; 10(8).

Data are discussed on 533 patients with hand mycetoma managed over a period of 24 years at the Mycetoma Research Center, Khartoum, Sudan. Of these patients, 83.3% had eumycetoma, which were treated with ketoconazole (400–800 mg daily) or itraconazole (200–400 mg daily). Actinomycetomas were treated with streptomycin sulfate (1 g daily), dapsone (100 mg daily), or streptomycin and trimethoprim-sulfamethoxazole (8/40 mg/kg/day), which was sometimes combined with amikacin (15 mg/kg/day) and administered in cycles.

The surgical treatment of mycetoma. Suleiman SH, Wadaella el S, Fahal AH. PLoS Negl Trop Dis 2016; 10(6).

The Mycetoma Research Centre, Khartoum, Sudan has extensive experience in the surgical management of mycetomas and discusses different surgical options, including wide local excision, repetitive debridement, and amputation.

Mycetoma: a unique neglected tropical disease. Zijlstra EE, van de Sande WW, Welsh O, et al. Lancet Infect Dis 2016; 16(1): 100–12.

The authors of this review are leaders in the field of mycetoma research and therapy. The authors include clinicians that are experts with extensive clinical experience in either actinomycetomas or eumycetomas. They have summarized the published studies to date of both drug therapies as well as surgical management of mycetomas and described the limitations of these studies. Given the difficulties of microbiological identification of the causative species and the lack of reliable serological testing, they describe progress in molecular techniques to identify the causative antigens.

Mycetoma in the Sudan: an update from the Mycetoma Research Centre, University of Khartoum, Sudan. Fahal A, Mahgoub el S, El Hassan AM, et al. PLoS Negl Trop Dis 2015; 9(3): e0003679.

This world-renowned center, which has seen the greatest number of mycetoma cases, describes their experience of 6792 patients seen during the period 1991–2014. *Madurella mycetomatis* eumycetoma was the most common type found in 70%.

Mycetoma: experience of 482 cases in a single center in Mexico. Bonifaz A, Tirado-Sánchez A, Calderón L, et al. PLoS Negl Trop Dis 2014; 8(8): e3102.

In this retrospective study, reporting epidemiological, clinical, and microbiological data on all cases of mycetoma seen over a 33-year period (1980–2013) in Mexico City, 92% of cases were actinomycetomas and 78% of these were due to *Nocardia brasiliensis*.

First-Line Therapies

• Sulfonamides	B
• Aminoglycosides	B
• Itraconazole	C

Actinomycetomas in Senegal. Study of 90 cases. Dieng MT, Niang SO, Diop B, et al. Bull Soc Pathol Exot Filiales 2005; 98: 18–20.

In Senegal, 90 patients with actinomycetomas (*Actinomadura pelletieri*, *n*=60; *A. madurae*, *n*=25; *S. somaliensis*, *n*=5) were treated with sulfamethoxazole monotherapy. Despite bone involvement in 55% of cases, cure was achieved after 1 year of treatment in 83% of patients; 50% of these cases were localized to the foot. Despite treatment, two patients died of visceral involvement.

Mycetoma in children: experience with 15 cases. Bonifaz A, Ibarra G, Saul A, et al. Pediatr Inf Dis J 2007; 26(1): 50–2.

Mycetomas are very rare in children but its clinical presentation and course is similar to that in adults. There were 13 cases of *Nocardia* actinomycetoma and two cases of *M. mycetomatis* eumycetoma. Sulfonamide combinations were advocated as first-line therapy for actinomycetomas and amoxicillin/clavulanate as second-line therapy. Itraconazole and ketoconazole were used in the management of eumycetomas.

A modified two-step treatment for actinomycetoma. Ramam M, Bhat R, Garg T, et al. Indian J Dermatol Venereol Leprol 2007; 73: 235–9.

The authors emphasize that although parenteral therapy regimens demonstrate high efficacy, they are costly in terms of inpatient stays. They describe a reduced parenteral regime (intravenous gentamicin 80 mg twice daily together with oral cotrimoxazole 320/1600 mg twice daily for 1 month), followed by a longer phase of oral medication (doxycycline 100 mg twice daily together with cotrimoxazole at the same dose). All 21 patients demonstrated significant clinical response at the end of the parenteral phase of treatment. The oral phase needed to be continued for 3.5–16 months (mean 9.1 months) until cure, and in the majority of these patients this included a treatment period of 5–6 months after complete healing of the lesions to prevent any relapse.

Clinical and mycologic findings and therapeutic outcome of 27 mycetoma patients from São Paulo, Brazil. Castro LG, Piquero-Casals J. Int J Dermatol 2008; 47(2): 160–3.

This article describes the treatment of 13 cases of eumycetoma (with itraconazole) and 14 cases of actinomycetoma (with cotrimoxazole). Combination drug therapy was used in more than half of the cases. There was higher efficacy in three patients with actinomycetoma treated with cotrimoxazole in combination with amikacin. However, two of these patients developed hearing loss after treatment. The authors emphasize the problems of diagnostic testing, even in secondary and tertiary health centers, and were only able to identify the etiological agent in fewer than half of their cases.

Improvement of eumycetoma with itraconazole. Smith EL, Kutbi S. *J Am Acad Dermatol* 1997; 34 (2 Part 1): 279–80.

This study from Saudi Arabia treated 25 patients with a follow-up period of 12 years. The authors recommend a combination itraconazole drug therapy together with surgical excision or debulking. Drainage of sinuses with removal of grains that can cause inflammation reduced pain and swelling.

Mycetoma in children. Fahal AH, Sabaa AH. *Trans R Soc Trop Med Hyg* 2010; 104(2): 117–21.

A large retrospective study of 722 children (age range 4–17 years) with confirmed mycetoma seen at the Mycetoma Research Center, Sudan, during a 20-year period until 2009. Diagnosis was established by cytological and ultrasound examinations of the lesions and histological examination of the surgical biopsies. Most of the patients had eumycetomas. Combined medical treatment and surgical excision was the standard treatment. Disease recurrence after surgical excision was reported in 17.9% of patients.

The safety and efficacy of itraconazole for the treatment of patients with eumycetoma due to *Madurella mycetomatis*. Fahal AH, Rahman IA, El-Hassan AM, et al. *Trans R Soc Trop Med Hyg* 2011; 105(3): 127–32.

This prospective study of 13 patients demonstrated that preoperative treatment with a 1-year course of itraconazole enhances lesion encapsulation, which facilitates wide local excision avoiding unnecessary mutilating surgery. Itraconazole was given at 400 mg daily for 3 months followed by a reduced dose of 200 mg daily for 9 months. All patients showed a good clinical response to the 400 mg daily dose but a slower response to the 200 mg daily dose. Posttreatment surgical exploration demonstrated that all lesions were well localized and encapsulated and easily removed. There was only a single recurrence after a follow-up period of 18–36 months.

Second Line Therapies

• Amoxicillin–clavulanate	B
• Terbinafine	B
• Ketoconazole	C
• Posaconazole	D
• Imipenem	D
• Voriconazole	D
• Ciprofloxacin	D
• Oxazolidinones	E

Last generation triazoles for imported eumycetoma in eleven consecutive adults. Crabol Y, Poiree S, Bounoux ME, et al. *PLoS Negl Trop Dis* 2014; 8(10): e3232.

Data is presented on 11 cases of eumycetoma (*Fusarium solani* complex, $n=3$; *Madurella mycetomatis*, $n=3$; *Exophiala jeanselmei*, $n=1$) that were treated by either voriconazole or posaconazole for a mean duration of 25.9 ± 18 months. There was complete response (major clinical and MRI improvement) in 5/11, partial response in 5/11, and failure in 1/11. Optimal outcome was associated with fungal species and initiation of drug therapy <65 months since first symptoms.

Treatment of actinomycetoma due to *Nocardia* spp. with amoxicillin-clavulanate. Bonifaz A, Flores P, Saul A, et al. *Br J Dermatol* 2007; 156(2): 308–11.

This study advocates coamoxiclav as rescue therapy in patients with *Nocardia* spp. refractory to other therapy regimes; 21 patients who had previously failed on other therapy regimes were treated

with oral coamoxiclav 875/125 mg twice daily. There was clinical and microbiological cure in 15 (71%) patients after a mean treatment period of 10 months. Patients with bone and visceral involvement required longer treatment periods.

Clinical efficacy and safety of oral terbinafine in fungal mycetoma. N'Diaye B, Dieng MT, Perez A, et al. *Int J Dermatol* 2006; 45: 54–157.

High dose terbinafine, 500 mg twice daily, was given to 23 patients with eumycetomas in Senegal. After 24–48 weeks of treatment, mycological cure was seen in 25% of patients, and a further 55% of patients demonstrated clinical improvement. Treatment was well-tolerated.

This is the only study of terbinafine monotherapy for the treatment of eumycetomas, perhaps because the drug is prohibitively expensive in countries endemic for the infection.

Ketoconazole in the treatment of eumycetoma due to *Madurella mycetomatis*. Mahgoub ES, Gumaa SA. *Trans R Soc Trop Med Hyg* 1984; 78: 376–9.

This trial consisted of 13 patients treated in the Sudan and Saudi Arabia. Ketoconazole was given at doses of 200–400 mg daily for 3–36 months (median 13 months). Treatment was well tolerated. Five patients were cured, and a further four improved. Response appeared to be dose dependent. The authors recommend a 400 mg daily dose of ketoconazole, and a minimum treatment period of 12 months where there is bony involvement irrespective of clinical improvement.

Given the availability of newer antifungals, there are few recent trials evaluating the use of ketoconazole for eumycetomas. However, it is a less expensive drug than itraconazole and therefore is more commonly used in endemic regions.

Posaconazole treatment of refractory eumycetoma and chromoblastomycosis. Negroni R, Tobon A, Bustamante B, et al. *Rev Inst Med Trop Sao Paulo* 2005; 47: 339–46.

In this study from Argentina, posaconazole (800 mg daily in divided doses) was given to six patients with eumycetoma (*M. grisea*, $n=3$; *M. mycetomatis*, $n=2$; *S. apiospermum*, $n=1$) resistant to standard therapy. There was partial and complete clinical response in five of the six patients. Treatment was well-tolerated, even after long-term administration of more than 2 years.

Efficacy of imipenem therapy for *Nocardia actinomycetomas* refractory to sulphonamides. Ameen M, Arenas R, Vásquez del Mercado, et al. *J Am Acad Dermatol* 2010; 62(2): 239–46.

Eight patients with severe and protracted infection (two with visceral and a further two with bone involvement) refractory to previous sulfonamide monotherapy received a 3-week course of parenteral imipenem (1.5 g daily, $n=3$) given as either monotherapy or in combination with amikacin (1 g daily, $n=5$). Treatment cycles were repeated at 6-month intervals. Oral cotrimoxazole was also given and continued between cycles. Treatment was well tolerated, and four patients achieved clinical and microbiological cure after one to two cycles of treatment, the others demonstrating greater than 75% clinical improvement and negative culture results.

This study also demonstrated that sulfonamides are effective for limited disease of relatively short duration. Their partial efficacy in severe cases was the reason for continuing treatment with sulfonamides in combination with imipenem.

***Madurella mycetomatis* mycetoma treated successfully with oral voriconazole.** Lacroix C, De Kerviller E, Morel P, et al. *Br J Dermatol* 2005; 152: 1067–8.

Voriconazole has been reported to be effective in the management of disseminated fungal infections with *Scedosporium* and *Fusarium* sp. This is the first report of successful treatment of a eumycetoma with oral voriconazole monotherapy given for 16 months at a dose of 300 mg twice daily. The treatment was well tolerated, and the patient remained disease-free 4 years after the end of treatment.

Scedosporium apiospermum mycetoma with bone involvement successfully treated with voriconazole. Porte L, Khatibi S, Hajj LE, et al. Trans R Soc Trop Med Hyg 2006; 100: 891–4.

Scedosporium apiospermum mycetoma usually requires limb amputation. This case with bone involvement, which had previously failed with itraconazole, fluconazole, and cotrimoxazole, was given voriconazole 400 mg daily for 18 months. There was a good clinical response and magnetic resonance imaging demonstrated impressive regression of bony lesions. Treatment, however, was discontinued because of hepatic impairment.

This report suggests voriconazole as a promising treatment option for *S. apiospermum* mycetomas.

Clinical experience with linezolid for the treatment of Nocardia infection. Moylett EH, Pacheco SE, Brown-Elliott BA, et al. Clin Infect Dis 2003; 36: 313–8.

Oral linezolid belongs to the new broad-spectrum oxazolidinones. This report describes its successful use in *Nocardia* infection. There was only a single case of cutaneous infection with *N. brasiliensis*. Linezolid produced clinical cure after only 2 months of treatment at a dose of 600 mg twice daily.

Actinomycetoma by Actinomyces madurae. Clinical and therapeutic characteristics of 18 cases with two treatment modalities. Bonifaz A, Tirado-Sánchez A, Vázquez-González D, et al. J Dermatolog Treat. 2020 Jul 20:1-5. doi: 10.1080/09546634.2020.1793887. Online ahead of print. PMID: 32643472.

In this retrospective study of 18 actinomycetoma cases, 12 were treated with streptomycin 1 g every third day plus trimethoprim-sulfamethoxazole (TMP-SMX) 800 mg/160 mg/12 h, followed by combination TMP-SMX and dapsone 100 mg daily. Six cases were treated with the same initial regimen but received ciprofloxacin 500 mg every 12 h instead of dapsone. Clinical and mycological cure was seen in 83% of patients who received ciprofloxacin vs. 57% in the dapsone arm. There was improvement in all patients who received ciprofloxacin, whereas 25% in the dapsone arm failed to respond.

Although the ciprofloxacin arm of this study was small ($n=6$), the more favorable response would suggest that it is more efficacious than dapsone when given in combination with TMP-SMX and perhaps merits further larger studies to investigate this.

Third-Line Therapies

• Rifampicin	C
• Amphotericin B	D
• Surgery	B

Modified Welsh regimen: a promising therapy for actinomycetoma. Damle DK, Mahajan PM, Pradhan SN, et al. J Drugs Dermatol 2008; 7(9): 853–6.

Eighteen patients with poor responses to previous therapies were treated with the standard 'Welsh regimen' consisting of amikacin and cotrimoxazole in combination with rifampicin. Sixteen patients who completed treatment were cured and remained in remission during a follow-up period of up to 18 months.

This study has demonstrated efficacy and tolerability of these three drugs in combination. There are also reported cases of rifampicin being added to sulfonamides to improve efficacy.

Scedosporium infection in immunocompromised patients: successful use of liposomal amphotericin B and itraconazole. Barbaric D, Shaw PJ. Med Pediatr Oncol 2001; 37: 122–5.

A report of five cases of *Scedosporium* infection in immunosuppressed patients; three of these patients died despite treatment with various combinations of amphotericin B (AmB) and itraconazole. Two patients were successfully treated with liposomal AmB and itraconazole.

Surgical management of eumycetoma: experience from Gezira Mycetoma Center, Sudan. Gismalla MDA, Ahmed GMA, MohamedAli MM, et al. Trop Med Health 2019; 14: 47: 6.

This was a retrospective, descriptive, hospital-based study, conducted to review the surgical treatment of 584 eumycetoma patients. Of this group 16.1% had recurrent mycetoma. Radiological examination demonstrated bone involvement in 17.3%. The paper does not describe fungal species identification but states that sinuses and discharging grains were identified in 78.9%. Surgical excision of mycetoma was the commonest operation performed in 87.8% patients in comparison with amputation in 12.2%. Below-knee amputation and toe amputation were the commonest types of amputation in 6.1% and 2.3% of patients, respectively. The clinical features that determined the type of operation performed included the size of the eumycetoma, bony involvement, and the feasibility of primary closure. The commonest procedure was wide surgical excision and primary skin closure for lesions < 5 cm without bony involvement. Lesions > 10 cm without bone involvement were treated with excision and flap/graft. Small mycetomas < 5 cm were also treated with oral itraconazole 100–200 mg daily postoperatively for 3 months. Lesions > 5 cm were treated with itraconazole for 6 months, which was sometimes started before the operative procedure. Bone involvement and large primary lesions were more likely to be managed by amputation. Recurrence of eumycetoma was observed in some patients with a history of bone involvement.

This center has one of the largest experiences globally of the surgical management of eumycetomas. Itraconazole is given concurrently to limit lesion size as well as to promote mycological cure decreasing any future risk of recurrence. However, long-term drug therapy with itraconazole is unaffordable for the majority of patients with eumycetoma, making surgical management the mainstay. This study highlights the prognostic indicators of successful surgery, which are smaller lesion size with no bone involvement.

Mycobacterial (atypical) skin infections

Rebecca C. Phillips



Atypical or non-tuberculous mycobacterial (NTM) skin infections are being increasingly reported. *Mycobacterium marinum* and the rapidly growing mycobacteria (RGM), *M. abscessus*, *M. chelonae*, and *M. fortuitum*, are the most common species in the United States. Worldwide, *M. ulcerans* has the highest prevalence. NTM are ubiquitous in the environment. They exhibit high levels of resistance to disinfectants and have been isolated from sources that may be considered clean, such as chlorinated tap water. Cutaneous infection arises after injury to the skin. Nosocomial infections have been associated with cosmetic and surgical procedures.

Specific Investigations

- Histopathology with acid-fast bacillus (AFB)-specific stains
- Tissue culture and antimicrobial susceptibility testing
- Polymerase chain reaction (PCR)

The diagnosis of atypical mycobacterial skin infections is challenging. Morphology is non-specific and lesions may take months to become apparent. Histopathology is varied and routine bacterial culture conditions are not optimal for growth of mycobacteria.

With clinical suspicion, both mycobacterial tissue culture and histopathology with special stains for AFB are recommended to increase diagnostic yield. Histopathology displays granulomatous and suppurative inflammation with variable pseudoepitheliomatous hyperplasia, ulceration, microabscesses, necrosis, and fibrosis. In immunosuppressed patients, the infiltrate tends to be more diffuse, with increased neutrophils and decreased granulomatous inflammation. Special stains to detect AFB, such as Fite or Ziehl-Neelsen, should be performed, but have low sensitivity (e.g., 34%–51% positive in tissue culture-confirmed cases). AFB are more readily seen with immunosuppression.

Tissue culture submitted specifically for mycobacterial detection is recommended. RGM and *M. marinum* grow best at 28–30°C, *M. ulcerans* grows at 25–33°C, and most other slowly growing mycobacteria grow at 35–37°C. Therefore, skin specimens for mycobacteria are typically incubated at both 28–30°C

and 35–37°C. Most cultures are incubated for 6 weeks, with growth typically in 2–3 weeks. *M. ulcerans* may require 8–12 weeks. The AFB smear performed from the specimen prior to culture often has low sensitivity, with one study reporting positive result in 15.1% of specimens ultimately yielding AFB-positive cultures.

Species identification and antimicrobial susceptibility testing are recommended. Evolving molecular techniques allow for rapid and accurate species identification.

An official ATS/IDSA statement: diagnosis, treatment and prevention of nontuberculous mycobacterial diseases. Griffith DE, Aksamit T, Brown-Elliott BA, et al. Am J Respir Crit Care Med 2007; 175(4): 367–416.

These are the most recent US guidelines for NTM infections. It discusses topics pertinent to cutaneous NTM infection, including culture conditions, species identification methods, recommended treatment algorithms, and susceptibility patterns.

Diagnosis of *Mycobacterium abscessus/chelonae* complex cutaneous infection: correlation of tissue culture and skin biopsy. Sardiña LA, Kaw U, Jour G, et al. J Cutan Pathol 2020; 47: 321–7.

Thirty-three skin biopsy specimens from patients with positive tissue culture were studied. Features included granulomatous inflammation (88%), suppurative inflammation (88%), clear spaces/vacuoles (82%), abscesses/microabscesses (73%), fibrosis (52%), and necrosis (52%). AFB stains were positive in 18 cases (51.5%). Histopathology is affected by the evolutionary stage of the lesion and immunologic status of the host.

The presence of neutrophil microabscesses and epithelioid granulomas should raise the possibility of NTM infection. Additionally, vacuoles within the infiltrate can be a clue.

MYCOBACTERIUM MARINUM

Cutaneous infection by *M. marinum* often presents on the arm and may exhibit sporotrichoid spread. The most common sources are aquariums and swimming pools. The infection is frequently limited to skin, but extension to deep structures can lead to tenosynovitis, septic arthritis, or osteomyelitis. Rarely, disseminated infection may occur, especially in the immunocompromised.

MANAGEMENT STRATEGY

Treatment recommendations are based upon anecdotal success in case series due to the lack of controlled trials. *Antibiotic therapy* with two or more agents is recommended for 3–4 months, or 1–2 months beyond clinical resolution. Monotherapy can be considered for limited infection. Routine susceptibility testing is not required for *M. marinum*, except in cases of treatment failure. Isolates are typically susceptible to macrolides, sulfonamides, rifampin, ethambutol, and amikacin, and are susceptible or intermediate in susceptibility to tetracyclines. Treatment failure is usually related to deep structure involvement, rather than a particular antibiotic. *Surgical treatment* should be reserved for limited disease refractory to antibiotic therapy or in cases of deep structure involvement that require synovectomy or tenosynovectomy due to extensive damage. Second-line treatments have been so designated due to less published experience or due to increased resistance potential (e.g., fluoroquinolones). Third-line treatments are best regarded as adjunctive.

First-Line Therapies

- Minocycline 100 mg twice daily **C**
- Doxycycline 100 mg twice daily **C**
- Clarithromycin 500 mg once or twice daily **C**
- Trimethoprim-sulfamethoxazole (TMP-SMX) 160 mg/800 mg twice daily **D**
- Clarithromycin + rifampin 600 mg daily **C**
- Clarithromycin + one of the following: ethambutol (800–1200 mg daily), minocycline, doxycycline, or TMP-SMX **D**
- Rifampin + one of the following: ethambutol, minocycline, or doxycycline **D**
- Clarithromycin + rifampin + ethambutol **D**
- Minocycline + TMP-SMX **E**

Epidemiological, clinical, and therapeutic pattern of *Mycobacterium marinum* infection: a retrospective series of 35 cases from southern France. Eberst E, Dereure O, Guillot B, et al. J Am Acad Dermatol 2012; 66: e15–6.

Success was noted in 34 of 35 (97%) after treatment for 4–24 weeks (mean 12.4 weeks). Monotherapy was successful in 24 patients, including minocycline ($n=14$), doxycycline ($n=5$), and clarithromycin ($n=5$). One patient failed first-line clarithromycin monotherapy. Nine patients were treated successfully with dual antibiotic therapy using clarithromycin in combination with doxycycline ($n=4$), minocycline ($n=2$), rifampicin ($n=2$), or ofloxacin ($n=1$). One patient was successfully treated using a triple combination of clarithromycin, rifabutin, and ethambutol.

This study demonstrated success with monotherapy and clarithromycin-based dual and triple therapy.

Sixty-three cases of *Mycobacterium marinum* infection. Clinical features, treatment and antibiotic susceptibility of causative isolates. Aubry A, Chosidow O, Caumes E, et al. Arch Intern Med 2002; 162: 1746–5.

Monotherapy was used in 23 patients (37%) and included minocycline ($n=14$), doxycycline ($n=5$), and clarithromycin ($n=4$). Monotherapy use was significantly associated with superficial infection. Forty patients (63%) received at least two antibiotics. Frequent combinations included clarithromycin plus rifampin ($n=20$), doxycycline ($n=4$), or minocycline ($n=7$); and rifampin plus ethambutol ($n=8$), doxycycline ($n=3$), or minocycline ($n=3$). Tetracyclines tended to be prescribed more for superficial infection, while rifampin, rifabutin, and ethambutol were prescribed more for deep infection. Clarithromycin was equally prescribed in superficial and deep infections. Duration of therapy was significantly longer for patients with deep infections (median 7.5 vs. 4 months), and 48% of patients also underwent surgery, which was significantly associated with deep structure infection. Cure was observed for 55 (87%) of patients.

Treatment failure was related to deep structure involvement and not to a particular antibiotic.

Fishing for a diagnosis, the impact of delayed diagnosis on the course of *Mycobacterium marinum* infection: 21 years of experience at a tertiary care hospital. Castillo NE, Gurram P, Sohail MR, et al. OFID 2020; 7(1): 1–7.

Retrospective review of 46 cases, of which 12 (26%) were complicated by tenosynovitis, septic arthritis, or osteomyelitis. Patients with complicated infection required significantly more

surgical procedures. Forty-three patients (93%) were treated with antibiotics. Monotherapy was prescribed in 52.1%, with trimethoprim-sulfamethoxazole (TMP-SMX) being the most common, followed by tetracyclines and clarithromycin. Eleven cases (25%) received a two-antibiotic regimen that included macrolides in 91%, in addition to tetracycline, TMP-SMX, rifampin, rifabutin, or ethambutol. The median duration was 4.5 months, and overall was longer in patients with complicated infection. Ninety percent of cases were cured. Clinical outcome was not impacted by number of medications.

The authors recommend avoidance of fluoroquinolones due to resistance. They recommend counseling patients with deep infections about the possibility of multiple surgeries and longer antibiotic treatment duration.

***Mycobacterium marinum* infection of the hand and wrist.** Cheung JP, Fung B, Wong SS, et al. J Orthop Surg 2010; 18: 98–103.

Review article. Due to rifampicin's excellent bone-penetrating ability, the authors recommend combination therapy with rifampicin plus ethambutol or minocycline for previously untreated patients for 6 months, or at least 2 months beyond clinical improvement. For relapse, they recommend triple therapy with clarithromycin, minocycline, and ethambutol. They advocate surgical excision/debridement for deep structure infections.

Second-Line Therapies

- Azithromycin 500 mg three times weekly **E**
- Rifampicin 450 mg daily + clarithromycin 500 mg twice daily + amikacin 400 mg intravenous once daily **E**
- Rifabutin 600 mg daily + clarithromycin 500 mg twice daily + ciprofloxacin 500 mg twice daily **E**
- Clarithromycin + fluoroquinolone (moxifloxacin, ciprofloxacin, ofloxacin) **E**

Successful treatment of refractory cutaneous infection caused by *Mycobacterium marinum* with a combined regimen containing amikacin. Huang Y, Xu X, Liu Y, et al. Clin Interv Aging 2012; 7: 533–8.

A rapidly progressive infection refractory to rifampicin, clarithromycin, and moxifloxacin responded promptly upon addition of amikacin and discontinuation of moxifloxacin. Complete resolution occurred after treatment with rifampicin, clarithromycin, and amikacin for 6 months.

Third-Line Therapies

- Simple excision **E**
- Curettage and electrodesiccation **E**
- Incision and drainage **E**
- Heat therapy **E**
- Photodynamic therapy **E**
- Cryotherapy **E**
- Adjunctive anti-TNF- α inhibitors **E**

Treatment of *Mycobacterium marinum* cutaneous infections. Rallis E, Koumantaki-Mathioudaki E. Expert Opin Pharmacother 2007; 8: 2965–78.

Surgical treatment may not be necessary or may even be contraindicated in some patients. Surgery can be considered

for cases with isolated superficial lesions non-responsive to systemic therapy, and in cases that require synovectomy or tenosynovectomy due to extensive damage of underlying tissues. Cryotherapy, electrodesiccation, photodynamic therapy, and local hyperthermic therapy have been reported with some success.

Local hyperthermia therapy for refractory cutaneous *Mycobacterium marinum* infection. Lee C, Lee JY. *Dermatologic Therapy* 2017; 30: 1–2.

Case of refractory infection successfully treated with adjunctive local heat therapy. Disposable chemical warm packets (40°C) were applied to skin lesions 5 hours daily for 3 months. Antibiotics were continued during heat therapy.

***Mycobacterium marinum* infection cured by photodynamic therapy.** Wiegell SR, Kongshoj B, Wulf HC. *Arch Dermatol* 2006; 142: 1241–2.

A patient intolerant of antibiotics was treated successfully with photodynamic therapy once weekly for 3 weeks. Methylaminolevulinate was applied for 3 hours, followed by illumination with 37 J/cm² of red light.

Possible role of anti-TNF monoclonal antibodies in the treatment of *Mycobacterium marinum* infection. Garzoni C, Adler S, Boller C, et al. *Rheumatology* 2010; 49: 1991–3.

A patient with *M. marinum* synovial infection of the foot was given triple combination therapy of ethambutol, clarithromycin, and rifampicin for 4 months. Clinical improvement was noted with the subsequent addition of infliximab 5 mg/kg/month.

TNF-α inhibitors should be used with caution and only as adjunctive treatment. Anti-TNF monoclonal antibodies may help to control inflammation caused by M. marinum infection.

RAPIDLY GROWING MYCOBACTERIA

The RGM, *M. fortuitum*, *M. chelonae*, and *M. abscessus*, are environmental pathogens. Risk factors include trauma, invasive procedure, or environmental exposure.

MANAGEMENT STRATEGY

Treatment of RGM infections is not standardized. Species identification and *in vitro* susceptibility testing should be performed to guide treatment. Antibiotic therapy with at least two antibiotics with *in vitro* susceptibility is recommended for a minimum of 4 months. Monotherapy should be used with caution due to risk of resistance. *M. chelonae* isolates have *in vitro* susceptibility or intermediate susceptibility to tobramycin (100%), clarithromycin (100%), linezolid (90%), imipenem (60%), amikacin (50%), doxycycline (25%), and ciprofloxacin (20%). Isolates are uniformly resistant to ceftazidime. *M. fortuitum* isolates display *in vitro* susceptibility to amikacin (100%), ciprofloxacin and ofloxacin (100%), sulfonamides (100%), ceftazidime (50%), imipenem (100%), clarithromycin (80%), and doxycycline (50%). Despite 80% *in vitro* susceptibility, macrolides should be used with caution due to an inducible *erm*(39) gene, which confers macrolide resistance. *M. abscessus* is often the most challenging to treat due to broad antibiotic resistance. *M. abscessus* subsp. *abscessus* and subsp. *bolletii* possess an *erm*(41) gene, which confers macrolide resistance. Surgery has an adjunctive role. Foreign material (e.g., breast implant) at the site of infection should be removed.

First-Line Therapies

Mycobacterium chelonae

• Clarithromycin 500mg twice daily ± surgery	C
• Azithromycin 250mg daily for at least 6 months	E
• Clarithromycin + fluoroquinolone (ciprofloxacin, moxifloxacin, levofloxacin) ± surgery	D
• Clarithromycin + doxycycline	D
• Clarithromycin + linezolid	D
• Clarithromycin + tobramycin ± tigecycline ± surgery	D
• Tigecycline + one or more of following: macrolide, amikacin, linezolid	E
• Adjunctive surgery	D

Systematic review of tattoo-associated skin infection with rapidly growing mycobacteria and public health investigation of a cluster in Scotland 2010. Conaglen PD, Laurenson IF, Sergeant A, et al. *Euro Surveill* 2013; 18: 20553.

Review of 25 publications of RGM infection associated with tattoos, including *M. chelonae* (most frequently). *M. chelonae* treatments included clarithromycin or azithromycin monotherapy, and clarithromycin in combination with moxifloxacin, levofloxacin, doxycycline, or tobramycin.

Clinical management of rapidly growing mycobacterial cutaneous infections in patients after mesotherapy. Regnier S, Cambau E, Meningaud JP, et al. *Clin Infect Dis* 2009; 49: 1358–64.

Sixteen patients were diagnosed with cutaneous RGM infection after mesotherapy. *M. chelonae* was identified in 11 patients. Surgery was performed for each patient. Fourteen patients were treated with antibiotics, including eight with dual therapy (clarithromycin 1–2g daily and ciprofloxacin 500 mg twice daily) and six with triple therapy (clarithromycin, tobramycin 3 mg/kg intravenously [IV] daily, and tigecycline initial 100 mg followed by 50 mg IV daily). Success was noted in all but one, with mean time to healing 6.2 months (range 1–15 months).

The authors do not recommend monotherapy due to risk of acquired resistance.

Induction therapy with linezolid/clarithromycin combination for *Mycobacterium chelonae* skin infections in immunocompromised hosts. Parize P, Hamelin A, Veziris N, et al. *JEADV* 2016; 30: 101–5.

The authors report successful treatment of *M. chelonae* infections in four immunocompromised patients with a combination of linezolid and clarithromycin. Three of the four patients experienced reversible adverse events, including thrombocytopenia, myalgia, and severe mitochondrial toxicity with pancytopenia, diarrhea, abdominal pain, and acute renal failure.

Due to potential linezolid toxicity, the authors recommend use of the combination for the first 4–8 weeks, with cautious monitoring of linezolid serum concentration, followed by use of clarithromycin alone for a total of 6 months.

Clinical experience in 52 patients with tigecycline-containing regimens for salvage treatment of *Mycobacterium abscessus* and *Mycobacterium chelonae* infections. Wallace RJ, Dukart G, Brown-Elliott BA, et al. *J Antimicrob Chemother* 2014; 69: 1945–53.

The authors evaluated use of tigecycline in patients with *M. abscessus* and *M. chelonae* infections for whom other options were limited. Concomitant antibiotics included macrolides, amikacin, and linezolid. Nine of 12 patients with extrapulmonary infection improved after mean duration of therapy of 143 days.

First-Line Therapies

Mycobacterium fortuitum

- Clarithromycin 500 mg twice daily + levofloxacin 500 mg twice daily, 3–6 months **C**
- Fluoroquinolone (ciprofloxacin, levofloxacin) monotherapy **E**
- Doxycycline monotherapy **E**
- Ciprofloxacin + TMP-SMX **E**
- Clarithromycin + one of the following: minocycline, TMP-SMX, ciprofloxacin **E**
- Amikacin + ofloxacin **E**
- Adjunctive surgery **D**

An outbreak of *Mycobacterium fortuitum* cutaneous infection associated with mesotherapy. Quiñones C, Ramalle-Gómara E, Perucha M, et al. J Eur Acad Dermatol Venereol 2010; 24: 604–6.

Thirty-nine patients were suspected of having cutaneous *M. fortuitum* infection after mesotherapy (12 culture-confirmed). All were successfully treated with clarithromycin and levofloxacin for 3–6 months. Two underwent excision of localized lesions.

Successful treatment of a widespread cutaneous *Mycobacterium fortuitum* infection with levofloxacin. Nakagawa K, Tsuruta D, Ishii M. Int J Dermatol 2006; 45: 1098–9.

An immunocompromised patient was treated successfully with levofloxacin 300 mg daily.

Cutaneous *Mycobacterium fortuitum* infection: successfully treated with amikacin and ofloxacin combination. Sethi S, Arora S, Gupta V, et al. Indian J Dermatol 2014; 59(4): 383–4.

A 16-year-old with cutaneous *M. fortuitum* refractory to multiple courses of antibiotics for 3 months healed after treatment with amikacin (15 mg/kg intramuscular daily for 1 month) and ofloxacin (400 mg oral daily for 4 months).

Cutaneous nontuberculous mycobacteria infections: a retrospective case series of 78 patients from the Texas Gulf Coast region. Philips RC, Hoyer PE, White SM, et al. J Am Acad Dermatol 2019; 81(3): 730–9.

This retrospective case series described clinical, diagnostic, treatment, and antimicrobial susceptibility of 78 cases of NTM infections, including 32 *M. abscessus* group, 18 *M. fortuitum* complex, and 14 *M. marinum*. Successful *M. fortuitum* treatment included doxycycline monotherapy, ciprofloxacin monotherapy, ciprofloxacin with TMP-SMX, and clarithromycin with either minocycline, TMP-SMX, ciprofloxacin, or moxifloxacin. Parenteral therapy was not required; however, in vitro susceptibility to amikacin was observed in all 14 *M. fortuitum* isolates tested.

Although monotherapy was successful in some cases of *M. fortuitum* infection, the authors recommend use of at least two antibiotics with in vitro susceptibility to reduce risk of acquired resistance.

First-Line Therapies

Mycobacterium abscessus

- Clarithromycin 1 g/day (adults) or 0.5 g/day (children) + adjunctive surgery, 3–6 months **B**
- Clarithromycin 250 mg twice daily + moxifloxacin 400 mg daily, 4–5 months **B**
- Clarithromycin 250–500 mg twice daily + intramuscular amikacin 250 mg three times weekly, 3–6 months **C**
- Tigecycline + one or more of following: macrolide, amikacin, linezolid **E**
- Amikacin + one or more of following: ceftioxin, imipenem, tigecycline, linezolid for 2–4 weeks, followed by oral treatment with clarithromycin + moxifloxacin **E**
- Multiple antibiotic therapy + adjunctive interferon- γ for refractory lesions **E**
- Adjunctive surgery **D**

Report on an outbreak of postinjection abscesses due to *Mycobacterium abscessus*, including management with surgery and clarithromycin therapy and comparison of strains by random amplified polymorphic DNA polymerase chain reaction. Villanueva A, Calderon RV, Vargas BA, et al. Clin Infect Dis 1997; 24: 1147–53.

A total of 350 patients were diagnosed with *M. abscessus* infection after an outbreak (205 culture-confirmed). Eight of 35 patients (23%) treated with clarithromycin alone were cured, seven of 22 patients (32%) treated with surgical resection alone were cured, and 140 of 148 patients (95%) treated with combined surgery and clarithromycin were cured.

Although clarithromycin was used as monotherapy, this should be done with caution due to risk of inducible resistance.

Clarithromycin and amikacin vs. clarithromycin and moxifloxacin for the treatment of post-acupuncture cutaneous infections due to *Mycobacterium abscessus*: a prospective observational study. Choi WS, Kim MJ, Park DW, et al. Clin Microbiol Infect 2011; 17: 1084–90.

A series of 52 patients with *M. abscessus* infection after acupuncture. Thirty-three were treated with oral clarithromycin 250 mg twice daily plus intramuscular amikacin 250 mg three times weekly, and 19 were treated with clarithromycin plus oral moxifloxacin 400 mg daily. The median time to resolution of lesions in the moxifloxacin group was significantly shorter (17 vs. 20 weeks, respectively). Complete resolution of cutaneous lesions within 12 weeks occurred in 14.8% and 15.4% in the amikacin and moxifloxacin groups, respectively, suggesting that 3 months is insufficient.

Atypical mycobacterial infections after plastic surgery procedures abroad: a multidisciplinary algorithm for diagnosis and treatment. Leto Barone AA, Grzelak MJ, Frost C, et al. Ann Plast Surg 2020; 84(3): 257–62.

The authors recommend initial IV amikacin plus one or more of the following for 2–4 weeks: ceftioxin, imipenem, tigecycline, linezolid. Then, clarithromycin $\pm$ moxifloxacin for minimum of 4.5 months. They recommend removal of all foreign materials, and endorse incision and drainage for small, limited lesions and wide undermining and excision for large lesions.

Treatment of refractory disseminated *Mycobacterium abscessus* infection with interferon gamma therapy. Colsky AS, Hanly A, Elgart Kerdel FA. Arch Dermatol 1999; 135: 125–7.

Successful treatment of refractory *M. abscessus* infection with adjunctive interferon- γ 50 mcg/m² subcutaneously three times a week for 7 months.

MYCOBACTERIUM ULCERANS

Mycobacterium ulcerans (Buruli ulcer) is the third most common mycobacterial infection, after leprosy and tuberculosis. It occurs in tropical and subtropical climates, including Africa and Australia. Children under 15 are frequently affected. After inoculation, *M. ulcerans* proliferates and produces mycolactone, a toxin that causes massive necrosis. Initially, firm, painless nodules, papules, or plaques develop. Ulceration occurs over 1–2 months. Although indolent in the majority, the ulcers can grow rapidly to greater than 15 cm, with potential for extensive scarring and deformity. Up to 13% of patients may develop systemic involvement.

MANAGEMENT STRATEGY

Smears from the ulcer base reveal AFB with Ziehl–Neelsen staining. Biopsy specimens should include the necrotic base and undermined edge with subcutaneous tissue. Histopathology reveals necrosis of the deep dermis with sparse inflammatory cells, presumably due to the immunosuppressive activity of the toxin. With healing, there is a granulomatous response and the ulcer is replaced by a depressed scar. *M. ulcerans* can be cultured from exudates or tissue fragments, but growth may require 8–12 weeks. PCR yields rapid results and has the highest sensitivity. For PCR, a 3-mm punch biopsy is used for non-ulcerative lesions and a swab is used for ulcers. Screening for coinfection with HIV is recommended in locations where the latter is endemic.

Until 2004, surgery to remove infected tissue with a margin of healthy tissue was considered to be the most effective treatment. Recurrence rates after surgery alone ranged from 16% to 28%. With the introduction of antibiotic therapy in 2004, recurrence rates of 0%–2% have been reported and the need for surgery has decreased. The World Health Organization (WHO) recommends *combination antibiotic therapy* for 8 weeks as first-line treatment for all stages of disease. In 2004, oral rifampicin and intramuscular streptomycin were recommended. Recent oral alternatives, such as rifampicin in combination with clarithromycin or moxifloxacin, show similar efficacy. In some cases, paradoxical worsening is observed after the start of antibiotics. This is an immunological reaction and does not indicate treatment failure. Wide excision of infected tissue is no longer necessary; however, *adjunctive surgical procedures* such as debridement and skin grafting can be considered to speed healing and minimize scarring.

First-Line Therapies

• Rifampicin PO 10 mg/kg/day + streptomycin IM 15 mg/kg/day, 8 weeks (contraindicated in pregnancy)	B
• Rifampicin PO 10 mg/kg/day + clarithromycin PO 7.5 mg/kg twice daily, 8 weeks (can use during pregnancy)	B
• Rifampicin PO 10 mg/kg/day + streptomycin IM 15 mg/kg/day, 4 weeks, followed by rifampicin PO 10 mg/kg/day + clarithromycin PO 7.5 mg/kg/day, 4 weeks	B
• Rifampicin PO 10 mg/kg/day + moxifloxacin 400 mg/day, 8 weeks	C
• Rifampicin + ciprofloxacin, 8 weeks	C
• Adjunctive surgery with antibiotics	B

Treatment of *Mycobacterium ulcerans* disease (Buruli ulcer): Guidance for health workers. World Health Organization. Switzerland, Geneva, 2012.

This is an informative guide on diagnosis and treatment of *M. ulcerans* disease. An 8-week course of at least two antibiotics is recommended as first-line treatment for all stages of disease.

Antimicrobial treatment for early, limited *Mycobacterium ulcerans* infection: a randomized controlled trial. Nienhuis WA, Stienstra Y, Thompson WA, et al. *Lancet* 2010; 375: 664–72.

In this open-label, randomized trial, early lesions of *M. ulcerans* were treated with oral rifampicin and intramuscular streptomycin alone for 8 weeks or rifampicin and streptomycin for 4 weeks followed by rifampicin and clarithromycin for 4 weeks. Efficacy was comparable, with 96% and 91% demonstrating complete healing at 1 year, respectively.

The authors recommend switching to oral clarithromycin after 4 weeks to limit the number of injections with streptomycin.

Clinical efficacy of combination of rifampin and streptomycin for treatment of *Mycobacterium ulcerans* disease. Sarfo FS, Phillips R, Asiedu K, et al. *Antimicrob Agents Chemother* 2010; 54: 3678–85.

A study of 160 patients with lesions ranging from early nodules to large ulcers who were treated with oral rifampicin and intramuscular streptomycin for 8 weeks; 152 patients (95%) healed without surgery. Surgical excision followed by skin grafting was performed in eight patients after completion of antibiotics. Complete healing was achieved between 2 and 48 weeks in 158 patients (98%). Two patients changed from streptomycin to moxifloxacin due to nausea, vomiting, and dizziness. A paradoxical response with new inflammatory lesions was seen in three patients. All new lesions healed without further antibiotic therapy.

This study demonstrates efficacy of rifampicin combined with streptomycin in all stages of disease.

Successful outcomes with oral fluoroquinolones combined with rifampicin in the treatment of *Mycobacterium ulcerans*: an observational cohort study. O'Brien DP, McDonald A, Callan P, et al. *PLoS Negl Trop Dis* 2012; 6: e1473.

A prospective study of 133 patients: 47 (34%) had surgery alone with 30% treatment failure, and 90 (66%) had combined surgical and medical treatment with no treatment failure. In the latter group, first-line antibiotics were rifampicin plus ciprofloxacin (61%) or clarithromycin (23%). There was no difference in efficacy between antibiotic regimens.

A combined antibiotic and surgical approach was more successful than surgery alone. Oral antibiotic therapy was successful.

Increasing experience with primary oral medical therapy for *Mycobacterium ulcerans* disease in an Australian cohort. Friedman ND, Athan E, Walton AL, et al. *Antimicrob Agents Chemother* 2016; 60(5): 2692–5.

An observational cohort study of 132 patients, with ulcerative lesions in 83% and WHO Stage 1 in 78%. Patients were treated with rifampin in combination with ciprofloxacin ($n=80$), clarithromycin ($n=50$), and moxifloxacin ($n=2$) for a median of 56 days. Thirty patients (22.7%) additionally had limited surgical debridement. Cure occurred in 131 patients (99.2%).

Lesions of all sizes are eligible for oral treatment. The authors note that over 20% of the cohort had stage 2 or 3 lesions and all successfully healed in 12 months.

***Mycobacterium ulcerans* treatment – can antibiotic duration be reduced in selected patients?** Cowan R, Athan E, Friedman ND, et al. PLoS Negl Trop Dis 2015; 9(2).

Retrospective review of 62 patients who received less than the recommended 8 weeks of antibiotic therapy. Early discontinuation was due to side effects in 55%. Overall 95% were successfully treated (98% with adjunctive surgery, 82% with antibiotics alone) with median duration of 29 days. Success was seen in 50% of cases treated less than 14 days, 94% of cases treated 14–27 days, and 100% of cases treated 28–55 days.

In some, antibiotic duration shorter than the recommended 8 weeks may be successful.

Histopathological changes and clinical responses of Buruli ulcer plaque lesions during chemotherapy: a role for surgical removal of necrotic tissue? Ruf MT, Sopoh GE, Brun LV, et al. PLoS Negl Trop Dis 2011; 5: e1334.

Twelve patients completed dual therapy with rifampicin and streptomycin for 8 weeks. Seven ulcerated during treatment, six of whom had surgery to remove necrotic tissue. An additional three

patients who developed induration without ulceration underwent surgery. Excisions were performed 7–39 days after completion of antibiotics.

The authors recommend debridement of ulcers that develop during the course of antibiotic therapy in order to remove necrotic tissue and promote healing. They note that ulceration during treatment should not be interpreted as treatment failure.

Second-Line Therapies

• Wide surgical excision alone	B
• Local heat (40°C)	D

Phase change material for thermotherapy of Buruli ulcer: a prospective observational single center proof-of-principle trial. Junghanss T, Um Boock A, Vogel M, et al. PLoS Negl Trop Dis 2009; 3: e380.

Six patients with ulcerative lesions received thermotherapy for 28–31 days in lesions < 2 cm (3 patients) and 50–55 days in lesions > 2 cm (3 patients). All had good outcomes.

Mycosis fungoides and Sézary syndrome

Timothy H. Almazan, Erica B. Wang, Youn H. Kim



Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma (CTCL). The disease is often limited to the skin, but may potentially involve the lymph nodes, blood, and viscera. Classically, the majority of patients with MF follow an indolent clinical course with stable or slow progression of lesions. Sézary syndrome (SS), a rarer presentation of CTCL, is closely related to but distinct from MF and is characterized by the presence of atypical T-cells in the skin causing diffuse erythema (erythroderma), along with significant blood involvement. In SS, the atypical T-cells in the skin and blood are clonally identical.

The clinical presentation of MF and SS may masquerade as other common dermatologic conditions; therefore, diagnosis and management may be delayed. Patients with erythrodermic MF or SS are often misdiagnosed as atopic dermatitis, pityriasis rubra pilaris, or psoriasis. Diagnosis is further complicated by the wide spectrum of clinical features, subtypes, and variants within MF and SS. Additionally, the histopathologic features of both MF and SS may resemble other non-MF/SS T-cell lymphomas, other lymphoproliferative conditions such as lymphomatoid papulosis, or benign conditions including drug-induced, reactive T-cell hyperplasia. The histopathologic findings of SS in the skin are generally similar to but may be more subtle than those seen in MF. Thus, evaluation of the blood compartment early on with flow cytometric and molecular methods is critical when suspecting SS.

In both MF and SS, a clinical–pathologic correlative interpretation with appropriate laboratory and/or imaging findings should be considered in order to achieve a proper diagnosis.

MANAGEMENT STRATEGY

A multidisciplinary team approach involving dermatology/hematology/oncology and radiation oncology is recommended for the diagnosis and management of patients with MF/SS, especially those with advanced disease, ideally at centers with expertise in the management of CTCL. The diagnosis of SS in erythrodermic patients may be especially challenging. If a diagnosis is unclear, whether it is erythrodermic MF/SS vs. dermatitis (or other

widespread inflammatory dermatoses), we recommend avoiding immunosuppressive agents (e.g., ciclosporin, TNF- α inhibitors).

The primary drivers of management are stage-based and risk-stratified patient information. The therapeutic armamentarium for MF/SS includes skin-directed therapies to address localized or widespread skin involvement and systemic therapies for patients who do not achieve an adequate response to skin-directed therapy alone or for those with advanced stage or high-risk disease. Other treatment options include therapies available through clinical trials or allogeneic hematopoietic stem cell transplantation.

Treatment selection incorporates the patient's clinical stage but also should incorporate tumor biology (indolent vs. aggressive) and disease burden (limited vs. widespread/extensive), given the heterogeneity of disease presentation even within a certain stage. The optimal treatment for any patient is highly individualized based on disease symptoms (e.g., pruritus, pain) and extent/severity (e.g., extensive plaques, folliculotropic-MF [f-MF], large-cell transformation [LCT]), age, comorbidities, ease of treatment access or administration, toxicities, and overall goals of therapy. Therefore, primary treatment options should be individualized for each patient. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines (NCCN.org) serve as a key reference for diagnosis, staging, and treatment of MF and SS.

Patients with CTCL may have only skin disease or have additional involvement of extracutaneous compartments (e.g., blood, lymph node, or viscera) that vary with their disease course. Thus, their treatment may need continued refinement and adjustment with disease course. Additionally, as the amount of skin, blood, and/or lymph node involvement varies with each presentation, many therapies can be used in combination to achieve maximal response. These may include more than one skin-directed treatment, skin-directed treatment combined with systemic treatment, or more than one systemic treatment.

MF stage IA patients with limited skin involvement (patches, papules, and/or plaques covering <10% body surface involvement [BSA]) are treated with skin-directed therapies. Potent topical steroids remain the initial preferred option of all the skin-directed therapies for stage IA disease, given ease of application, efficacy, and accessibility. Other skin-directed options include topical mechlorethamine (nitrogen mustard), topical retinoids (bexarotene, tazarotene), phototherapy (narrowband ultraviolet B [NB-UVB] for patches and thin plaques), topical imiquimod, or local radiation therapy (particularly useful for unilesional presentations or thicker plaques).

Stage IB disease comprises non-erythrodermic patients with skin involvement greater than 10% BSA, and thus includes patients with a wider range of skin disease burden. Those with relatively limited skin disease burden (e.g., predominantly patch disease) may be treated with localized skin-directed therapies, similar to stage IA patients. Stage IB patients with higher and diffuse skin disease burden may be candidates for more generalized skin-directed therapies (including NB-UVB phototherapy for patches/thin plaques, PUVA, or low-dose total skin electron beam therapy [TSEBT] for widespread thicker plaques), as well as systemic therapies, either alone or in combination with skin-directed treatment. Low-dose TSEBT (dose range 12 Gy) has demonstrated particular efficacy in the treatment of MF while minimizing toxicities that are more frequent at higher doses of 30–36 Gy. Patients with more extensive or advanced type folliculotropic disease may benefit from incorporating low-dose TSEBT or may require escalating therapy to include a systemic treatment sooner. Systemic treatments are used in stage IB disease

refractory to skin-directed therapies or in those with thicker disease or other adverse prognostic factors such as F-MF or LCT; options include systemic retinoids (bexarotene, acitretin), methotrexate, interferons (such as interferon- α or interferon- γ), vorinostat, or brentuximab vedotin. Systemic treatments that may be of particular use if there is low-level blood involvement (e.g., <1000/mcL Sézary cells) is similar to options used in erythrodermic MF (stage III) and include bexarotene, methotrexate, extracorporeal photopheresis (ECP), or mogamulizumab. Skin-directed or symptom supportive therapies are always optimized and used in addition to systemic therapies.

Stage IIB MF is characterized by skin tumor-type disease, which can present variably as either one to a few skin tumors (with coexisting patches/plaques) to widespread coalescing tumor lesions. Local radiation therapy may be useful if tumors are discrete or limited, while TSEBT is useful for widespread tumors, or tumors arising within thick plaques. As tumor-type MF marks the threshold for advanced-stage disease, systemic therapy is usually indicated and mirrors drugs used in high burden stage IB. As the disease may undergo LCT in the setting of tumor lesion development, repeat skin biopsy is recommended if LCT is suspected in order to capture this significant change in tumor biology. LCT is a poor prognostic factor indicative of aggressive disease and is treated with radiation therapy if limited or systemic therapies if generalized. Systemic therapies that have demonstrated efficacy in LCT include brentuximab vedotin (particularly in the setting of CD30 expression), pralatrexate, romidepsin, or liposomal doxorubicin.

Stage III MF includes those with erythroderma with at most low-level blood involvement, while stage IV disease comprises patients with B2 level blood involvement of $\geq 1000/\text{mcL}$ Sézary cells (IVA1), lymph node involvement (IVA2), or visceral involvement (IVB). Sézary syndrome, by definition, is defined as at least stage IV disease given B2 level blood disease with clonally identical atypical T-cells in both blood and skin. Systemic therapies are often used upfront in stage III and IV disease, though especially in erythrodermic patients, the use of combination and/or supportive skin-directed therapies is essential for optimal clinical outcome and management of pruritus. In stage III erythrodermic MF without significant blood involvement, or stage IV disease with low-level blood involvement (e.g., less than 1000–1500/ mm^3 Sézary cells) and no lymph node or visceral involvement, treatment options include bexarotene, methotrexate (target dose of $\approx 25 \text{ mg/week}$), ECP, interferons, mogamulizumab, or histone deacetylase (HDAC) inhibitors (e.g., vorinostat or romidepsin). For high burden blood involvement (absolute Sézary cells $> 5000/\text{mm}^3$), treatment options include agents that are particularly useful at targeting leukemic cells, including mogamulizumab and romidepsin. Low-dose, subcutaneously administered alemtuzumab may be useful if preferred regimens fail to acutely reduce blood disease, followed by transitioning to systemic therapies that are better utilized for continued treatment.

As multiple compartments may be involved at the same time (skin, blood, lymph node), combination therapies are often used to optimize response. For skin and low-level blood involvement, skin-directed and systemic combinations may include phototherapy + ECP, phototherapy + interferon, phototherapy + systemic retinoid, or low-dose TSEBT + interferon and/or ECP. Systemic combinations useful in the setting of low-level blood involvement include ECP + interferon, and/or retinoid, or retinoid + interferon. For higher burden blood involvement, one may combine skin-directed therapies with mogamulizumab, and for skin, blood, and lymph node involvement (especially with

LCT), romidepsin combined with skin-directed therapies may be particularly useful.

Patients with disease achieving clinical benefit and/or those with disease responding to treatment should be considered for maintenance or tapering regimens to optimize response duration. If persistent or progressive disease is noted despite treatment, or if disease relapses after response, it is recommended to attempt an alternative systemic therapy. Most patients with advanced disease (stages IIB–IV) are treated with multiple single agents before receiving multiagent chemotherapy. Less commonly used options for refractory disease when preferred systemic treatments fail include pembrolizumab, gemcitabine, cyclophosphamide, etoposide, temozolomide (if central nervous system involvement), lenalidomide, or bortezomib. Combination chemotherapy regimens used in systemic T-cell lymphoma would be considered in patients with extensive or bulky extracutaneous disease especially in those bridging to allogeneic hematopoietic stem cell transplantation. Patients should be considered for clinical trial whenever appropriate.

Supportive care measures to address itch and quality of life is a key facet in the care of MF/SS patients. Topical steroids treat both underlying disease and associated pruritus and may be used under occlusion to optimize potency. First-line oral anti-itch agents for pruritus include H1 antihistamines (either as single agents or combining antihistamines from different classes) and/or gabapentin. The addition of low-dose mirtazapine, aprepitant, or selective serotonin reuptake inhibitors may be useful. As chronic skin colonization with *Staphylococcus aureus* (*S. aureus*) may precipitate/exacerbate skin flares, skin culture to evaluate for *S. aureus* burden is recommended; patients may benefit from oral antibiotics during active disease (specific choice based on culture and drug sensitivity data). Dilute bleach baths at least 2–3 times a week additionally serve to keep staph burden low. Other infections such as herpes simplex or varicella/zoster can disseminate rapidly on abnormal skin and, thus, should be considered when appropriate.

Specific Investigations

- Complete blood count with differential
- Comprehensive metabolic panel
- Serum lactate dehydrogenase
- Skin biopsy with immunohistochemistry and T-cell clonality analysis
- If suspicion for advanced disease:
 - Peripheral blood flow cytometry for Sézary cells (aberrant T-cell population)
 - T-cell clonality analysis on peripheral blood or extracutaneous tissue
 - Whole body positron emission tomography/computed tomography (PET-CT) or C/A/P ($\pm$ neck) CT with contrast
 - Biopsy of suspected extracutaneous site (e.g., lymph node)

National Comprehensive Cancer Network. Clinical practice guidelines in oncology. V 1.2021: Primary Cutaneous Lymphomas. Horwitz SM, Ansell S, Ai WZ, et al.

The NCCN evidence-based guidelines discuss diagnosis, workup, clinical staging, and treatment regimens for MF and SS. Treatment regimens are stratified by clinical stage, disease severity, and other prognostic factors and updated based on published evidence and consensus. The 2020 NCCN guidelines incorporated

mogamulizumab, which recently received US Food and Drug Administration (FDA) approval for Sézary syndrome.

Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. Olsen EA, Whittaker S, Kim YH, et al. *J Clin Oncol* 2011; 29(18): 2598–607.

The ISCL/EORTC recommended revisions to the TNM classification and staging system for MF/SS as well as initial evaluation/work-up.

First-Line Therapies

Early-stage MF: I–IIA (patch/plaque skin disease)

- Topical corticosteroids **B**
- Topical mechlorethamine **B**
- Phototherapy (NB-UVB) **D**

Advanced-stage MF or SS: IIB–IVB (tumor, erythrodermic, extracutaneous disease)

- Oral bexarotene (or other retinoids*) **B, D***
- NB-UVB or PUVA ± interferons **B**
- NB-UVB or PUVA ± retinoids **D**
- Methotrexate **D**
- ECP (if blood disease) ± interferon **B**
- Brentuximab vedotin (especially if skin tumors, lymph node disease) **B**
- Mogamulizumab (especially if high blood burden SS) **B**
- TSEBT ± systemic therapy **B**

Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. Lessin SR, Duvic M, Guitart J, et al. *JAMA Dermatol* 2013; 149: 25–32.

Randomized, controlled, multicenter trial evaluating the efficacy and safety of mechlorethamine hydrochloride 0.02% gel and mechlorethamine 0.02% compounded ointment in 260 patients with stage IA–IIA MF who had not used topical mechlorethamine within 2 years. Mechlorethamine was applied once daily for up to 12 months. Response rates for mechlorethamine gel vs. ointment were 58.5% vs. 47.7% by the Composite Assessment of Index Lesion Severity and 46.9% vs. 46.2% by the Modified Severity-Weighted Assessment Tool. No drug-related serious adverse events were seen. Approximately 20.3% of enrolled patients in the gel treatment arm and 17.3% of enrolled patients in the ointment treatment arm withdrew because of drug-related skin irritation. No systemic absorption of the study medication was detected.

Low-dose total skin electron beam therapy as an effective modality to reduce disease burden in patients with mycosis fungoides: results of a pooled analysis from 3 phase-II clinical trials. Hoppe RT, Harrison C, Tavallae M, et al. *J Am Acad Dermatol* 2015; 72(2): 286–92.

This study evaluated the efficacy and tolerability associated with low-dose (12 Gy) TSEBT using pooled data from three clinical trials using low-dose (12 Gy) TSEBT. In all trials, TSEBT-naïve patients with stage IB–IIIA MF were treated with TSEBT (12 Gy, 1 Gy per fraction over 3 weeks). The primary end point was clinical response

rate. In total, 33 patients were enrolled with overall response rate (ORR) of 88% (29/33), including nine patients with complete response. Median time to response was 7.6 weeks (3–12.4 weeks). Median duration of clinical benefit was 70.7 weeks.

Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II–III trial results. Duvic M, Hymes K, Heald P, et al. *J Clin Oncol* 2001; 19: 2456–71.

Bexarotene is an FDA-approved treatment for early- and advanced-stage CTCL based on two clinical studies. One of these studies was a multinational, single-arm, phase II–III trial of 94 patients with advanced-stage (IIB–IVB) CTCL treated with oral bexarotene that demonstrated response rates of 45% and 55% with 300 mg/m²/day or greater doses of bexarotene, respectively. Most frequent, but reversible, drug-related side effects included hypertriglyceridemia, hypercholesterolemia, hypothyroidism, and headache. The study concluded that bexarotene is safe, effective, and generally well tolerated.

Low-dose methotrexate to treat mycosis fungoides: a retrospective study in 69 patients. Zackheim HS, Kashani-Sabet M, McMillan A. *J Am Acad Dermatol* 2003; 49: 873–8.

Low-dose methotrexate to treat erythrodermic CTCL: results in 29 patients. Zackheim HS, Mashani-Sabet M, Hwang ST, J Am Acad Dermatol 1996; 34: 626–31.

This was a retrospective review of 69 patients with patch/plaque T2 and tumor T3 MF disease treated with oral methotrexate, median dose of 25 mg weekly until treatment failure. Low-dose methotrexate had an ORR of 33% in patch/plaque MF, 14% in tumor disease, and 58% in erythrodermic patients.

Treatment of erythrodermic cutaneous T-cell lymphoma with extracorporeal photochemotherapy. Heald P, Rook A, Perez M, et al. *J Am Acad Dermatol* 1992; 27(3): 427–33.

Long-term follow-up of 29 erythrodermic CTCL patients treated with photopheresis demonstrated six patients that achieved complete remission and another six patients that had more than 50% improvement of skin scores. Five patients had either no change or progression of disease in the skin; remaining patients had an improvement in skin scores associated with improvement in quality of life.

Long-term follow-up of patients with cutaneous T-cell lymphoma treated with extracorporeal photochemotherapy. Zic JA, Stricklin GP, Greer JP, et al. *J Am Acad Dermatol* 1996; 35: 935–45.

Twenty patients with refractory CTCL in various stages of cutaneous involvement who had received at least 6 months of ECP between September 1988 and April 1991 were evaluated retrospectively. A complete response (disappearance of all lesions) was obtained in five patients (25%) and a partial response (disappearance of at least 50% of lesions) in five patients (25%). Of the 10 responders, seven (70%) were weaned from ECP. Ten patients (50%) showed no response to ECP. No statistically significant differences between responders and non-responders were found with respect to demographic, clinical, or laboratory variables. Adverse effects were minimal.

Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Prince HM, Kim YH, Horwitz SM, et al. *The Lancet* 2018; 390: 555–66.

This study aimed to assess the efficacy and safety of brentuximab vedotin vs. conventional therapy for previously treated patients with CD30-positive CTCL. This was an international, open-label, randomized, phase 3 trial where patients with CD30-positive MF or primary cutaneous anaplastic large-cell lymphoma who had been previously treated were enrolled. Patients were randomly assigned (1:1) to receive intravenous brentuximab vedotin 1.8 mg/kg once every 3 weeks, for up to 16 cycles, or physician's choice (oral methotrexate 5–50 mg once per week or oral bexarotene 300 mg/m² once per day) for up to 48 weeks. In the intention-to-treat population, 128 patients were analyzed (64 in each arm). At a median follow-up of 22.9 months, the proportion of patients achieving an objective global response lasting at least 4 months was 56.3% (36 of 64 patients) with brentuximab vedotin vs. 12.5% (8 of 64) with physician's choice. Grade 3–4 adverse events were reported in 27 (41%) of 66 patients in the brentuximab vedotin group and 29 (47%) of 62 patients in the physician's choice group. Peripheral neuropathy was seen in 44 (67%) of 66 patients in the brentuximab vedotin group ($n=21$ grade 2, $n=6$ grade 3) and four (6%) of 62 patients in the physician's choice group.

Phase II investigator-initiated study of brentuximab vedotin in mycosis fungoides and Sézary syndrome with variable CD30 expression level: a multi-institution collaborative project. Kim YH, Tavalae M, Sundram U, et al. *J Clin Oncol* 2015; 33(32): 3750–8.

Phase 2 study evaluated the clinical activity and safety of brentuximab vedotin in MF and SS across differing levels of CD30 expression. Patients with MF or SS with negligible to 100% CD30 expression levels were treated with brentuximab vedotin (1.8 mg/kg) every 3 weeks for a maximum of 16 doses. The primary end point was overall global response rate. Secondary end points included correlation of tissue CD30 expression level with clinical response, time to response, duration of response, and progression-free and event-free survivals. Of the 32 patients enrolled and treated, 30 patients had available efficacy evaluations. Objective global response was observed in 21 (70%) of 30 patients. CD30 expression assessed by immunohistochemistry was highly variable, with a median CD30max of 13% (range 0% to 100%). Those with <5% CD30 expression had a lower likelihood of global response than did those with 5% or greater CD30 expression ($p < 0.005$). Peripheral neuropathy was the most common adverse event. The study demonstrated that brentuximab vedotin had significant clinical activity in treatment-refractory or advanced MF or SS with a wide range of CD30 expression levels.

Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Kim YH, Bagot M, Pinter-Brown L, et al. *Lancet Oncol* 2018; 19: 1192–204.

Mogamulizumab, a monoclonal antibody targeting the chemokine receptor type 4 (CCR4), was approved by the FDA for MF or SS based on the MAVORIC trial. This pivotal international, open-label, phase III, randomized-controlled trial compared mogamulizumab 1 mg/kg intravenously weekly for the first month, then on days 1 and 15 of subsequent cycles with vorinostat 400 mg daily in 370 patients, excluding LCT. Mogamulizumab was superior to vorinostat in investigator-assessed progression-free survival (PFS) for patients with MF or SS, with median of 7.7 months compared with 3.1 months, respectively. ORRs were significantly higher for patients treated with mogamulizumab than for vorinostat (28%

vs. 5%). In patient subgroups, ORRs were higher for patients with SS than with MF (37% vs. 21%). Blood response rate was significantly higher for patients treated with mogamulizumab compared with vorinostat (68% vs. 19%). Overall duration of response was also significantly higher for patients treated with mogamulizumab than vorinostat (14.1 vs. 9.1 months). Thus, mogamulizumab is particularly effective for patients with SS due to its high complete response rate in blood compartment. The most common adverse events were infusion-related reactions, drug rash, diarrhea, and fatigue.

Second-Line Therapies

Early-stage MF: I–IIA (patch/plaque skin disease)

- Topical bexarotene or other retinoid (tazarotene*) **B, D***
- Topical imiquimod **C**
- PUVA **D**
- Low-dose TSEBT **B**
- Oral bexarotene (or other retinoids* – acitretin, isotretinoin) **B, D***
- Methotrexate **D**
- NB-UVB or PUVA + interferon **B**
- NB-UVB or PUVA + retinoid **D**

Advanced-stage MF or SS: IIB–IV (tumor, erythrodermic, extracutaneous disease)

- Systemic retinoid + interferon **B**
- Romidepsin **B**
- Vorinostat **B**
- Pralatrexate **B**
- Liposomal doxorubicin (especially if skin tumors, lymph node disease) **B**

Phase 1 and 2 trial of bexarotene gel for skin directed treatment of patients with cutaneous T cell lymphoma. Breneman D, Duvic M, Kuzel T, et al. *Arch Dermatol* 2002; 138: 325–32.

This phase 1 and 2, open-label, dose-escalation clinical trial of bexarotene gel evaluated the safety, dose tolerance, and efficacy of topical bexarotene gel in patients with early-stage CTCL. The study participants included 67 adults with early-stage (stages IA–IIA) MF. Bexarotene gel, 0.1%, 0.5%, and 1.0%, was applied to areas of disease involvement in incremental dose adjustments from 0.1% gel every day to 1.0% gel four times daily or the maximal tolerated dose. Patients achieved an ORR of 63% and a clinical complete response rate of 21%. Median projected time to onset of response was 20.1 weeks (range 4.0–86.0 weeks), and the estimated median response duration from the start of therapy was 99 weeks.

Treatment of patch and plaque stage mycosis fungoides with imiquimod 5% cream. Deeths MJ, Chapman JT, Dellavalle RP, et al. *J Am Acad Dermatol* 2005; 52: 275–80.

This study evaluated the safety and efficacy of topical imiquimod 5% cream for the treatment of patch and plaque MF. Six patients with stage IA–IIB MF were treated with topical imiquimod 5% cream three times per week for 12 weeks in this open-label pilot study. Index lesions were biopsied pre- and posttreatment, and up to four additional treated lesions were monitored for 16 weeks. Three of six patients had histologic clearance of disease in index lesions. A fourth patient had two of four lesions respond

clinically. Application site reactions were limited to those patients responding to treatment, although the medication was overall well tolerated.

Phase 2 and 3 clinical trial of oral bexarotene for treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Duvic M, Martin AG, Kim Y, et al. *Arch Dermatol* 2001; 137: 581–93.

Multicenter trial of 58 patients with refractory early-stage MF (stages IA–IIA). At preferred daily dose of 300 mg/m², responses were seen in 54% (15 of 28). Patients were treated until disease progression or intolerable toxicity. Rate of progressive disease was 21%. Most common toxicities included hyperlipidemia (>70%), headache, central hypothyroidism, and leukopenia. Anti-lipid treatment and thyroid replacement was frequently utilized.

Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. Whittaker SJ, Demierre MF, Kim EJ, et al. *J Clin Oncol* 2010; 28: 4485–91.

Romidepsin is FDA approved for patients with CTCL (MF or SS) who received at least one prior systemic therapy. This international, open-label, single-arm phase II study assessed response of intravenous romidepsin infusion at a dose of 14 mg/m² on days 1, 8, and 15 every 28 days in 96 patients with stage IB–IVA MF or SS, including LCT. Response rate was 34%, with a median time to response of 2 months and median duration of response of 15 months. Clinically meaningful improvement in pruritus was seen in 43% of 65 patients, with a median duration of pruritus reduction of 6 months. Mild drug-related adverse events included gastrointestinal disturbances and fatigue. This study concluded that romidepsin is an effective single-agent therapy for CTCL patients across all stages, including advanced disease and blood and/or lymph node involvement.

Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma. Horwitz SM, Kim YH, Foss F, et al. *Blood* 2012; 119: 4115–22.

Pralatrexate is FDA approved for treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL), based on the pivotal PROPEL trial that included transformed MF only. Instead of the PTCL dosing of intravenous pralatrexate at 30 mg/m²/week for 6 weeks out of a 7-week cycle, this dose deescalation study identified a recommended regimen in relapsed/refractory CTCL (MF, SS, or primary cutaneous anaplastic large-cell lymphoma) population for pralatrexate dosing that demonstrated high efficacy and tolerability of pralatrexate, which was 15 mg/m²/week for 3 out of every 4 weeks. In 29 patients treated with this recommended dosing regimen, response rate was 45%, with better evidence for MF, LCT, and lymph node disease than SS. The most frequent adverse events were mucositis and fatigue. Vitamin B₁₂ and folate supplementation are recommended to reduce risk of mucositis with treatment.

Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012. Dummer R, Quaglino P, Becker JC, et al. *J Clin Oncol* 2012; 30: 4091–7.

This study assessed 49 patients with advanced MF treated with a maximum of six cycles of pegylated liposomal doxorubicin 20 mg/m² on days 1 and 15 of every 28-day cycle. Response rate was 40.8%, with a median duration of response of 6 months. Cardiovascular toxicity and disease progression resulted in two deaths.

Third-Line Therapies

Early-stage MF: I–IIA (patch/plaque skin disease)

• Brentuximab vedotin	B
• Mogamulizumab	B
• Vorinostat	B
• Romidepsin	B
• Clinical trials	

Advanced-stage MF or SS: IIB–IV (tumor, erythrodermic, extracutaneous disease)

• Pembrolizumab	B
• Alemtuzumab (especially if blood disease)	C
• Gemcitabine	B
• Clinical trials	
• Combination chemotherapy (especially as bridge to transplant)	D
• Consider allogeneic hematopoietic stem cell transplant	B

Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. Olsen EA, Kim YH, Kuzel TM, et al. *J Clin Oncol* 2007; 25: 3109–15.

This phase IIb study evaluated the activity and safety of vorinostat 400 mg orally daily in 74 patients with at least stage IB MF or SS. The overall objective response rate was 29.7%, with 29.5% response rate in patients with stage IIB or higher. The most common adverse events were diarrhea, fatigue, nausea, and anorexia.

Alemtuzumab for relapsed and refractory erythrodermic cutaneous T-cell lymphoma: a single institution experience from the Robert H. Lurie Comprehensive Cancer Center. Querfeld C, Mehta N, Rosen ST, et al. *Leuk Lymphoma* 2009; 50: 1969–76.

This was an open-label clinical trial investigating the clinical use of alemtuzumab in 19 patients with advanced erythrodermic CTCL, including erythrodermic MF and SS. Ten patients received alemtuzumab intravenously using an escalating dose regimen with a final dose of 30 mg three times weekly for 4 weeks followed by subcutaneous administration for 8 weeks. Nine patients were treated with only the subcutaneous or IV dosing. The ORR was 84%, with nine (47%) complete and seven (37%) partial remissions. The median follow-up was 24 months. Median overall survival was 41 months, whereas median PFS was 6 months. Toxicities included myelosuppression and infections; however, the majority of side effects were of Grade 2 in severity and transient.

Pembrolizumab in relapsed and refractory mycosis fungoides and Sézary syndrome: a multicenter phase II study. Khodadoust MS, Rook AH, Porcu P, et al. *J Clin Oncol* 2019.

The aim of this multicenter, single-arm, phase II trial was to assess the efficacy and safety of pembrolizumab 2 mg/kg every 3 weeks for up to 24 months in 24 patients with advanced MF or SS. ORR was 38% and PFS at 1 year was 65%. Disease flare with a transient worsening of erythroderma and pruritus were uniquely noted in 53% of SS patients, but did not cause treatment discontinuation. Exploratory biomarker studies did not identify a significant association of PD-L1 expression and clinical response. Thus, this study concluded that pembrolizumab had significant clinical activity with durable response.

Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma. Duvic M, Talpur R, Wen S, et al. Clin Lymphoma Myeloma 2006; 7: 51–8.

Twenty-five patients with CTCL on a phase II open-label trial and eight patients off study received intravenous gemcitabine (1000 mg/m²) on days 1, 8, and 15 for > or = six cycles. Thirty-one patients with MF (stage IB [*n* = 2], stage IIA [*n* = 1], stage IIB [*n* = 13], stage IVA [*n* = 7], and stage IVB [*n* = 8]) were enrolled along with two patients with CD30 positive anaplastic large T-cell lymphoma. Responses were seen in 17 of 25 (68%) study patients (2 complete responses [8%]) and 4 of 8 patients (1 complete response) off protocol. Seven of 13 with stage IIB MF responded, 10 had tumor burden reductions, and 8 of 11 patients with SS responded. Gemcitabine was well tolerated. Myelosuppression, hemolytic uremic syndrome (in 2 elderly with SS), pulmonary embolism, and one episode each of congestive heart failure, acute myocardial infarction, and stable angina were observed.

Allogeneic Hematopoietic Stem Cell Transplantation

Nonmyeloablative allogeneic transplantation achieves clinical and molecular remission in cutaneous T-cell lymphoma. Weng WK, Arai S, Rezvani A, et al. Blood Adv 2020; 4(18): 4482.

A prospective phase 2 clinical trial of a novel non-myeloablative allogeneic stem cell transplantation (SCT) in 35 patients with refractory advanced-stage MF or SS who received multiple systemic therapies. All patients received conditioning using TSEBT, total lymphoid irradiation, and antithymocyte globulin prior to allograft infusion as outpatients. Non-relapse mortality at 1

and 2 years were 3% and 14%, respectively. Incidence of grade 2 to grade 4 acute graft-versus-host disease (GVHD) at day +190 was 16%. The overall survival (OS) rates at 2, 3, and 5 years were 68%, 62%, and 56%. There was a high ORR, with 57% of patients achieving clinical remission. Using high-throughput sequencing of the T-cell receptor for minimal residual disease evaluation, it was observed that 43% of patients achieved molecular remission. The study demonstrated that this non-myeloablative allotransplant is safe and effective in CTCL.

Allogeneic stem-cell transplantation in patients with cutaneous lymphoma: updated results from a single institution. Hosing C, Bassett R, Dabaja B, et al. Ann Oncol 2015; 26(12): 2490–5.

Prospective case series of 47 CTCL patients who underwent *allogeneic* SCT after failure of standard therapy between July 2001 and September 2013 at a single academic institution. The Kaplan–Meier estimates of OS and PFS at 4 years were 51% and 26%, respectively. There was no statistical difference in the OS in patients who had MF alone, SS, MF with LCT, or SS with LCT. The incidence of disease progression/relapse following SCT was 50%. A majority of patients progressed within 6 months of SCT. At the time of the report, 27 of the 47 patients who underwent SCT were alive; of these patients, 20 were in CR. A total of 22 patients received additional therapy post-transplant for relapsed disease; eight of 22 achieved a second CR. Most patients who relapsed or progressed posttransplant received a combination of immunosuppression withdrawal, skin-directed therapies, ECP, and/or chemotherapy. The study demonstrated that *allogeneic* SCT may result in long-term remissions in a subset of patients with advanced CTCL.

Myiasis

Stephanie Liu, Robert G. Phelps



Myiasis is the infestation of human and animal tissue by the larval or pupal stages of two-winged true flies (Diptera), most commonly the *Dermatobia hominis* (botfly) and *Cordylobia anthropophaga* (tumbu fly). It is typically found in tropical and subtropical regions and is rare elsewhere. Its development is associated with poor hygiene, poor housing conditions, and an overall debilitated state. Patients present with enlarging insect bites, ulceration, furuncle, or wound ulceration with sensation of irritation and lancinating pain. Larvae infest necrotic or viable skin but may also infest the eyes, ears, nose, and gastrointestinal (GI) or genitourinary (GU) sites.

MANAGEMENT STRATEGY

Myiasis was a major public health concern in the early 20th century. Improvements in hygiene and wound care have significantly decreased its incidence. Manner of transmission differs depending on the species of flies. Furuncular myiasis is the most common and occurs through larvae burrowing into normal skin.

Therapy objectives include complete larvae removal and prevention of secondary infestations and bacterial infections. Risk of exposure is often linked to travel. Visitors to rural regions should be covered at all times with long-sleeved garments and hats. Because many larvae vectors include blood-seeking arthropods, sleeping

with a mosquito net at night is recommended. Liberal use of insect repellents is likewise useful. All clothing should be hot ironed and thoroughly dried to remove any residual eggs. To prevent barefoot transmission of fly eggs from the soil, appropriate footwear should be utilized. Wound myiasis can be prevented using antiseptic techniques. Wound cleaning, irrigation, and regular dressing changes are usually sufficient. As a precaution, patients with large wounds should sleep indoors only and with windows closed.

Once infestation has occurred, therapy consists of surgical removal of all larvae with minimal trauma to the organisms. Simple infiltration of the area with lidocaine and surgical removal is the standard of care when few organisms are present. Occlusive therapy (using petroleum jelly or strips of bacon), inducing larvae to protrude their abdomen to reach air, may be helpful when many larvae are present. Careful technique must be used to extract the larvae whole; otherwise, a considerable foreign body reaction may ensue. If there is secondary pyogenic infection, this should be treated with antibiotics. Supplemental treatments including isopropyl alcohol, Dakin solution, iodine, or hydrogen peroxide can be included in wound care. Anecdotal reports suggest use of topical and systemic ivermectin for complicated conditions (extensive or multiple lesions, substantial involvement of orbital or oral cavities, or failure of surgical extraction).

Specific Investigations

- Detailed travel history
- Morphologic and molecular identification of the parasite

A blow to the fly—*Lucilia cuprina* draft genome and transcriptome to support advances in biology and biotechnology. Anstead CA, Batterham P, Korhonen PK, et al. Biotechnol Adv 2016; 34: 605–20.

Draft genome and transcriptome of the blow fly give new and global insights into its biology and aspects of insecticide resistance at the molecular level, and aid the design of new and improved interventions for myiasis.

Molecular identification of two species of myiasis – causing *Cuterebra* by multiplex PCR and RFLP. Noel S, Tessier N, Angers B, et al. Med Vet Entomol 2004; 18: 161–6.

The fly larvae should be extracted whole and specific identification attempted. The adult fly should be identified, if possible often in consultation with an entomologist. Scanning electron microscopy and multiplex polymerase chain reaction (PCR) may aid identification.

Wound myiasis: the role of entodermoscopy. Gontijo JR, Bitencourt FV. An Bras Dermatol 2018; 93(5): 746–8.

The use of a dermatoscope helped identify live larvae in a patient with seborrheic dermatitis but without the clinical history of a wound or an ulcer.

Identification of subcutaneous myiasis using bedside emergency physician performed ultrasound. Schechter E, Lazar J, Nix ME, et al. J Emerg Med 2011; 40: e1–3.

Ultrasound diagnosis of patient with *C. anthropophaga* maggot infestation with hyperechoic areas.

First-Line Therapies

Surgical therapy

- Surgical removal with local anesthesia with or without adjuvant suffocation techniques **D**

Asphyxiation therapy

- Vaseline therapy **E**
- Bacon therapy **E**
- Pork fat therapy **E**
- Hair gel therapy **E**
- Occlusion with *chimo* (paste-like form of smokeless tobacco) **E**
- Small wad of cotton soaked in the sap of the *Thevetia ahouai* (Apocynaceae) tree **E**

Myiasis in travelers. Lachish T, Marhoom E, Kosta Y, et al. *J Travel Med* 2015; 22: 232–6.

This retrospective, observational study identified 90 patients diagnosed with myiasis from posttravel clinics in Israel. Of these cases, 76% were managed by manual extraction, performed after covering the central pore of the lesion with a sealing ointment such as paraffin.

Myiasis: a traveler's dilemma. Mammino J, Lal K. *J Clin Aesthet Dermatol* 2013; 6: 47–9.

Scalp myiasis successfully extracted with excisional biopsy technique under local anesthesia. This assures that the larvae are fully removed.

Cutaneous myiasis. Krajewski A, Allen B, Hoss D, et al. *J Plast Reconstr Aesthet Surg* 2009; 62: e383–6.

The favored treatment modality is complete surgical extraction of larvae from the lesion to prevent the risk of secondary infection associated with retained larvae.

One catches not only mice with bacon. An atraumatic treatment for cutaneous myiasis. Schulte C, Schunk M, Krebs B. *Dtsch Med Wochenschr* 2002; 127: 266–8.

A piece of raw bacon, serving as occlusion material, was fixated on the affected skin for 2 hours. After retraction of the bacon it was possible to grasp the emerged end of the larvae with tweezers and pull them out completely.

Alternatives to bacon therapy. Biggar RJ. *JAMA* 1994; 271: 901–2.

The authors use Vaseline over the wound to smother the larvae, and they emerge spontaneously.

Traditional methods encourage the larva to exit on its own, taking advantage of its need for oxygen, by using various occlusive dressings to suffocate it.

Dermal myiasis: the porcine lipid cure. Sauder DN, Hall RP, Wurster CF. *Arch Dermatol* 1981; 117: 681–2.

Pork fat was placed on the lesions and covered with an occlusive tape, and the emerging larvae were extracted with forceps.

Second-Line Therapies

- Systemic ivermectin **E**
- Topical ivermectin **E**
- Chlorhexidine gluconate rinses **E**
- Pyrantel pamoate **E**
- Radiation therapy **E**
- Chloroform/ether **E**
- Mineral turpentine **E**
- Ethanol spray **E**
- Oil of betel leaf **E**
- Mineral turpentine **E**

Oral myiasis: a rare case report and literature review. Shikha S, Prasad Guru R, Ashutoshdutt P, et al. *J Dent (Tehran)* 2015; 12: 456–9.

For extensive disease in the oral cavity, the treatment was systemic ivermectin 6mg once daily for 3 days, oral amoxicillin 250mg three times daily for 7 days and mouth rinse twice daily with 0.2% chlorhexidine gluconate for 15 days.

Use of ivermectin in the treatment of orbital myiasis caused by *Cochliomyia hominivorax*. De Tarso P, Pierre-Filho P, Minguin N, et al. *Scand J Infect Dis* 2004; 36: 503–5.

One dose of ivermectin (200mcg/kg) was used for infestation with *Hypoderma lineatum* and led to spontaneous migration of the maggots.

Myiasis owing to *Dermatobia hominis* in a HIV-infected subject: treatment by topical ivermectin. Clyti E, Nacher M, Merrien L, et al. *Int J Dermatol* 2007; 46: 52–4.

Human immunodeficiency virus (HIV) infection did not modify the pathogenicity of myiasis but did contribute unusually extensive and voluminous inflammatory nodules. Use of topical ivermectin killed the larvae and facilitated their extraction.

Myiasis: successful treatment with topical ivermectin. Victoria J, Trujillo R, Barreto M. *Int J Dermatol* 1999; 38: 142–4.

Four patients presented with traumatic myiasis caused by *C. hominivorax* with 50–100 larvae were treated with 1% topical ivermectin in a propylene glycol solution for 2 hours, followed by gentle washing with normal saline or sterile water. Within 1 hour, almost all larvae stopped moving, and within 24 hours, all died.

Nasal myiasis: a case report. White ZL, Chu MW, Hood RJ. *Ear Nose Throat J* 2015; 94: e24–5.

Two patients without necrosis or large masses were successfully treated with conservative therapy, consisting of a single dose of pyrantel pamoate, daily sinus irrigation with saline, and daily bedside endoscopic debridement.

Head and neck myiasis, cutaneous malignancy, and infection: a case series and review of the literature. Jennifer A, Villwock JA, Harris TM. *J Emerg Med* 2014; 47: e37–41.

One patient in the case series received radiation beam therapy for her concurrent squamous cell carcinoma, which serendipitously eradicated the larvae infection. Use of this modality for myiasis treatment has not been previously reported.

Larvicidal effects of mineral turpentine, low aromatic white spirits, aqueous extracts of *Cassia alata*, and aqueous extracts, ethanolic extracts and essential oil of betel leaf (*Piper betle*) on *Chrysomya megacephala*. Kumarasinghe SP, Karunaweera ND, Ihalamulla RL, et al. *Int J Dermatol* 2002; 41: 877–80.

Mineral turpentine and its main ingredient, low aromatic white spirits, were shown to kill all *Chrysomya* larvae within 4 hours. Betel oil dilutions of 3% and 4% were effective in killing all of the larvae within 3 and a half hours, and a dilution of 2% was effective in killing 96.7% of larvae in four hours.

Management of malignant wound myiasis with ivermectin, albendazole, and clindamycin (triple therapy) in advanced head-and-neck cancer patients: a prospective observational study. Patel BC, Ostwal S, Sanghavi PR, et al. *Indian J Palliat Care* 2018; 24(4): 459.

Twenty-five adult head-and-neck cancer patients with myiasis were given triple therapy with ivermectin 12 mg, albendazole

400 mg twice a day, and clindamycin 300 mg three times a day. Turpentine oil was also applied twice a day and larvae were removed manually. Patients had a significant reduction (92.62%) of larvae by day 3, with complete resolution by day 4. The treatment was well tolerated, with the most common side effects reported as diarrhea, headache, and giddiness, which resolved.

Maggot infestation: various treatment modalities. Sunny B, Sulthana L, James A, et al. *J Am Coll Clin Wound Spec* 2016; 8(1–3): 51–3.

Injection of lidocaine may serve as a way to force larvae to the surface. Lidocaine is injected into the base of the tissue beneath the larva and causes a local swelling. This is only useful for single or small numbers of larvae due to lidocaine toxicity.

Treatment of nasal myiasis with ivermectin irrigation. Tay SY, Ramasamy BR, Watson DA, et al. *BMJ Case Reports* 2018; 2018: bcr-2017.

After failed attempts to manually remove larvae, the patient's nostrils were irrigated with 0.04% ivermectin solution. Numerous larvae were expelled within 15 min after sneezing and coughing. A repeated nasal irrigation after 3 days did not produce additional larvae.

Myxoid cyst

David de Berker



Myxoid cysts are also known as *digital mucus cysts* or *pseudocysts* and represent a ganglion of the distal interphalangeal joint. They arise in different forms in soft tissues, typically above or distal to the distal interphalangeal joint. The most common presentation is as a translucent nodule on the dorsum of the digit. Additional patterns of presentation include as a pseudofibroma emerging between the proximal nailfold and dorsal aspect of the nail plate, or as a tumor beneath the nail matrix causing a red lunula, increased transverse curvature of the nail, and sometimes its disintegration.

MANAGEMENT STRATEGY

Myxoid cysts contain gelatinous material that has escaped from the distal interphalangeal joint. Treatment can involve evacuation combined with measures to prevent further escape from the joint. *Simple drainage* through an incision can achieve the first, but normally there is recurrence within a few weeks. Measures to prevent the further accumulation of fluid are directed at reducing joint pathology or blocking the pathway of escape of fluid. The first category includes the use of *injected triamcinolone*, which might reduce synovial inflammation and the pressure of fluid within the joint, and *surgery* for osteophytes. Osteophytes appear to weaken the joint capsule and possibly contribute to joint pathology and synovial fluid production. Their removal is associated with resolution of the myxoid cyst but at the risk of alteration of joint function.

Blockage of the path of fluid escape is achieved by a range of traumatic and scarring procedures. The challenge is to produce an effective scar over the joint without excess morbidity or a long-term nail dystrophy.

A practical compromise of morbidity, complexity of treatment, and efficacy is to employ *cryosurgery* in the first instance. This is best used with a distal block using lidocaine or bupivacaine. The cyst is then incised and drained. Two freezes of between 10 and 20

seconds with liquid nitrogen are given, with a complete thaw in between. Over the next 2 weeks the wound is dressed. This results in success in about 50% of cases involving fingers. Those that fail can be retreated in the same way or proceed to surgery. Morbidity is least when there is *precise surgery* to the path of fluid escape. This can be identified and then ligatured following methylene blue injection into the joint and then raising a flap in a distal-to-proximal path, containing the cyst in the roof of the flap. In many instances it is possible to gain the same benefit without preliminary dye injection. The flap is sutured back in place, and success is reported as 94% in the fingers. In some instances, patient preference or medical considerations may mean that surgery is the first-line therapy.

Specific Investigations

- Transillumination
- Pricking and expression of gelatinous material
- Ultrasound
- Magnetic resonance imaging (MRI)

Transillumination is a useful clinical aid. Dermoscopy can be used, but rarely improves on transillumination. Where there is diagnostic doubt, simple incision can be helpful to demonstrate the gelatinous material. Alternatively, high-resolution ultrasound or MRI can be employed. The first can only help define whether the structure is cystic or not. The latter provides better anatomic definition and in over 80% of cases allows location of the pedicle communicating between the cyst and joint. Plain X-ray may reveal osteophytes of osteoarthritis, but this will not usually alter treatment.

Dermoscopic features of digital mucous cysts: a study of 23 cases. Chae JB, Ohn J, Mun JH. *J Dermatol* 2017 Nov; 44(11): 1309–12.

Benign tumors and pseudotumors of the nail: a novel application of sonography. Wortsman X, Wortsman J, Soto R, et al. *J Ultrasound Med* 2010; 29: 803–16.

MR imaging of digital mucoid cysts. Drapé JL, Idy Peretti I, Goettmann S. *Radiology* 1996; 200: 531–6.

First-Line Therapies

• Cryosurgery	B
• Puncture	D
• Laser therapy	C
• Sclerosant	C

Myxoid cysts of the finger: treatment by liquid nitrogen spray cryosurgery. Dawber RPR, Sonnex T, Leonard J, et al. *Clin Exp Dermatol* 1983; 8: 153–7.

Fourteen patients were treated with two 30-second freezes and no evacuation of the cyst. Follow-up was between 14 and 40 months, with an 86% cure rate. One patient had a significant nail dystrophy as a long-term complication.

Removal of the overlying cyst or evacuation of the contents might reduce the duration of cryosurgery needed. Longer freeze times increase morbidity and risk of scarring.

Specific indications for cryosurgery of the nail unit. Kuflik EG. *J Dermatol Surg Oncol* 1992; 18: 702–6.

Forty-nine patients were treated with a range of single cryosurgical doses, from 20 to 30 seconds using open spray, and 30 to 40

seconds using the cryoprobe. This was combined with curettage in 23 patients and simple deroofting in the remainder. There was resolution in 63% over the follow-up period of 1–60 months.

A simple technique for managing digital mucous cysts.

Epstein E. Arch Dermatol 1979; 115: 1315–6.

Repeated puncture of myxoid cysts in 40 patients led to resolution in 72% after two to five treatments, but no follow-up period is given.

Blunt force may be an effective treatment for ganglion cysts.

Trivedi NN, Schreiber JJ, Daluiski A. HSS J 2016; 12: 100–4.

Review of reports of aspiration treatment suggests overall success rate of 53%.
Blunt force alone may be sufficient as reported by Trivedi et al. based on online self-reporting. But details are not well documented, as it is usually done as self-care.

Treatment of digital myxoid cysts with carbon dioxide laser vaporization.

Huerter CJ, Wheeland RG, Bailin PL, et al. J Dermatol Surg Oncol 1987; 13: 723–7.

Carbon dioxide laser cured 10 patients with follow-up of 35 months.

Treatment of digital mucous cysts with intralesional sodium tetradecyl sulfate injection.

Park SE, Park EJ, Kim SS, et al. Dermatol Surg 2014; 40: 1249–54.

The sclerosant sodium tetradecyl sulfate 1% (fingers) or 3% (toes) 0.2–0.5 mL was injected into a lesion after aspiration of the gel. It was then repeated every 4 weeks if the cyst persisted, up to seven times (mean 2.3), with eventual resolution in 80% and subsequent relapse in a further two patients (10%) after a mean follow-up of 16 months (range 2–38 months).

Treatment of 63 subjects with digital mucous cysts with percutaneous sclerotherapy using polidocanol.

Esson GA, Holme SA. Dermatol Surg 2016; 42: 59–62.

Three percent polidocanol (0.02–0.5 mL) is a sclerosant that can be used in a similar way with similar results.

An 18-month follow-up of digital myxoid cysts after therapy with percutaneous sclerotherapy with polidocanol.

Mesa-Álvarez L, Salgado-Boquete L, Flórez-Menéndez MÁ. Dermatol Surg 2018; 44(1): 140–2.

A relapse rate of 10% is reported during 18-month follow-up with similar treatment.
Some reports have described necrosis of the nailfold, but this is seldom extensive. The theoretical complication of sclerosant entering the joint does not appear to occur.

Second-Line Therapy

- Surgery

B

Marginal osteophyte excision in treatment of mucous cysts.

Eaton RG, Dobranski AI, Littler JW. J Bone Joint Surg 1973; 55A: 570–4.

In this series, surgery that entailed tracing of the communication between cyst and joint, excision of the cyst, and, in some instances, surgery to the osteophytes provided success in 43 of 44 patients, with follow-up of between 6 months and 10 years.

There is a theoretical possibility of operating on the osteophytes alone, leaving the cyst in place and allowing it to involute once the precipitating pathology has been removed.

Etiology and treatment of the so-called mucous cyst of the finger.

Kleinert HE, Kutz JE, Fishman JH, et al. J Bone Joint Surg 1972; 54: 1455–8.

Similar surgery, but with less emphasis on osteophyte debridement, resulted in success for all of 36 patients followed for between 12 and 18 months postoperatively.

Use of Wolfe graft for the treatment of mucous cysts.

Jamnadas-Khoda B, Agarwal R, Harper R, et al. J Hand Surg Eur 2009; 34: 519–21.

Forty-nine patients with 51 myxoid cysts underwent excision of the cyst on the dorsum of a finger with repair using a full-thickness graft taken from the flexor crease of the wrist. Recurrence rate rose from zero at 4 months to at least 4% longer term.

Proximal nail fold flap dissection for digital myxoid cysts – a 7 year experience.

Eke U, Ahmed I, Ilchysyn A. Dermatol Surg 2014; 40: 206–8.

Flap repair with a longer follow-up in 18 patients revealed 37% relapse rate over 5–84 months (median 29.7).

Ganglion of the distal interphalangeal joint (myxoid cyst): therapy by identification and repair of the leak of joint fluid.

de Berker D, Lawrence C. Arch Dermatol 2001; 137: 607–10.

A study of 54 patients used methylene blue dye injected into the distal interphalangeal joint to identify the communication between the joint and the cyst. A skin flap was designed around the cyst. The communication was sutured and the flap replaced with no tissue excision. In 89% of patients the communication was identified. At 8 months, 48 patients remained cured with no visible scarring. Myxoid cysts of the toes had a higher relapse rate than those of the fingers.

Skin excision and osteophyte removal is not required in the surgical treatment of digital myxoid cysts.

Lawrence C. Arch Dermatol 2005; 141: 1560–4.

The procedure in this study was limited to raising a flap overlying the distal interphalangeal joint, draining the mucoid content of the cyst, and cauterizing the underlying soft tissues on the joint. The flap was sutured back in place. Over 8 months, 24 of 26 (92%) of finger myxoid cysts remained cured. Cure rate for myxoid cysts of the toes was 33.3%.

Third-Line Therapy

- Flurandrenolide tape

D

The most likely course of action after failure of surgery is either to repeat the surgery or to modify the surgical approach to include osteophyte surgery if these were not treated in the first instance. If a CO₂ laser is available, this might also be chosen, given the good results reported in the small published series. Alternatively, sclerosant could be used, although again, multiple treatments could be anticipated.

Treatment of myxoid cyst with flurandrenolide tape.

Ronchese F. R I Med J 1970; 57: 154–5.

After the failure of electrodesiccation, five patients were treated with corticosteroid tape for 2–3 months, and success was reported in all during a follow-up of 2–3 years. The rationale for this choice is where the joint appears inflamed with more marked osteoarthritis and managing the inflammation may diminish the production and efflux of synovial fluid.

Nail psoriasis

Matilde Iorizzo, Antonella Tosti



Nail changes are reported in up to 50%–60% of psoriatic patients; among patients with psoriatic arthritis, the prevalence is even higher (80%). Isolated nail psoriasis is present instead in 5%–10% of psoriatic patients. Depending on the anatomic area affected, the disease presents with different clinical signs: irregular pitting, leukonychia, red spots in the lunula, nail plate thickening and crumbling (typical of nail matrix inflammation); salmon patches, onycholysis, splinter hemorrhages and subungual hyperkeratosis (typical of nail bed inflammation); and paronychia (typical of nailfold inflammation). All these signs could present together in the same patient and even in the same nail.

MANAGEMENT STRATEGY

When dealing with possible nail psoriasis, it is very helpful to look for specific clinical signs with the aid of a dermatoscope. A biopsy is rarely necessary, but if it has to be performed, it is important to choose the right anatomical area based on nail changes, selecting the nail bed as the biopsy site when possible.

Due to the association with psoriatic arthritis, it is mandatory to ask about pain and swelling, referring the patient to a rheumatologist, if necessary. Associated conditions like onychomycosis should be always ruled out and treated first.

Nail disorders in general are difficult and frustrating to treat – nail psoriasis is no exception.

Due to the slow growth rate of the nail plate and the difficulty for drugs to penetrate the nail tissues, it is usually necessary to wait several months before seeing improvement. Clinicians are often reluctant to prescribe systemic treatment when the disease is localized only to the nails. Treatment should be selected according to the types and severity of clinical signs, number of affected nails, the extent of psoriasis on the skin/joints, comorbidities, considering previous successful/unsuccessful treatments, patient age, and, above all, QoL.

For mild-to-moderate cases, a cream containing *calcipotriol* and *betamethasone dipropionate* is useful, in particular for nail bed disease. Effectiveness can be improved with an overnight occlusion,

after trimming the onycholytic plate. Application of *topical tazarotene* 0.1%, with or without occlusion, is another good option, but irritation of the nailfolds occurs frequently. Both *calcipotriol* and *tazarotene* are unable to reach the nail matrix if applied on the proximal nailfold. In case of nail matrix psoriasis, a *high potency steroid* (clobetasol propionate 0.05%) is a better option, but it has been proven that if applied for a long time, it may cause bone atrophy. Intralesional monthly injections of *triamcinolone acetonide* 5–10 mg/mL are then more appropriate, but feasible only for matrix psoriasis, as it is too painful in the nail bed. In severe cases systemic treatment should be considered. Oral *acitretin* at low dosage is a good option both for matrix and bed psoriasis. Subungual hyperkeratosis and thickening improve more than onycholysis and pitting, but when the nail plate is thin and fragile *acitretin* is not recommended because it could worsen the condition. *Methotrexate* and oral *ciclosporin* are therefore better options, with *methotrexate* seeming to give better results for matrix psoriasis and oral *ciclosporin* for bed psoriasis. The presence of psoriasis in other body areas is also very important in the choice of the drug, since *acitretin* and *ciclosporin* are much more effective on skin than joints psoriasis.

Apremilast, a small-molecule inhibitor of PDE 4, is not approved yet for nail psoriasis alone, but both matrix and bed psoriasis improved significantly in clinical studies on psoriasis. The same has been for *tofacitinib*, an oral Janus kinase (JAK) 1/3 inhibitor.

The higher success rate in clinical studies has been, however, achieved by biologicals. They act very fast compared with conventional drugs with the exception of *ciclosporin*. *Adalimumab* is the only biological approved for nail psoriasis (US Food and Drug Administration [FDA] only). Others should be used off-label. They include *brodalumab*, *certolizumab pegol*, *etanercept*, *golimumab*, *guselkumab*, *infliximab*, *ixekizumab*, *risankizumab*, *secukinumab*, *tildrakizumab*, and *ustekinumab*. Research is, however, very active in this field and many new drugs are currently on trial.

Recommendations for the definition, evaluation, and treatment of nail psoriasis in adult patients with no or mild skin psoriasis: a dermatologist and nail expert group consensus. Rigopoulos D, Baran R, Chiheb S, et al. *J Am Acad Dermatol* 2019; 81: 228–40.

A consensus group, made up of a panel of dermatologists with special expertise in nail disorders, established an agreement regarding the definition, severity, and treatment response of nail psoriasis. In the case of matrix involvement only, intralesional steroid injections were considered the treatment of choice. Topical steroids alone or in combination with topical vitamin D analogs were suggested for nail psoriasis limited to the nail bed. For the systemic treatment of nail psoriasis, *acitretin*, *methotrexate*, *ciclosporin*, small molecules, and biologics are all recommended.

Specific Investigations

- Record Nail Psoriasis Severity Index (NAPSI)
- Dermoscopy
- Biopsy/clippings
- Imaging

The availability of sensitive, responsive, specific, and validated scoring is essential for drug research and comparison of clinical trials. This kind of evaluation is still missing in nail psoriasis. NAPSI is the tool most commonly used, followed by target-NAPSI, where only the most seriously affected nail is taken into

account, remaining always the same even if it is no longer the most affected.

Dermoscopy can be a valid aid to distinguish clinically between nail psoriasis and traumatic onycholysis (homogeneous background with a linear line of detachment of the plate from the bed). Additionally, it can identify the presence of fungi (white–yellow longitudinal indentations). When applied to the hyponychium, it diagnoses nail psoriasis through the presence of dilated, tortuous, elongated, and irregularly distributed capillaries. Dermoscopy can be used also to monitor treatment outcomes.

Ultrasound imaging (HFUS), reflectance confocal microscopy (RCM), and optical coherence tomography (OCT) have been recently recognized as adjunct tools in the early diagnosis and monitoring of nail psoriasis. They recognize submillimeter lesions and the nail unit blood flow in real time. Each of these modalities varies in depth of penetration, resolution, and visual representation. HFUS provides the deepest penetration depth and RCM has the best resolution. OCT has the advantage of capturing images in both the horizontal and vertical planes, but the main advantage is the capability of producing 3-D images of dynamic blood perfusion within the microcirculatory tissue beds without the use of any contrast agent.

First-Line Therapies

• Topical corticosteroids (alone/combination)	A
• Topical vitamin D derivatives	A
• Topical tazarotene	A
• Topical tacrolimus	B
• Intralesional triamcinolone acetonide	C

Comparison of nail lacquer clobetasol efficacy at 0.05%, 1% and 8% in nail psoriasis treatment: prospective, controlled and randomized pilot study. Nakamura RC, Abreu L, Duque-Estrada B, et al. *Ann Bras Dermatol* 2012; 87: 203–11.

A split-hand study of 15 patients was performed with application of 0.05%, 1%, or 8% clobetasol nail lacquer on the left hand and a placebo lacquer on the right hand 2/week for 16 weeks. The treated group showed 51% improvement in modified NAPSI compared with baseline.

No difference was observed across different concentrations of lacquers. Improvements were observed more on nail bed signs.

Treatment of nail psoriasis with topical application of clobetasol propionate 0.05% solution: a pilot study. Brandi N, Starace M, Alessandrini A, et al. *Eur J Dermatol* 2018; 28: 111–2.

Topical application of clobetasol propionate 0.05% solution once daily for 4–6 months on the periungual tissues and nail bed was studied in mild nail psoriasis: 10/15 patients showed marked improvement of the nail lesions and 5/15 achieved complete resolution.

Nail bed signs responded more, but matrix signs also improved.

Calcipotriol ointment in nail psoriasis: a controlled double-blind comparison with betamethasone dipropionate and salicylic acid. Tosti A, Piraccini BM, Cameli N, et al. *Br J Dermatol* 1998; 139: 655–9.

This study compared twice-daily application of calcipotriol ointment (50 mcg/g) to betamethasone dipropionate (64 mg/g) plus salicylic acid (0.03 g/g) ointment to the nails of 58 patients for 3–5 months. There was 49.2% and 51.7% reduction in finger-nail subungual hyperkeratosis and 20.1% and 22.9% reduction in the toenails in the calcipotriol and betamethasone dipropionate

plus salicylic acid groups, respectively; however, the difference between the two treatment groups was not statistically significant.

Even severe nail bed psoriasis can be improved, with results being seen in 3 months.

Nail psoriasis: a combined treatment using calcipotriol cream and clobetasol propionate cream. Rigopoulos D, Ioannides D, Prastitis N, et al. *Acta Derm Venereol* 2002; 82: 140.

Calcipotriol cream is used overnight for five times a week and clobetasol cream overnight twice a week. This combination produced a greater improvement of subungual hyperkeratosis (77%), maintained with the steroid cream only, used overnight twice a week.

This is an option to minimize the side effects related to superpotent topical steroids, but the greatest effects are obtained on nail bed psoriasis.

Treatment of nail psoriasis with a two-compound formulation of calcipotriol plus betamethasone dipropionate ointment. Rigopoulos D, Gregoriou S, Daniel CR, et al. *Dermatology* 2009; 218: 338–41.

Calcipotriol-betamethasone valerate ointment was applied once a day for 12 weeks: significant improvement was recorded for hyperkeratosis and onycholysis, moderate improvement for oil drops, and slight improvement for pitting.

NAPSI at baseline was 5.8 ± 1.7 , meaning an extremely mild nail psoriasis and, again, greater improvement achieved for bed psoriasis.

Nail psoriasis: treatment with tazarotene 0.1% hydrophilic ointment. Fischer-Levancini C, Sánchez-Regaña M, Llambí F, et al. *Actas Dermosifiliogr* 2012; 103: 725–8.

Six patients applied tazarotene 0.1% ointment under occlusion every night for 6 months. A statistically significant improvement was observed in all patients. Percentage improvement at the end of treatment was 87.9%.

This study, like all the studies on topical steroids (alone or in combination), showed a better response for nail bed signs of psoriasis. However, tazarotene is irritating and not well tolerated even if not under occlusion.

Treatment of psoriatic nails with tazarotene 0.1% cream vs. clobetasol propionate 0.05% cream: a double-blind study. Rigopoulos D, Gregoriou S, Katsambas A. *Acta Derm Venereol* 2007; 87: 167–8.

A group of patients was instructed to apply tazarotene 0.1% cream to nail plates, nailfolds, and periungual skin under occlusion overnight for 12 weeks. The second group was instructed to apply clobetasol propionate 0.05% cream in the same way. Patients showed a significant improvement of pitting, onycholysis, hyperkeratosis, and salmon patches with both agents.

Discontinuation of therapy resulted in regression of the signs for both groups, with the exception of hyperkeratosis, which seemed to retain significant improvement 12 weeks after the end of treatment for the patients applying tazarotene.

Tacrolimus 0.1% ointment in nail psoriasis: a randomized controlled open-label study. De Simone C, Maiorino A, Tasone F, et al. *J Eur Acad Dermatol Venereol* 2013; 27: 1003–6.

A single-blind, split-hand study of 21 patients treated with tacrolimus 0.1% ointment nightly for 12 weeks showed a significant 13-point reduction in NAPSI in the treated hands and a 3-point reduction in the untreated hands compared with baseline.

In our experience, topical tacrolimus is well tolerated by patients with nail psoriasis.

A simplified protocol of nail steroid injection for psoriatic nail dystrophy. de Berker D, Lawrence CM. Br J Dermatol 1998; 138: 90–5.

Subungual hyperkeratosis, pitting, onycholysis, ridging, and thickening were scored at baseline and 2 months after injection of triamcinolone acetonide (0.4 mL, 10 mg/mL) and then at 3-monthly intervals. Onycholysis improved in 50% of cases. Pitting improved in 45% of cases. Subungual hyperkeratosis always improved. Ridging improved in all but one instance. Thickening improved in 83% of cases.

The intralesional route of administration is considered an optimal targeted therapy. When the nail matrix is affected, injections are quite tolerable for patients. Injections in the nail bed are instead very painful without a digital/wrist block anesthesia.

Second-Line Therapies

• Methotrexate	A
• Acitretin	B
• Ciclosporin	B
• Apremilast	A
• Biologics	A

Evaluation of the efficacy of acitretin therapy for nail psoriasis. Tosti A, Ricotti C, Romanelli P, et al. Arch Dermatol 2009; 145: 269–71.

Thirty-six patients with moderate-to-severe nail psoriasis were treated with low-dose acitretin (0.2–0.3 mg/kg/day) for 6 months. There was a 41% reduction in NAPSI and 50% reduction in modified NAPSI of the target nail: 25% showed almost complete clearance, 27% moderate improvement, 33% mild improvement, and 11% no improvement.

Use of acitretin may be limited by patient comorbidities and in females of childbearing potential, but even if slow acting, it is a good option both for matrix and bed psoriasis. Dose should be low, to prevent side effects on nails. Subungual hyperkeratosis and thickening improve more than onycholysis and pitting.

Evaluation of the efficacy of methotrexate and cyclosporine therapies on psoriatic nails: a one-blind, randomized study. Gümüçel M, Ozdemir M, Mevlitoglu I, et al. J Eur Acad Dermatol Venereol 2011; 25: 1080–4.

Thirty-four patients received subcutaneous methotrexate (15 mg weekly for first 3 months, then 10 mg weekly for the second 3 months) or ciclosporin (5 mg/kg/day for the first 3 months, then 2.5–3.5 mg/kg/day for the second 3 months), which led to a moderate reduction in NAPSI scores by 43% and 37%, respectively, after 6 months.

Both drugs were effective, with methotrexate more effective for nail matrix psoriasis and ciclosporin for nail bed psoriasis.

Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with difficult-to-treat nail and scalp psoriasis: results of 2 phase III randomized, controlled trials (ESTEEM 1 and ESTEEM 2). Rich P, Gooderham M, Bachelez H, et al. J Am Acad Dermatol 2016; 74: 134–42.

At week 16, apremilast 30 mg twice daily produced greater improvements in target-NAPSI score versus placebo (–22% vs. +6.5% in ESTEEM 1 and 29% vs. –7.1% in ESTEEM 2). Both nail

matrix and nail bed psoriasis improved. Improvements were generally maintained over 52 weeks, but only in patients with PASI response at week 32.

Because apremilast is generally well tolerated and has no need for laboratory follow-up, it may be an attractive choice for patients, but the high costs may limit its use.

Biological therapies may be considered the fastest and most effective treatments for nail psoriasis. Unfortunately, comparing biologics is hard or even impossible due to the heterogeneity in type and report of nail psoriasis outcome instruments.

As stated before, adalimumab is the only biological drug (FDA only) approved for nail psoriasis. The others, listed below in alphabetical order, should be used off-label for psoriasis limited to the nails. The choice of a specific molecule should then be driven by the specific case we are facing, i.e., by the concomitant presence of skin/joints psoriasis, comorbidities, previous treatments, and QoL. It is very important to match the biological and the patient, switching from disease-care to patient-care.

Adalimumab for nail psoriasis: efficacy and safety over 52 weeks from a phase-3, randomized, placebo-controlled trial. Elewski BE, Baker CS, Crowley JJ, et al. J Eur Acad Dermatol Venereol 2019; 33: 2168–78.

Safety and efficacy of the anti-tumor necrosis factor (TNF)- α fully human antibody adalimumab (ADA) at 52 weeks was evaluated in patients with moderate-to-severe plaque and fingernails psoriasis. Results from the first 26 weeks have already been reported (Period A: Elewski BE, et al. J Am Acad Dermatol 2018;78:90–99). Patients receiving 40 mg ADA every other week or placebo in Period A continued with or switched to 40 mg ADA every other week in the subsequent 26-week open-label extension (OLE) period. At 26 weeks of ADA treatment, 47.4% achieved a 75% improvement in modified NAPSI, increasing to 54.5% at week 52. Complete clearance was achieved in 6.6% at week 26, which increased 17.9% at week 52.

Summarizing all the data, it emerges that adalimumab is a powerful drug with efficacy proven by a solid number of studies.

Improvement of nail psoriasis with brodalumab in phase 3 trials. Lebwohl MG, Hsu S, Rastogi S, et al. J Am Acad Dermatol 2017; 76: AB410.

Brodalumab is a fully human monoclonal antibody that binds to the IL-17 receptor A. Nail psoriasis has never been investigated as a primary end point, but in a subgroup analysis of the IMAGINE-1, -2, and -3 trials, it was associated with significant improvements in NAPSI score. After the 12-week induction phase, improvements of 11.6%, 37.5%, and 46.3% were observed in the placebo, brodalumab 140 mg every 2 weeks, and brodalumab 210 mg every 4 weeks, respectively.

Effects on nail psoriasis are slower and less effective than those on skin where it has a very fast action. IL17RA inhibition may lead to increased levels of IL-17 and possible flare-ups after discontinuation. Caution is then to be taken if treatment adherence is poor.

4-year results from the RAPID-PsA phase 3 randomised placebo-controlled trial of certolizumab pegol in psoriatic arthritis. van der Heijde D, Deodhar A, FitzGerald O, et al. RMD Open 2018; 4: e000582.

After the 2014 RAPID-PsA study, patients previously randomized to certolizumab pegol (CZP) continued their assignment. Patients randomized to placebo were instead rerandomized to CZP 200 mg every 2 weeks or 400 mg every 4 weeks at week 16 or

after the double-blind phase. Nail psoriasis was not a primary end point, but 4-year follow-up data showed a total resolution rate for nail psoriasis of 65%.

The advantage of CZP, an anti-TNF- α humanized antibody, is that it does not induce antibody-dependent cell-mediated cytotoxicity or complement-dependent cytotoxicity, as it does not have an Fc-fragment. Moreover, it does not cross the placenta and can be utilized during pregnancy.

A 24-week randomized clinical trial investigating the efficacy and safety of two doses of etanercept in nail psoriasis. Ortonne JP, Paul C, Berardesca E, et al. *Br J Dermatol* 2013; 168: 1080–7.

Etanercept is a fusion protein of the TNF receptor and Fc end of the IgG1 antibody, which binds with and antagonizes the action of TNF- α . Group 1 received etanercept 50 mg twice weekly for 12 weeks followed by once weekly for 12 weeks. Group 2 received etanercept 50 mg once weekly for 24 weeks. NAPS1 score decreased from 6.0 to 1.7 (72% improvement) in group 1 and decreased from 5.8 to 1.4 (75% improvement) in group 2 at 24 weeks. Target fingernail NAPS1-50 was achieved by 82.3% and 80.7% of patients in group 1 and group 2, respectively.

Both regimens were effective. Overall, etanercept seems to have comparable effectiveness in reducing signs of nail psoriasis to adalimumab, infliximab, and ustekinumab.

Clinical efficacy, radiographic and safety findings through 5 years of subcutaneous golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of a randomised, placebo-controlled trial (the GO-REVEAL study). Kavanaugh A, McInnes IB, Mease P, et al. *Ann Rheum Dis* 2014; 73: 1689–94.

Golimumab is a fully human monoclonal anti-TNF- α antibody. Adults with active PsA were randomly assigned to subcutaneous placebo, golimumab 50 mg, or golimumab 100 mg every 4 weeks through week 20. All patients received golimumab 50 mg or 100 mg every 4 weeks from week 24 forward. Methotrexate was allowed and taken by approximately half the patients. NAPS1 improved in both groups, but the improvement was slightly more in the 100-mg group.

Long-term golimumab safety/efficacy was demonstrated through 5 years, but this drug is registered only for psoriatic arthritis, thus limiting its prescription by dermatologists.

Efficacy of guselkumab compared with adalimumab and placebo for psoriasis in specific body regions: a secondary analysis of 2 randomized clinical trials. Foley P, Gordon K, Griffiths CEM, et al. *JAMA Dermatol* 2018; 154: 676–83.

Guselkumab is a fully human monoclonal antibody that targets the p19 subunit of IL-23. Patients were randomized to guselkumab 100 mg (weeks 0 and 4, then every 8 weeks); placebo followed by guselkumab 100 mg, starting at week 16; or adalimumab (80 mg [week 0] and 40 mg [week 1, then every 2 weeks]). Efficacy was assessed through week 24. End points included numbers of patients achieving scores of 0 or 1 (clear or near clear) or 0 (clear) on the fingernail Physician's Global Assessment (PGA) and percentage of improvement in target-NAPS1.

Guselkumab was associated with significant improvement in psoriasis on the scalp and palms and/or soles; improvement in fingernails did not differ between the two treatments. For this reason, guselkumab is a good option when other body regions are affected or in the presence of comorbidities. The low number of injections per year is another attractive option.

Efficacy and safety of dose escalation of infliximab therapy in Japanese patients with psoriasis: results of the SPREAD study. Torii H, Nakano M, Yano T, et al. *J Dermatol* 2017; 44: 552–9.

Infliximab is a chimeric anti-TNF- α IgG1 monoclonal antibody comprising human antibody constant regions and murine variable regions. This may result in a higher formation of neutralizing antibodies compared with fully human or humanized antibodies decreasing its efficacy over time and requiring increased infusion frequencies (and higher infusion reactions) and higher doses to maintain clinical response and disease control. The aim of this phase III trial is to evaluate efficacy and safety of dose escalation (10 mg/kg every 8 weeks) in psoriasis patients with loss of efficacy to standard-dose therapy.

Dose escalation was likely to be effective in nail psoriasis patients with loss of efficacy to standard-dose therapy, suggesting that dose escalation may be a useful therapeutic option.

Improvement of scalp and nail lesions with ixekizumab in a phase 2 trial in patients with chronic plaque psoriasis. Langley RG, Rich P, Menter A, et al. *J Eur Acad Dermatol Venereol* 2015; 29: 1763–70.

The placebo, ixekizumab 75 mg, and ixekizumab 150 mg groups had NAPS1 reductions of 1.7%, 63.8%, and 52.6%, respectively, at 20 weeks. By week 48 in the OLE (ixekizumab 120 mg every 4 weeks) involving 51 patients, 51% of nail psoriasis patients treated with ixekizumab 150 mg showed complete nail psoriasis clearance.

Ixekizumab, a humanized monoclonal antibody against IL-17A, has shown benefits for the treatment of nail psoriasis with excellent and fast results reported.

Risankizumab profile in nail, scalp, and palmoplantar psoriasis: efficacy and safety at 52 weeks in an integrated analysis of patients with moderate-to-severe plaque psoriasis. Elewski BE, Rich P, Crowley J, et al. 24th World Congress of Dermatology; Milan (Italy), June 2019.

Risankizumab is a humanized monoclonal antibody targeting IL-23A. Its efficacy has been compared with ustekinumab in treating nail psoriasis. At week 52 patients on risankizumab showed more reduction in NAPS1 (–66%) than patients on ustekinumab (–46%).

Little is known about the efficacy in treating nail psoriasis; more data are needed.

Effect of secukinumab on the clinical activity and disease burden of nail psoriasis: 32-week results from the randomized placebo-controlled TRANSFIGURE trial. Reich K, Sullivan J, Arenberger P, et al. *Br J Dermatol* 2019; 181: 954–66.

Secukinumab was superior to placebo at week 16 (NAPS1 improvements of –45.3%, –37.9%, and –10.8% for secukinumab 300 mg and 150 mg and placebo, respectively). Improvement continued to week 32: NAPS1 percentage change reached –63.2% and –52.6% for secukinumab 300 mg and 150 mg, respectively.

Secukinumab, a fully human monoclonal antibody against IL-17A, demonstrated a beneficial effect on nail psoriasis and QoL improvements up to week 32.

Clinical improvement in psoriatic nail disease and psoriatic arthritis with tildrakizumab treatment. Ismail FF, May J, Moi J, et al. *Dermatol Ther* 2020; e13216.

This is a single case report about the use of 100 mg tildrakizumab, a humanized monoclonal antibody against the subunit p19 of IL-23, in a patient with psoriatic nail dystrophy and

psoriatic arthritis resistant to conventional treatments that successfully improved after 12 weeks.

The clinical response observed suggests that tildrakizumab may be an effective option for refractory psoriatic nail disease, but more data are needed.

Ustekinumab improves nail disease in patients with moderate-to-severe psoriasis: results from PHOENIX 1. Rich P, Bourcier M, Sofen H, et al. *Br J Dermatol* 2014; 170: 398–407.

A double-blind, randomized, placebo-controlled, crossover trial in nail psoriasis patients treated with ustekinumab (45 mg or 90 mg at weeks 0 and 4 with a maintenance dose every 12 weeks) showed NAPS I improvement of 46.5% in the 45 mg group and 48.7% in the 90 mg group at 24 weeks. Further improvement was observed through week 52.

Ustekinumab, a fully human monoclonal IgG antibody that blocks IL-12 and IL-23, significantly improves nail psoriasis, and improvements continue over time until up to 1 year of treatment.

Third-Line Therapies

• Tofacitinib	A
• Pulsed dye laser	A
• Nd:YAG laser	B
• Intense pulsed light (IPL)	D
• Topical anthralin	D
• Intralesional methotrexate	C

Efficacy of tofacitinib for the treatment of nail psoriasis: two 52-week, randomized, controlled phase 3 studies in patients with moderate-to-severe plaque psoriasis. Merola JF, Elewski B, Tatulych S, et al. *J Am Acad Dermatol* 2017; 77: 79–87.

Patients were randomized 2:2:1 to receive tofacitinib 5 mg, tofacitinib 10 mg, or placebo, twice daily. At week 16, placebo-treated patients were rerandomized to tofacitinib.

At week 16, significantly more patients receiving tofacitinib 5 mg and tofacitinib 10 mg versus placebo twice daily achieved NAPS I50 (32.8%, 44.2% vs. 12.0%), NAPS I75 (16.9%, 28.1% vs. 6.8%), and NAPS I100 (10.3%, 18.2% vs. 5.1%), respectively. Improvements were sustained to week 52.

Both matrix and bed psoriasis improved with best results seen in patients without joint involvement. However, a proper rheumatologic evaluation was not performed. Moreover, nails need time to improve, so it is surprising to have a response at week 16.

The effect of different pulse durations in the treatment of nail psoriasis with 595-nm pulsed dye laser: a randomized, double-blind, intrapatient left-to-right study. Treewittayapoom C, Singvahanont P, Chanpraph K, et al. *J Am Acad Dermatol* 2012; 66: 807–12.

Patients were treated monthly with 6 ms pulse duration and 9 J/cm² PDL settings on one hand and 0.45 ms pulse duration and 6 J/cm² PDL settings on the other for 6 months. NAPS I improved significantly in both groups within the first 3 months without significant difference between the two pulse duration groups. Participants reported greater pain with the longer pulse duration.

Surprisingly, more positive results were observed with nail matrix signs compared with bed signs.

Treatment of nail psoriasis with Pulse Dye Laser plus calcipotriol betamethasone gel vs. Nd:YAG plus calcipotriol betamethasone gel: an inpatient left-to-right controlled study. Arango-Duque LC, Roncero-Riesco M, Usero Barcena T, et al. *Actas Dermo* 2017; 108: 140–4.

The right hand of each patient received treatment with PDL (0.4 ms pulse duration and 6 J/cm² settings) and the left hand with Nd:YAG (35 ms pulse duration, 40 J/cm² settings) for a total of four sessions. Betamethasone calcipotriol gel was applied once a day during the first week after each laser session. All patients showed improvement in nail bed and nail matrix psoriasis. The global NAPS I mean declined 44%.

Not clear if the improvement was due to the laser or to the gel. Nd:YAG laser was judged more painful.

Topical anthralin therapy for refractory nail psoriasis. Yamamoto T, Katayama I, Nishioka K. *J Dermatol* 1998; 25: 231–3.

In this uncontrolled study of 20 patients who applied 0.4%–2.0% anthralin in petrolatum daily for 30 min, 12 had greater than 50% improvement of their nails, and four had no response after 5 months. Patients started with low doses that were increased in case of lack of improvement.

Anthralin worked most effectively for onycholysis and thickened nails and less for pitting, whereas transverse or longitudinal lines did not respond. The main side effect is reversible pigmentation of the nail plate.

Role of nail bed methotrexate injections in isolated nail psoriasis: conventional drug via an unconventional route. Grover C, Daulatabad D, Singal A. *Clin Exp Derm* 2017; 42: 420–3.

Four patients (30 involved nails) were treated with injections of methotrexate (0.1 mL of a 25 mg/mL solution) into the nail bed at 3-weekly intervals. Mean baseline NAPS I was 4.77, dropping successively at each visit to 2.43 at 15 weeks. Reported adverse effects were pain, injection site pigmentation, and nail bed hemorrhage.

Administration of specific targeted therapy to the nail bed may help in managing nail psoriasis effectively. Further studies are then necessary to understand if improvement is due to the drug or to the reverse Koebner phenomenon (disappearance of a dermatosis at the site of injury).

Necrobiosis lipoidica

Tina M. Tian, Ian H. Coulson



Necrobiosis lipoidica (NL) is a chronic cutaneous granulomatous condition with degenerative connective tissue changes. It is only seen in 1 in 300 diabetics but may be unassociated with glucose intolerance. NL may rarely be complicated by ulceration and squamous cell carcinoma.

MANAGEMENT STRATEGY

Smoking cessation and avoiding trauma to the affected shins are key factors to avoid transformation from an unsightly plaque into a painful, recalcitrant ulcer. The progression of new lesions may be halted by *intralesional or occluded potent topical corticosteroids* applied to the margins of the lesions. *Topical tacrolimus* can also be effective. Once atrophy has developed, there is little that will reverse this, although *topical retinoids* may be tried. Telangiectasia is often marked and has been treated with *pulsed dye laser*. Extensive lesions may justify trials of *nicotinamide* or *prednisolone*. Antiplatelet therapy in the form of *aspirin* or *dipyridamole* has its enthusiasts, though responses are inconclusive. Phototherapies such as *topical psoralen and ultraviolet (UV) A (PUVA)* and *UVA-1*, as well as *photodynamic therapy*, have received recent interest and may arrest progression and improve the appearance. A variety of systemic antiinflammatory and immunosuppressive agents have been tried with some success, including *mycophenolate mofetil*, *fumaric acid esters*, *cyclosporin*, *antimalarials*, *thalidomide*, and *pentoxifylline*. Biologics, especially anti-TNFs (*adalimumab*, *infliximab*, and *etanercept*), and more recently *ustekinumab*, have also been proposed. *Platelet-rich plasma* has some evidence of efficacy.

The chronically ulcerated lesion is a challenge; antibiotics deal with secondary infection, appropriate dressings may be required,

and growth factors such as *becaplermin* and *granulocyte-macrophage colony-stimulating factor (GM-CSF)* may accelerate healing. Because diabetics may have coexisting large vessel atherosclerosis that may contribute to ulceration, non-invasive arterial studies or angiography needs to be considered if clinically indicated.

Excision and grafting including punch grafting may transform the patient's quality of life and improve cosmesis. Work with the diabetologist to optimize diabetic control.

Specific Investigations

- HbA1c
- Skin biopsy
- Consider angiography or venous circulation studies
- Consider a biopsy to exclude sarcoidosis, which may mimic NL, or if clinical features suggest, the rare development of squamous cell carcinoma
- Consider thyroid function tests

Squamous cell carcinoma arising in an area of long-standing necrobiosis lipoidica. Lim C, Tschuchnigg M, Lim J. *J Cutan Pathol* 2006; 33: 581–3.

Case report of a squamous cell carcinoma arising de novo in an area of NL.

Unilateral necrobiosis lipoidica of the ischemic limb – a case report. Naschitz JE, Fields M, Isseroff H, et al. *Angiology* 2003; 54: 239–42.

A possible ischemic pathogenesis of NL emerges from a case of unilateral large vessel arteriosclerotic ischemia with ipsilateral NL. The authors report a severely ulcerated area of NL that only started to heal after the opening of severe femoropopliteal atheroma.

Updated results of 100 patients on clinical features and therapeutic options in necrobiosis lipoidica in a retrospective multicenter study. Erfurt-Berge C, Dissemond J, Schwede K, et al. *Eur J Dermatol* 2015; 25: 595–601.

This multicenter retrospective study included 100 patients with NL lesions on the lower leg. Thyroid disorders were found in 15% of all cases.

First-Line Therapies

• Stop smoking and optimize diabetic control	C
• Intralesional or topical corticosteroids under occlusion	D

Necrobiosis lipoidica diabeticorum: association with background retinopathy, smoking, and proteinuria. A case controlled study. Kelly WF, Nicholas J, Adams J, et al. *Diabet Med* 1993; 10: 725–8.

Fifteen diabetics with NL were each matched with five control subjects with diabetes mellitus. Background retinopathy, proteinuria, and smoking were all more common with NL. No differences were noted between those with NL and controls in the prevalence of vascular disease and neuropathy. Glycosylated hemoglobin concentrations were higher in patients with NL.

Stop smoking and control diabetes mellitus.

Granuloma annulare and necrobiosis lipoidica treated by jet injector. Sparrow G, Abell E. *Br J Dermatol* 1975; 93: 85–9.

Three of five cases of NL underwent complete resolution, and one had partial improvement with 5 mg/mL triamcinolone injection to the edges of lesions. No serious complications of this type of treatment were observed.

Treatment of psoriasis and other dermatoses with a single application of a corticosteroid left under a hydrocolloid occlusive dressing for a week. Juhlin L. *Acta Dermatol Venereol* 1989; 69: 355–7.

A 0.1% betamethasone alcoholic lotion under a hydrocolloid dressing was an effective, well-tolerated treatment, and three applications only were required.

Second-Line Therapies

• Systemic corticosteroids	D
• Aspirin and dipyridamole	C
• Pentoxifylline	D
• Nicotinamide	D
• Clofazimine	D
• Topical PUVA	D
• Topical tacrolimus	D
• Fumaric acid esters	C
• Photodynamic therapy	C

Necrobiosis lipidica: treatment with systemic corticosteroids. Petzelbauer P, Wolff K, Tappeiner G. *Br J Dermatol* 1992; 126: 542–5.

Oral methylprednisolone was given to six patients with non-ulcerating NL for 5 weeks; in all there was cessation of disease activity during the 7-month follow-up period. Initial dosage was 1 mg/kg daily for 1 week, then 40 mg daily for 4 weeks, followed by tapering and termination in 2 weeks. All patients, including the diabetics, tolerated the treatment well. There was no improvement in atrophy. Benefit was maintained at the end of the 7-month follow-up period.

Careful monitoring of blood glucose is mandatory in all diabetic patients with NL treated with systemic corticosteroids.

Pentoxifylline: an effective therapy for necrobiosis lipidica. Wee E, Kelly R. *Australas J Dermatol* 2015 Nov 12 [Epub ahead of print].

Three cases of biopsy-proven NL were treated with pentoxifylline 400 mg three times daily. Patients 1 and 2 had early-stage NL, presenting with indurated, red-brown plaques. Pentoxifylline reversed the inflammation and induration completely after 7 and 12 months, respectively. No recurrence in activity was seen in patient 1 after 12 months. In patient 3, pentoxifylline was effective in reversing ulceration completely after 10 months of treatment. Some areas of atrophy remained in all patients. None of the patients reported significant side effects.

Healing of necrobiotic ulcers with antiplatelet therapy. Correlation with plasma thromboxane levels. Heng MC, Song MK, Heng MK. *Int J Dermatol* 1989; 28: 195–7.

NL in diabetics has been considered a cutaneous manifestation of diabetic microangiopathy. Seven diabetic patients with necrobiotic ulcers of recent onset that healed after administration of 80 mg/day of acetylsalicylic acid and 75 mg three times daily of dipyridamole had elevated thromboxane levels. Healing was associated with depression of the elevated thromboxane levels in all seven patients.

Treatment of necrobiosis lipidica with low-dose acetylsalicylic acid. A randomized double-blind trial. Beck HI, Bjerring P, Rasmussen I, et al. *Acta Dermatol Venereol* 1985; 65: 230–4.

No response was seen with the use of 40 mg acetylsalicylic acid daily for 24 weeks, despite documented platelet aggregation inhibition.

High dose nicotinamide in the treatment of necrobiosis lipidica. Handfield-Jones S, Jones S, Peachey R. *Br J Dermatol* 1988; 118: 693–6.

An open study of high-dose nicotinamide (1.5 g/day) in the treatment of 15 patients with NL. Of 13 patients who remained on treatment for more than 1 month, eight improved. A reduction in pain, soreness, and erythema, and the healing of ulcers if present, was noted. There were no significant side effects, particularly with respect to diabetic control. Lesions tended to relapse if treatment was stopped.

Clofazimine – therapeutic alternative in necrobiosis lipidica and granuloma annulare. Mensing H. *Int J Dermatol* 1989; 28: 195–7.

Ten patients with NL were treated with clofazimine 200 mg orally daily. Six of 10 patients responded: three of the responders achieved complete remission of the dermatosis. All the patients treated had reddening of the skin, but this was reversible after the end of therapy, as were the other side effects (i.e., diarrhea and dryness of the skin).

Topical PUVA treatment for necrobiosis lipidica. McKenna DB, Cooper EJ, Tidman MJ. *Br J Dermatol* 2000; 143: 71.

Four of eight patients with NL responded favorably to topical PUVA using a 0.15% methoxsalen emulsion, with weekly treatments, starting with 0.5 J/cm² with 20% incremental increases until erythema developed at the edge of the lesions. The mean number of treatments administered was 39.

Successful treatment of chronic ulcerated necrobiosis lipidica with 0.1% topical tacrolimus ointment. Clayton T, Harrison P. *Br J Dermatol* 2005; 152: 581–2.

A case report of ulcerated NL that healed successfully with 0.1% tacrolimus ointment applied twice daily for 1 month.

Third-Line Therapies

• Topical retinoids	E
• Ciclosporin	D
• Heparin	E
• Antimalarials	D
• Mycophenolate mofetil	E
• Colchicine	E
• Tumor necrosis factor (TNF) antagonists	D
• Promogran for ulceration	E
• GM-CSF for ulceration	D
• Becaplermin for ulceration	E
• Pulsed dye laser for telangiectasia	E
• Surgery for ulceration	E
• Thalidomide	E
• Intravenous immunoglobulins and methylprednisolone	E
• Ultraviolet A1 phototherapy	D
• Platelet-rich plasma	C
• Janus kinase inhibitor	E
• CO ₂ laser	D
• Laser fractional er:glass	E
• Pioglitazone	E
• Potassium chloride	D
• Timolol	E
• Ustekinumab	E
• Hyperbaric oxygen	E
• Benzyl peroxide	E

Necrobiosis lipidica treated with topical tretinoin. Heymann WR. *Cutis* 1996; 58: 53–4.

A case is presented in which atrophy was diminished by the application of topical tretinoin.

Persistent ulcerated necrobiosis lipidica responding to treatment with cyclosporine. Darvay A, Acland KM, Russell-Jones R. *Br J Dermatol* 1999; 141: 725–7.

In two patients with severely ulcerated NL the ulceration healed completely after 4 months of ciclosporin therapy, and both patients have remained free of ulceration since. Effective doses were between 3 mg/kg and 5 mg/kg daily. Three other reports of the effective use of ciclosporin therapy in ulcerated NL now exist.

Significant improvement in ulcerative necrobiosis lipidica with hydroxychloroquine. Kavala M, Sudogan S, Zindanci I, et al. *Int J Dermatol* 2010; 49: 467–9.

A 62-year-old woman with type 2 diabetes mellitus and ulcerative NL on both shins achieved almost complete clearance of ulcerations after taking oral hydroxychloroquine, 200 mg twice daily, for 10 weeks.

Ulcerative necrobiosis lipidica responsive to colchicine. Schofield C, Sladden MJ. *Australas J Dermatol* 2012; 53: e54–7.

Single report of 10 years of bilateral ulcerative NL achieved complete resolution of ulcers after 2 months of colchicine 500 mcg twice daily.

Successful treatment of ulcerated necrobiosis lipidica with mycophenolate mofetil. Reinhard G, Lohmann F, Uerlich M, et al. *Acta Dermatol Venereol* 2000; 80: 312–3.

A 61-year-old woman with NL for over 30 years was started on mycophenolate mofetil 0.5 g twice daily, and the lesions regressed within 4 weeks. The dose was reduced to 0.5 g over the next 4 months and then stopped. Within 14 days of stopping mycophenolate mofetil the ulceration recurred.

Effectiveness of platelet-rich plasma in healing necrobiosis lipidica diabetorum ulcers. Motolese A, Vignati F, Antelmi A, et al. *Clin Exp Dermatol* 2015; 40: 39–41.

Fifteen patients with recalcitrant NL on the legs were treated with homologous platelet-rich plasma. All patients responded with a mean reduction in wound size of 79% after 84–126 days without any adverse effects.

Successful treatment of ulcerative necrobiosis lipidica diabetorum with intravenous immunoglobulin in a patient with common variable immunodeficiency. Barouti N, Qian Cao A, Ferrara D, et al. *JAMA Dermatol* 2013; 149: 879–81.

A 63-year-old female with recurrent ear, nose, and throat infections and 7 years of ulcerating NL lesions was found to have common variable immunodeficiency (CVID). The patient was treated with intravenous immunoglobulin (0.4 g/kg/day) for 5 consecutive days. Three weeks after this single cycle, all ulcerations healed completely with no recurrence after 2 years.

Intralesional infliximab in noninfectious cutaneous granulomas: three cases of necrobiosis lipidica. Barde C, Laffitte E, Campanelli A, et al. *Dermatology* 2011; 222: 212–6.

Three patients with NL had three cycles of three weekly injections of intralesional infliximab with a 1-week treatment interruption between each cycle. Two patients experienced almost complete remission for up to 18 months. The third patient showed

partial improvement. No serious side effects were noticed, apart from pain at injection sites.

Treatment of necrobiosis lipidica with etanercept and adalimumab. Zhang KS, Quan LT, Hsu S. *Dermatol Online J* 2009; 15: 12.

A 29-year-old with noninsulin-dependent diabetes and more than 9 years' history of NL on her legs and trunk received subcutaneous etanercept 50-mg injections twice weekly for 3 months and then weekly after that. She achieved significant improvement and complete pain resolution by 4 months. Due to insurance reasons, the patient was switched to subcutaneous adalimumab (40 mg) injections for 3 months, which did not result in any improvement. Six months after switching back to etanercept, the patient reported progressive improvement in the NL lesions. No significant side effects were reported apart from tiredness.

Fumaric acid esters in necrobiosis lipidica: results of a prospective noncontrolled study. Kreuter A, Knierim C, Stücker M, et al. *Br J Dermatol* 2005; 153: 802–7.

Eighteen patients with NL were given the standard Fumaderm regimen as used in psoriasis for at least 6 months. Three discontinued therapy, but the rest gained significant clinical, ultrasonographic, and histologic improvement.

The management of hard-to-heal necrobiosis with PROMOGRAN. Omugha N, Jones AM. *Br J Nurs* 2003; 15: S14–20.

A single case study with nonhealing ulcerated NL of 3 years' duration. Treatment with a new protease-modulating matrix (freeze-dried matrix composed of collagen and oxidized regenerated cellulose) resulted in complete healing of the ulcer after 8 weeks, where other dressing regimens had failed to effect healing over a period of 2.5 years.

Healing of chronic leg ulcers in diabetic necrobiosis lipidica with local granulocyte-macrophage colony-stimulating factor treatment. Remes K, Ronnema T. *J Diabetes Complications* 1999; 13: 115–8.

Topical recombinant human GM-CSF healed two patients with ulcerated NL within 10 weeks. A reduction in the size of the ulcers was already evident after the first topical applications. The ulcers have remained healed for more than 3 years.

Becaplermin and necrobiosis lipidicum diabetorum: results of a case control pilot study. Stephens E, Robinson JA, Gottlieb PA. *J Diabetes Complications* 2001; 15: 55–6.

Five patients with type 1 diabetes mellitus and NL were treated with topical becaplermin gel (recombinant platelet-derived growth factor). The index patient had ulcerated NL, and this healed. Three of the five patients with non-ulcerated NL reported a subjective improvement in sensation and lightening of color of the lesions. However, serial photographs and measurements over the 5-month treatment period showed no significant change in the size of the treated areas.

The surgical treatment of necrobiosis lipidica diabetorum. Dubin BJ, Kaplan EN. *Plast Reconstruct Surg* 1977; 60: 421–8.

Seven cases treated by excision of the lesions down to the deep fascia, ligation of the associated perforating blood vessels, and the use of split-skin grafts to cover the defects. There were no recurrences.

Thalidomide for the treatment of refractory necrobiosis lipidica. Kukreja T, Peterson J. *Arch Dermatol* 2006; 142: 20–2.

A 51-year-old woman was treated successfully with a dose of thalidomide 150mg daily, tapering to 50mg twice weekly. A response was seen after 4 months and maintained after 2 years.

Treatment of ulcerated necrobiosis lipoidica with intravenous immunoglobulin and methylprednisolone. Batchelor JM, Todd PM. *J Drugs Dermatol* 2012; 11: 256–9.

The authors report a case of a female patient with recalcitrant ulcerated NL that was resistant to several systemic agents but who initially responded to intravenous immunoglobulin. However, this became less effective over time, but a course of intravenous methylprednisolone led to regression.

Improvement in ulcerative necrobiosis lipoidica after Janus kinase-inhibitor therapy for polycythemia vera. Lee JJ, English JC 3rd. *JAMA Dermatol* 2018; 154: 733–4.

One patient with concomitant underlying polycythemia rubra vera was treated with ruxolitinib 10mg, orally twice daily, after failing treatment with high-potency topical steroids, hydroxychloroquine, mycophenolate mofetil, and infliximab. She experienced substantial clinical improvement after 3 months, with closure of all ulcers.

Fractional CO₂ laser: a novel therapeutic device for refractory necrobiosis lipoidica. Buggiani G1, Tsampau D, Krysenka A, et al. *Dermatol Ther* 2012; 25: 612–4.

Eleven patients with non-ulcerative NL were treated with 1–4 sessions of CO₂ laser, with an interval of 30 days between treatments. In nine of 11 patients, there was significant improvement in plaques, erythema, atrophy, and complete resolution of pain and dysaesthesia. The protocol was laser fluence (2.77J/cm²), dwell/exposure time (1000ms), and DOT spacing (500mm).

Potassium iodide for cutaneous inflammatory disorders: a monocentric, retrospective study. Anzengruber F, Mergenthaler C, Murer C, et al. *Dermatology* 2019; 235: 137–43.

A retrospective study of oral potassium iodide for dermatological disease included seven patients with NL; two had improvement. The dosing regimen was variable, but the most commonly used dose was 900mg daily, for up to 20 weeks.

Ultraviolet A1 phototherapy: one center's experience. Attali SK, Dawe RS, Ibbotson SH. *Indian J Dermatol Venereol Leprol* 2017; 83: 60–5.

Retrospective review of patients treated with UVA1 phototherapy at a UK center. Benefit was seen in four of 13 NL patients, with two showing near complete clearance of their disease. One did not improve with low-output TL-10 lamps (maximum dose reached = 25.8J/cm²), but noted improvement with the metal halide high-output lamps (maximum tolerated dose = 97J/cm²).

Ustekinumab to target granulomatous dermatitis in recalcitrant ulcerative necrobiosis lipoidica: case report and

proposed mechanism. Hassoun LA, Sivamani RK, Sharon VR, et al. *Dermatol Online J* 2017; 15: 23.

A 42-year-old woman with a 5-year history of ulcerative NL with recalcitrant disease after treatment with multiple treatment including pentoxifylline, ciclosporin, mycophenolate mofetil, etanercept, adalimumab, and infliximab. She was treated with ustekinumab 45mg every 9 weeks, with significant reduction in symptoms, and has been ulcer free for 6 months.

Photodynamic therapy of necrobiosis lipoidica using methyl aminolevulinate: a retrospective follow-up study. Kaae J, Philipsen PA, Wulf HC. *Photodiagnosis Photodyn Ther* 2018; 22: 223–6.

This retrospective study evaluated the long-term efficacy of methyl-aminolevulinate-based photodynamic therapy (MAL-PDT) on 65 unselected NL patients. The 100% cure rate was 66%, and there was no difference between conventional and daylight PDT.

Anti-TNF α treatment for recalcitrant ulcerative necrobiosis lipoidica diabetorum: a case report and review of the literature. Basoulis D, Fragiadaki K, Tentolouris N, et al. *Metabolism* 2016; 65: 569–73.

A 17-year-old woman with extensively ulcerated NL, resistant to corticosteroids and hyperbaric oxygen, achieved complete resolution of ulceration with four monthly sessions of 5mg/kg intravenous infliximab.

Treatment of necrobiosis lipoidica with pioglitazone. Boyd AS. *J Am Acad Dermatol* 2007; 57(5 Suppl): S120–1.

A 32-year-old woman with NL failed treatment with topical tretinoin 0.05% and high-potency steroid creams under occlusion. There was no evidence of diabetes mellitus. She responded to low-dose 7.5mg of pioglitazone within 1 month, with complete resolution of smaller patches and involution of the larger ones. Pioglitazone was increased to 15mg daily. After 5 months, there were several smaller lesions on the foot and ankles; however, more proximal involvement continued to involute.

Treatment of necrobiosis lipoidica with pulsed dye laser. Gutierrez D, Steuer AB, Marji JS, et al. *Dermatol Surg* 2019 [Epub ahead of print].

A 22-year-old woman with type 1 diabetes mellitus and NL had been treated with topical and intralesional steroids and calcineurin inhibitors with no improvement. Pulse dye laser spot test was performed using 595-nm wavelength with 7.5-J/cm² energy fluence, 7-mm spot size, and 6-ms pulse duration. The patches on the left leg were treated completely without overlapping pulses without immediate purpura. After 3 months, there was decrease in erythema and telangiectasia. Further 2-monthly treatments to both legs were conducted. At 1 year, there were persistent improvements in erythema, thickness, and scale of her lesions. She was retreated once more for a total of five treatments.

Necrolytic acral erythema

Ellen Anshelevich, Carrie Kovarik



Hepatitis C virus (HCV) infection is one of the most common bloodborne infections globally, with approximately 3% and 1% of the world and US adult population affected, respectively. The Centers for Disease Control and Prevention estimates approximately three-fourths of all persons living with HCV infection in the United States were born between 1945 and 1965.

Although HCV infection primarily affects the liver, it has also been associated with several mucocutaneous manifestations, including leukocytoclastic vasculitis, cryoglobulinemia, lichen planus, porphyria cutanea tarda, polyarteritis nodosa, and generalized pruritus. NAE is another distinct cutaneous manifestation of HCV infection first described in 1996 in seven patients with chronic HCV infection in Egypt.

Necrolytic acral erythema (NAE) is characterized as sharply demarcated, erythematous to violaceous, hyperpigmented, hyperkeratotic plaques with variable scale and occasional erosions, surrounded by a rim of erythema. The lesions of NAE tend to affect the dorsal hands and feet (especially the great toe) but have also been reported to extend to the legs and trunk. The head, neck, palms, soles, nail plate, nail bed, and mucous membranes are typically spared, though exceptions have been noted. Less commonly, NAE may present with acute blistering lesions.

MANAGEMENT STRATEGY

Some have categorized the evolution of NAE into three distinct stages. The initial stage consists of a small (2–3 mm),

erythematous papule that grows in surface area and thickness to become covered in scale. The center of the papule may become dusky or develop an erosion. The fully developed stage consists of increasing surface area and confluence of the initial stage lesions, leading to sharply demarcated erythematous lichenified plaques with overlying scale. Thin crust, vesicles, pustules, and weeping may also be seen in this stage. The late stage is characterized by thinning and hyperpigmentation of previously developed lesions, followed by spontaneous relapse and remission. The lesions of NAE are often locally pruritic, although in some cases, the pruritus can be generalized. Other patients have complained the lesions cause aching or burning pain.

Although the exact pathogenesis of NAE is not known, infection with hepatitis C seems to have an essential role in its development. The lack of NAE lesions in patients with other cirrhotic conditions, such as alcoholic hepatitis or hepatitis B infection, excludes chronic liver damage as the sole cause. Attempts to identify hepatitis C viral particles or RNA in NAE biopsies using electron microscopy and reverse transcription polymerase chain reaction (RT-PCR) have not been successful. Reduced amino acid levels, elevated glucagon levels, reduced fatty acid levels, reduced serum zinc, and reduced epidermal zinc have all been implicated in NAE and may be related to HCV-induced metabolic alterations. Zinc deficiency, especially, has been suggested as a pathogenic factor given the responsiveness of some cases of NAE to oral zinc sulfate. Although many patients with NAE who respond to oral zinc have normal serum zinc levels, some have postulated that these patients may have low cutaneous zinc levels. The role of zinc in the pathogenesis of NAE remains unclear. Because zinc is believed to be antiapoptotic, some have postulated that its deficiency may lead to epidermal necrolysis. Zinc deficiency may also impair the transport of essential nutrients like vitamin A to the epidermis. Because not all patients with NAE are responsive to oral zinc supplementation, it is likely the etiology of NAE is multifactorial.

In one study, 87% of patients diagnosed with NAE were unaware of their underlying HCV infection. Hence, identification of NAE suggests the need to test for HCV.

Early NAE may present with vesicular lesions on the dorsal hands or feet that may be confused with acute eczematous reactions, contact dermatitis, or stasis changes when it is limited to the feet and/or legs. Chronic NAE may mimic lichen simplex chronicus. The necrolytic erythemas include necrolytic migratory erythema, acrodermatitis enteropathica, pellagra, and NAE. Although these entities may all share some clinical and histologic features, they can be distinguished based on cutaneous distribution and underlying biochemical abnormalities. Necrolytic migratory erythema presents with elevated glucagon levels, whereas acrodermatitis enteropathica presents with depressed zinc levels, and pellagra is associated with niacin deficiency. NAE may also be distinguished based on its association with HCV and acral distribution.

On histology, NAE demonstrates psoriasiform hyperplasia, acanthosis, papillomatosis, and parakeratosis. Vascular ectasia can be seen within the dermal papillae, along with pigment incontinence. Most cases show a superficial, patchy, dermal, perivascular lymphocytic and neutrophilic infiltrate with extension into the epidermis, and necrotic keratinocytes in the superficial epidermis. In the absence of necrotic keratinocytes, NAE can be easily confused with psoriasis, histologically. Because NAE lacks pathognomonic histology, a high index of suspicion and clinical–pathologic correlation is required for diagnosis.

Specific Investigations

- Liver function tests
- Serology for hepatitis C
- Skin biopsy

In patients who may have NAE, a hepatitis panel and liver function tests can help to clarify the diagnosis. Other tests that may distinguish NAE from entities in the differential diagnosis include serum albumin, total protein, amino acids, zinc, biotin, and glucagon levels.

A cutaneous sign of hepatitis C virus infection. Abdallah MA, Ghazzi MY, Monib HA, et al. *J Am Acad Dermatol* 2005; 53: 247–51.

Many patients diagnosed with NAE have historically been from Egypt, where the high burden of HCV infection has affected 15%–20% of the population. The increased prevalence of NAE in Egypt may also be related to HCV genotype 4, which is endemic there, a genetic predisposition in the population, or an environmental cofactor. In the United States the prevalence of NAE among patients with chronic HCV infection appears to be low, around 1.7%.

Low prevalence of necrolytic acral erythema in patients with chronic hepatitis C virus infection. Raphael B, Dorey-Stein ZL, Lott J, et al. *J Am Acad Dermatol* 2012; 67: 962–8.

Most patients in the United States with NAE are African American, and there does not appear to be a gender predilection. The vast majority of NAE has been observed in patients with HCV infection. However, several cases of seronegative NAE have been reported.

First-Line Treatments

- Zinc sulfate **C**
- Treatment of underlying hepatitis C **C**

Necrolytic acral erythema as a cutaneous marker of hepatitis C: report of two cases and review. Tabibian JH, Gerstenblith MR, Tedford RJ, et al. *Dig Dis Sci* 2010; 55: 2735–43.

Necrolytic acral erythema: a review of the literature. Geria AN, Holcomb KZ, Scheinfeld NS. *Cutis* 2009; 83: 309–14.

The treatment of NAE is challenging because there is little available information, and no large clinical trials have been done to establish optimal treatment. The cost, safety, and previous success of oral zinc supplementation in treating NAE make it first-line therapy. A response to oral zinc supplementation is usually observed within several weeks. The response to oral zinc seems to be dose dependent, with less improvement when a lower dose, such as 60 mg/day, is used. Although some patients successfully treated with oral zinc demonstrate low zinc levels, many are responsive to oral zinc supplementation despite normal zinc levels. Remission of lesions after a combination of oral zinc and intralesional injections of interferon- α_{2b} and/or ribavirin have also been reported, suggesting treatment with oral zinc may be enhanced by interferon.

Necrolytic acral erythema in seronegative hepatitis C. Srisuwanwattana P, Vachiramon V. *Case Rep Dermatol* 2017; 9(1): 69–73.

Thus far, oral zinc supplementation with 220 mg oral zinc sulfate twice daily seems to be the most effective treatment for NAE with the fewest side effects. In one case of seronegative NAE, where the patient's plasma zinc levels were normal and no improvement was observed with 220 mg/day zinc sulfate, the patient was prescribed 440 mg/day, after which there was some resolution. Many reported improvement in and remission of NAE with long-term oral zinc supplementation.

Successful treatment of NAE often leaves behind postinflammatory pigmentation with complete resolution of symptoms. The mechanism by which oral zinc treats NAE is not yet understood. It is possible patients with HCV have metabolic derangements that lead to low zinc levels or these patients have low cutaneous zinc levels, even in the setting of normal plasma zinc. Zinc may also have an antiinflammatory, antiviral, and immune-stimulatory effect. Those patients being treated with long-term zinc supplementation should have serum copper levels monitored, as zinc therapy may alter copper bioavailability.

Successful treatment of necrolytic acral erythema with ledipasvir and sofosbuvir. Shaikh GFR, Yagerman S, Franks AG Jr. *J Clin Dermatol Ther* 2015; 3: 016.

NAE has also been shown to improve with treatment of HCV with new antiviral agents. For example, a 58-year-old woman with a history of hepatitis C presented with NAE lesions on the feet, ankles, and left calf. Previous treatments with topical steroids and zinc supplementation resulted in minimal improvement. Treatment for hepatitis C with ledipasvir and sofosbuvir (Harvoni) with ribavirin resulted in substantial improvement of her lesions and resolution of symptomatology 2 months after treatment initiation.

Second-Line Therapies

- Narrowband ultraviolet B (NB-UVB) phototherapy **E**
- Topical tacrolimus **E**

Modest improvement of NAE has been reported after NB-UVB therapy, and one patient completely cleared and maintained remission after a liver transplant. Improvement in NAE has also been reported after treatment of the underlying HCV with interferon- α , with or without ribavirin. However, NAE may relapse after the interferon treatment is discontinued.

Necrolytic acral erythema: successful treatment with topical tacrolimus ointment. Manzur A, Siddiqui AH. *Int J Dermatol* 2008; 47: 1073–5.

There is one report of complete resolution of NAE after application of 0.1% topical tacrolimus ointment for 4 weeks. There have also been variable responses of NAE to topical and systemic corticosteroids, which may be added to zinc supplementation or phototherapy. NAE generally does not respond to intralesional triamcinolone injections.

Necrolytic migratory erythema

Allison M. Perz, Sandra A. Kopp, Analisa Vincent Halpern



Necrolytic migratory erythema (NME) is a characteristic paraneoplastic cutaneous reaction classically associated with an underlying gastroenteropancreatic neuroendocrine tumor (NET), most commonly a pancreatic islet α -cell neoplasm. NME has also been associated with the pseudoglucagonoma syndrome (hyperglucagonemia in the absence of a glucagon-secreting tumor), metastatic NET, glucagon infusion-dependent states, hepatic disease, gluten-sensitive enteropathy, pancreatic insufficiency, glucagon cell adenomatosis, other malabsorption or malnutritional states, and cholangiocarcinoma. It may be associated with a polyfunctional endocrine tumor (MEN1).

NME is a rare disease that has an estimated yearly prevalence of one in 20,000,000. Most cases are associated with a glucagonoma, which make up a small proportion of the 1% of pancreatic tumors that are classified as NETs. NME presenting without glucagonoma has been reported largely through case reports and is likely to be even more uncommon. NME is the presenting symptom in over 70% of cases of glucagonoma, and, on presentation, 40–50% of glucagonomas are already metastatic, making the recognition of this rare clinical entity paramount for patient outcomes.

NME typically presents in the fifth decade of life and is classically accompanied by weight loss, new-onset or worsening diabetes mellitus, normocytic anemia, and hyperglucagonemia.

The lesions begin as pruritic or painful erythematous patches with central bullae formation leading to the classic appearance of a centrally crusted, annular erosive plaque with a psoriasiform border.

NME can be widespread but has a predilection for areas subject to pressure and friction such as the buttocks, inferior abdomen, lower extremities, and intertriginous areas.

Parakeratosis and upper-level keratinocyte vacuolization are characteristic on histopathologic examination of early lesions. The pathogenesis of NME has not been fully elucidated, although

several theories have emerged from observations of patient responses to various treatment strategies. One theory suggests that the catabolic effects of glucagon lead to a hypermetabolic state, resulting in the deficiency of zinc and essential fatty acids. Given the multitude of various diseases that have been associated with NME, a multifactorial model for the pathogenesis of the disease has been hypothesized: (1) hyperglucagonemia-induced hypoalbuminemia leads to deficiencies in zinc (Zn), essential fatty acids (EFA), and amino acids (AA) such as tryptophan (albumin binds and circulates Zn, AA, and EFA throughout the body); (2) Zn deficiency induces primary cutaneous inflammation, as Zn plays a major role in restoring prostaglandin-mediated inflammatory response in the epidermis; and (3) subsequent tryptophan deficiency causes keratinocyte degradation without concomitant new cell formation. Tryptophan is essential for niacin biosynthesis; without adequate niacin, keratinocytes cannot regulate proper cellular turnover, capillary tone, and appropriate maturation of epidermis and mucosal epithelia. Theoretically, this constellation of elevated serum glucagon, hypoalbuminemia, zinc, EFA and AA deficiency, and potentially hepatic dysfunction ultimately leads to the increase in epidermal inflammation, breakdown, and necrolysis observed in NME.

Necrolytic acral erythema (NAE), often associated with hepatitis C virus infection, is considered by some to be an acral variant of NME. One should consider the diagnosis of atypical NAE in the differential diagnosis of NME.

MANAGEMENT STRATEGY

Addressing the underlying cause of NME is paramount for treatment. In the setting of glucagonoma, *surgical resection* of the tumor is ideal; however, metastasis is commonly present at the time of diagnosis, obfuscating complete cure. Glucagonomas grow slowly and tend to be encapsulated, so if identified early and fully excised adjunctive therapy is usually unnecessary. The *somatostatin agonists*, octreotide and lanreotide, are considered the first-line treatment of choice in NME with or without associated glucagonoma. Streptozotocin (STZ)-based *combination chemotherapy*, such as STZ and doxorubicin (DOX) or 5-FU, may be considered for moderately and well-differentiated NETs. More recently, the combination of temozolomide and capecitabine has been studied for the treatment of advanced pancreatic NETs. For poorly differentiated NETs, a platinum-based chemotherapeutic regimen, such as STZ, 5-FU, and cisplatin (FCiSt), should be considered. *Peptide receptor radioligand* therapy with radiolabeled somatostatin agonists has been tried with moderate success, and the agent 177-LUDOTATE was recently approved by the US Food and Drug Administration for the treatment of gastroenteropancreatic NETs. *Sunitinib*, an inhibitor of the multiple receptor tyrosine kinases, and *everolimus*, an inhibitor of the mammalian target of rapamycin (mTOR), have also demonstrated increased progression-free survival in patients with progressive, advanced pancreatic NETs. Adjunctive *deep vein thrombosis prophylaxis* should also be advised due to the risk of thromboembolism with glucagonoma. Additionally, correcting any nutritional deficiencies in general (with correction of AA, EFA, or zinc specifically) should be undertaken immediately, as supplementation has been associated with a marked improvement of the cutaneous lesions of NME.

A diagnosis of NME in the absence of glucagonoma should make one suspect possible underlying nutritional deficiencies or pseudoglucagonoma syndrome. These conditions can be encountered in hepatic disease and other causes of chronic malabsorption such as celiac disease, inflammatory bowel disease, chronic pancreatitis, or metastatic NET and cholangiocarcinoma.

Glucagon cell adenomatosis, the diffuse enlargement of islets of Langerhans cells with resulting glucagon hypersecretion, should be expected when there is no evidence of a detectable pancreatic mass on imaging. If MEN1 or a polyfunctional endocrine tumor is suspected, one should consider investigating levels of fasting *insulin, prolactin, parathyroid hormone, calcium, vasoactive intestinal peptide (VIP), gastrin, and adrenocorticotrophic hormone (ACTH)* in the workup.

Specific Investigations

- Serum glucagon, chromogranin **A**
- Serum zinc, amino acids (tryptophan), total protein, albumin, essential fatty acid, riboflavin, niacin, pyridoxine (vitamin B₆), cyanocobalamin (vitamin B₁₂), biotin, folic acid, pantothenic acid, methylmalonic acid, and propionic acid levels
- Hemoglobin/hematocrit
- Serum fasting glucose
- Serum liver function tests and hepatitis B and C profile
- Abdominal computed tomography scan, endoscopic ultrasound, celiac angiography, and/or somatostatin receptor scintigraphy
- Multiple endocrine neoplasia type 1 (MEN1) gene
- Serum fasting insulin, prolactin, calcium, VIP, gastrin, parathyroid hormone, ACTH
- Skin biopsy (H&E)

A review of cutaneous manifestations within glucagonoma syndrome: necrolytic migratory erythema. Tolliver S, Graham J, Kaffenberger B. *Int J Dermatol* 2018; 57: 642–5.

This case report, which describes a patient presenting with NME who is diagnosed with glucagonoma, highlights the importance of recognizing NME as a presenting sign of glucagonoma.

Diarrhea: a missed D in the 4D glucagonoma syndrome. Cunha-Silva M, da Costa JG, Faria GAS, et al. *Autops Case Rep* 2019; 9: e2019129.

This case report highlights diarrhea as an uncommon component of glucagonoma syndrome that can cause significant nutritional impairment, leading to poor patient outcomes.

NCCN Guidelines Insights: Neuroendocrine and Adrenal Tumors, Version 2. 2018. Shah MH, Goldner WS, Halfdanarson TR, et al. *J Natl Compr Canc Netw* 2018; 16: 693–702.

These guidelines, developed by the National Comprehensive Cancer Center, were updated in 2018. Important additions include the upgraded recommendation of everolimus or peptide receptor radionuclide therapy (PRRT) with Lu-DOTATATE for progressive disease in pancreatic NETs.

Octreotide-responsive necrolytic migratory erythema in a patient with pseudoglucagonoma syndrome. Virani S, Prajapati V, Devani A, et al. *J Am Acad Dermatol* 2013; 68: e44–6.

A 56-year-old female with a history of ectopic Cushing syndrome with liver metastases was diagnosed with NME secondary to pseudoglucagonoma syndrome. Near resolution of lesions was observed after 4 weeks of subcutaneous administration of octreotide.

Necrolytic migratory erythema-like presentation for cystic fibrosis. Koch LH, Lewis D, Williams JV. *J Am Acad Dermatol* 2008; 58: S29–30.

This case report supports the chronic malabsorption syndrome (CMS) theory as a cause of NME. Patients with CMS secondary to cystic fibrosis can present with psoriasiform lesions similar to NME. In this case report, the patient's NME-like lesions resolved after nutritional therapy with zinc and hydrolyzed protein formula.

Glucagon cell adenomatosis: a newly recognized disease of the endocrine pancreas. Henopp T, Anlauf M, Schmitt A, et al. *J Clin Endocrinol Metab* 2009; 94: 213–7.

This report describes four cases of a newly recognized condition of the endocrine pancreas: glucagon cell adenomatosis, including one patient who presented with features of glucagonoma syndrome including NME.

First-Line Therapies

- Lanreotide **A**
- Peptide receptor radionuclide therapy [¹⁷⁷Lu-DOTATATE] **B**
- Radioactive microspheres **B**
- Tumor resection **C**

Lanreotide in metastatic enteropancreatic neuroendocrine tumors. Caplin ME, Pavel M, Cwikla JBE, et al. *N Engl J Med* 2014; 17: 224–33.

This randomized, double-blind, placebo-controlled, multinational study of the somatostatin analog lanreotide was shown to significantly prolong progression-free survival among patients with metastatic enteropancreatic NETs of grade 1 or 2.

Long-term efficacy, survival, and safety of [¹⁷⁷Lu-DOTA0,Tyr3] octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. Brabander T, van der Zwan W, Teunissen J, et al. *Clin Cancer Res* 2017; 23: 4617–24.

This non-randomized study of 443 gastroenteropancreatic and bronchial neuroendocrine tumors reports progression-free survival of 30 months in pancreatic NET patients treated with [¹⁷⁷Lu-DOTA0,Tyr] octreotate, a radiolabeled somatostatin analog, in the treatment.

Factors predicting response and survival after yttrium-90 radioembolization of unresectable neuroendocrine tumor liver metastases: a critical appraisal of 48 cases. Saxena A, Chua TC, Bester L, et al. *Ann Surg* 2010; 251: 910–6.

This is a prospective study of 48 patients with unresectable liver metastases from NETs who underwent yttrium-90 radioembolization. Median survival after treatment was 35 months.

Surgical treatment of pancreatic neuroendocrine tumors: report of 112 cases. Gao C, Fu X, Pan Y, et al. *Dig Surg* 2010; 27: 197–204.

A retrospective review of 112 cases of pancreatic NETs. Pancreatic NETs can be safely resected with aggressive radical surgery to improve long-term survival. Patients' 5-year survival rate was significantly correlated with vascular invasion and resection margin.

Second-Line Therapy

- Nutritional supplementation with amino acids, zinc, or essential fatty acids **D**

Rapid clearance of necrolytic migratory erythema following intravenous administration of amino acids. Thomaidou E, Nahmias A, Gilead L, et al. *JAMA Dermatol* 2016; 152: 345–6.

A patient with NME secondary to glucagonoma experienced marked improvement of cutaneous symptoms within 24 hours of treatment with IV amino acid infusion.

Third-Line Therapies

Chemotherapy

• Streptozocin ± fluorouracil or doxorubicin	C
• Capecitabine/temozolomide [CAPTEM]	B
• Dacarbazine [DTIC]	C
• Everolimus	A
• Sunitinib	A
• Liver transplantation	C
• Ciclosporin	E

Streptozocin and 5-fluorouracil for the treatment of pancreatic neuroendocrine tumors: efficacy, prognostic factors and toxicity. Clewemar Antonodimitrak P, Sundin A, Wassberg C, et al. *Neuroendocrinology* 2016; 103: 345–53.

This retrospective study of 133 patients with pancreatic NETs evaluated the use of combination streptozocin and 5-fluorouracil. Progression-free survival was 23 months and median survival from the start of treatment was 51.9 months.

A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: a trial of the ECOG-ACRIN Cancer Research Group (E2211). Kunz PL, Catalano PJ, Nimeiri H, et al. *J Clin Oncol* 2018; 36: 4004.

This randomized, open-label, phase II clinical trial compared temozolomide to temozolomide and capecitabine (CAPTEM) in 144 patients with advanced pancreatic NETs. CAPTEM had improved progression-free survival of 22.7 months compared with 14.4 months in the temozolomide-only arm.

Low dose DTIC is effective and safe in pretreated patients with well differentiated neuroendocrine tumors. Mueller D, Krug S, Majumder M, et al. *BMC Cancer* 2018; 16: 645.

This retrospective analysis of 75 patients with gastroenteropancreatic NETs reports an objective response rate of 32% for pancreatic NETs with a median progression-free survival of 7 months.

Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study. Faivre S, Niccoli P, Castellano D, et al. *Ann Oncol* 2017; 28: 339–43.

This study presents the updated progression-free survival and overall survival data for the phase III, randomized, double-blind, placebo-controlled study of sunitinib in patients with advanced and/or metastatic well-differentiated pancreatic NETs. Progression-free survival was 12.6 months for the sunitinib arm and 5.8 months for the placebo arm.

Everolimus for the treatment of advanced pancreatic neuroendocrine tumors: overall survival and circulating biomarkers from the randomized, phase III RADIANT-3 Study. Yao JC, Pavel M, Lombard-Bohas C, et al. *J Clin Oncol* 2016; 34: 3906–13.

This study presents the final, overall survival data for the RADIANT III trial, a randomized, double-blind, placebo-controlled, phase III clinical trial of patients with progressive, advanced pancreatic NETs. Everolimus was associated with an overall survival of 44 months and improved median progression-free survival by 6.3 months compared with placebo.

Liver transplantation for metastatic neuroendocrine tumors: outcomes and prognostic variables. Sher LS, Levi DM, Wechsler JS, et al. *J Surg Oncol* 2015; 112: 125–32.

A retrospective analysis of a multicenter database that assesses outcomes and prognostic variables for 85 patients who underwent liver transplant for metastatic neuroendocrine tumors. Survival rates for 1, 3, and 5 years were 83%, 60%, and 52%, respectively.

Necrolytic migratory erythema associated with glucagonoma treated successfully with cyclosporine. Jimenez-Gallo D, Ossorio-Garcia L, de la Varga-Martinez R, et al. *Dermatol Ther* 2017; 30.

In this case report, a 57-year-old man with unresectable glucagonoma and NME refractory to octreotide and multiple chemotherapy regimens was treated with 3 mg/kg/day of ciclosporin with full clinical resolution of his NME.

Neurofibromatosis, type 1

R. Matthew McLarney, Rhonda E. Schnur



Type 1 neurofibromatosis (NF1), or von Recklinghausen disease, is an autosomal dominant multisystem disorder with highly variable expression. NF1 is caused by pathogenic variants of the neurofibromin gene (*NF1*) on chromosome 17. The neurofibromin protein is a tumor suppressor. Specifically, NF1 is a GTPase-activating protein that negatively regulates RAS protein signal transduction, which controls the expression of genes involved in apoptosis, the cell cycle, cell differentiation or migration. NF1 pathogenic variants lead to 'gain of function' for RAS (as RAS-GTP) with overactivation of the downstream pathways, including the PI3K/AKT/mTOR and Raf/mitogen-activated protein kinase (MAPK)/MEK/ERK pathways, resulting in increased cell growth and potential for malignant transformation. There are five different isoforms of the *NF1* gene expressed in different tissues and the variation in phenotype depends on the location, type of variant, and relative amounts of these isoforms expressed.

Cutaneous and ocular lesions are hallmarks. Cutaneous lesions include café au lait spots (CALs), cutaneous neurofibromas (CNs), and plexiform neurofibromas (PNs). Ocular lesions include Lisch nodules (iris hamartomas), optic pathway gliomas (OPGs), and orbital plexiform lesions. CNs may be smaller, benign subcutaneous lesions or larger, plexiform tumors that follow nerves and/or extend into deeper bony and visceral structures. Malignant peripheral nerve sheath tumors (MPNSTs) may develop, particularly within larger plexiform lesions. MPNSTs and vasculopathy are the greatest contributors to mortality in NF1. CALs are typically the first lesions to appear in infancy and early childhood. The paucity of typical lesions in very young children may hamper diagnosis.

MANAGEMENT STRATEGY

The diagnosis of NF1 can usually be established by clinical criteria. *NF1* variant identification is useful in reproductive

counseling, confirming the diagnosis, and differentiating NF1 from other RASopathy-related conditions with overlapping phenotypes. The nature of the variant may also affect the prognosis; large deletions or null mutations may be associated with more severe disease, including more severe intellectual disability and greater tumor burdens. There is variable expression of the phenotype from the genotype. There are also more specific genotype-phenotype correlations. For example, the variant p.Met992del is associated with a milder phenotype without CNs or PNs. Variants at amino acid residue 1809 are not associated with PNs, CNs, or symptomatic OPGs, but can be associated with Noonan-like features and pulmonic stenosis. Missense changes at codons 844-848 are associated with a more severe phenotype including PNs and spinal neurofibromas, OPGs, other malignancies, and bone abnormalities. Approximately 50% of *NF1* variants arise as de novo events.

Treatment for NF1 was traditionally limited to surgery but targeted non-surgical treatment approaches that exploit the molecular biology of the NF1 protein are actively being developed. For small, benign CNs causing cosmetic concerns and discomfort, simple excision using a scalpel or punch biopsy is appropriate, but surgery is not practical for large tumors. Unfortunately, surgery is not curative; lesions may continue to progress, requiring repeated procedures.

Treatment of PNs is particularly challenging; these tumors are often highly vascular and invasive. Symptomatic lesions should be evaluated by MRI or PET scans because of the risk for evolution into MPNSTs from the accumulation of additional mutations in *TP53* or *INK4-ARF* (*CDKN2A/B*) tumor suppressor genes. Unexplained pain or rapid growth within a PN and areas displaying necrosis or an unusual appearance on imaging studies merit biopsy to exclude malignant transformation. cDNA gene expression profiling may be useful to help distinguish benign from premalignant and malignant lesions. Sirolimus, which blocks the mTOR pathway, and pegylated interferon- α_{2b} may slow the progression of PNs via its antiproliferative and immunoregulatory activities.

Other proposed therapeutic agents have included angiogenesis inhibitors and antiinflammatory agents to inhibit cell growth and induce apoptosis, and drugs that target RAS signal transduction. Agents that impact the microenvironment of NF1 tumors via limiting the induction of other signaling pathways and through interactions with other cell lines have been studied, as well as combinations of these agents with mTOR inhibitors. Referral of a patient with aggressive MPNSTs to an oncologist for chemoradiotherapy may be warranted.

Other therapies that have been tried for NF1 include keto-tifen and pirfenidone, but neither have shown reproducible efficacy. Statins have also been explored as treatment for NF1-related cognitive difficulties because of their known inhibition of p21Ras/MAPK activity, but studies to date have not verified effectiveness.

MEK inhibitors such as selumetinib resulted in PN shrinkage in 71% of subjects in a phase I study in children with inoperable PNs, leading to the designation of selumetinib as a 'breakthrough therapy' for NF1 by the US Food and Drug Administration (FDA). In a recent phase 2 trial with selumetinib, the majority of 50 children with NF1 and inoperable PNs showed long-lasting tumor shrinkage and clinical benefit, including reduced pain related to PNs. Combination approaches using selumetinib with an mTOR inhibitor are also actively under investigation. Information about ongoing clinical trials can be found at www.ctf.org/research/clinical-drug-pipeline and www.ClinicalTrials.gov.

Specific Investigations

- Annual complete cutaneous examinations, particularly in patients with large plexiform lesions
- Complete baseline ophthalmologic exam, with slit lamp and dilated funduscopy. Annual ocular exams to screen for OPGs should be continued through age 8 and every 2 years thereafter from ages 8–18
- Skin and eye exams for first-degree relatives (or targeted DNA testing)
- Regular developmental assessment in children: evaluation and management of learning disability and attention deficits
- Regular blood pressure checks to screen for renal artery stenosis or pheochromocytoma
- MRI of brain, optic nerves, and spinal cord with and without contrast based on symptoms and/or focal neurologic signs
- MRI or PET scan, with and without contrast, to evaluate deep or changing plexiform neurofibromas
- Biopsy or excision of changing or suspicious lesions
- Radiographs if osseous involvement is suspected
- DNA sequencing of cDNA and genomic DNA (often via panel testing that includes both *NF1* and *SPRED1*, possibly other RASopathy genes), and deletion/duplication analysis, particularly in young children who do not meet clinical criteria, in those with features of 'NF1–Noonan syndrome' and/or cardiac disease and in individuals with reproductive questions. Chromosome microarray analysis may also detect larger genomic deletions that include *NF1*

Neurofibromatosis 1. Friedman JM. 1998 Oct 2 [Updated 2019 Jun 6]. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews [Internet]. Seattle (WA): University of Washington; 1993–2020. <https://www.ncbi.nlm.nih.gov/books/NBK1109>.

This is one of the most comprehensive reviews of NF1, which is frequently updated.

First International Conference on RASopathies and Neurofibromatoses in Asia: identification and advances of new therapeutics. Rauen KA, Alsaegh A, Ben-Shachar S, et al. *Am J Med Genet A*. 2019; 179: 1091–7.

Comprehensive summary of recent advances in NF1, NF2, and other rasopathies, including treatment.

First-Line Therapies

In the future, systemic treatments aimed at preventing growth of lesions will make the most sense. Until then, removal of individual or multiple lesions that are causing disfigurement, impaired function, and pain is the mainstay of treatment.

- Surgical excision **C**
- Laser therapy **B**
- Electrodesiccation **D**

Comprehensive and global approach of soft-tissue deformities in craniofacial neurofibromatosis type 1. Denadi R, Buzzo CL, Takata JPL, et al. *Ann Plast Surg* 2016; 77: 190–4.

In total, 20 patients (mean age 25.8 years, range 5–60) underwent 149 craniofacial soft-tissue surgical procedures to correct

facial deformities associated with NF1. All patients underwent procedures for en bloc excision, 60% for facial suspension, 15% for eyebrow suspension, 10% for ear suspension, 45% for lateral canthopexy, and 25% and 5% for shortening of the lower and upper eyelids, respectively. Three patients had surgical complications. The authors concluded that the surgical approach for patients with NF1 should be global, comprehensive, and individualized given the spectrum of soft-tissue deformities.

The use of electrodesiccation in the treatment of cutaneous neurofibromatosis: a retrospective patient satisfaction outcome assessment. Lutterodt C, Mohan A, Kirkpatrick N. *J Plast Reconstr Aest* 2016; 69: 765–9.

Six patients were treated with electrodesiccation under general anesthesia for an average of three sessions, treating hundreds of lesions per session with minimal complications. Five of six patients preferred electrodesiccation to surgical excision. The authors proposed that electrodesiccation is a simple and effective method for treating larger numbers of cutaneous lesions.

Treatment of neurofibromas with a carbon dioxide laser: a retrospective cross-sectional study of 106 patients. Méni C, Sbidian E, Moreno JC, et al. *Dermatology* 2015; 230: 263–8.

Carbon dioxide laser treatment was well tolerated and resulted in satisfactory patient outcomes in over 106 patients with neurofibromas.

Treatment of neurofibromatosis 1-associated malignant peripheral nerve sheath tumors: a systematic review. Tora MS, Xenos D, Texakalidis P, et al. *Neurosurg Rev* 2019 [Epub ahead of print].

In this study, 50 patients with MPNSTs associated with neurofibromatosis 1 were analyzed. Patients underwent different combinations of surgery, chemotherapy (CT) and/or radiotherapy (RT). The authors concluded that a clear role for adjuvant CT or RT in the treatment of NF-1 associated MPNSTs was not verified.

Second-Line Therapy

- Chemotherapy **C**

Nonrandomized comparison of neurofibromatosis type 1 and non-neurofibromatosis type 1 children who received carboplatin and vincristine for progressive low-grade glioma: a report from the Children's Oncology Group. Ater JL, Xia C, Mazewski CM, et al. *Cancer* 2016; 122: 1928–36.

This report found that 127 patients with NF-1 and low-grade gliomas who were treated with carboplatin and vincristine had significantly better 5-year event-free survival (69%) compared with 137 patients without NF-1 who were similarly treated (39% 5-year event-free survival).

Third-Line and Future Therapies

- mTOR inhibitor (sirolimus, rapamycin) **B, E**
- VEGF/c-Kit inhibitor (bevacizumab, cediranib) **D, E**
- Multikinase inhibitor (sorafenib) **E**
- Statins (simvastatin) **A, B, D**
- BRAF inhibitors (vemurafenib) **E**
- Interferon- α **B**
- MEK inhibitors (trametinib, selumetinib) **B, E**

Emerging therapeutic targets for neurofibromatosis type 1. Walker JA, Upadhyaya M. *Expert Opin Ther Targets* 2018; 22: 419–37.

This is a comprehensive review of new therapeutic approaches. Most drugs currently employed for treating NF1 are repurposed agents used against cancer. Genomic, transcriptomic, proteomic, and methylation studies, combined with molecular, cellular, and biochemical analyses of signaling pathways have identified several targets for NF1 therapy. Strategies to restore defective neurofibromin, small molecule inhibitors of RAS signaling, and other more specific pathways involved in NF1 represent targets for therapeutic intervention.

Sirolimus for progressive neurofibromatosis type 1-associated plexiform neurofibromas: a neurofibromatosis Clinical Trials Consortium phase II study. Weiss B, Widemann B, Wolters P, et al. *Neuro Oncol* 2015; 17: 596–603.

This study was focused on patients with inoperable, NF1-associated progressive PNs: 29 patients were treated with sirolimus and 49 with placebo. Dosing of sirolimus was initially 0.8 mg/m² body surface area by mouth twice daily, and adjusted to achieve trough concentration of 10–15 ng/mL. Two subjects were removed from the trial for severe sirolimus toxicity (grade 2 pneumonitis; both cases reversed with cessation of therapy). Sirolimus prolonged the time to progression of PNs by almost 4 months in these NF1 patients. A previous study by this group suggested that sirolimus should not be used for non-progressive PNs.

Phase I trial and pharmacokinetic study of sorafenib in children with neurofibromatosis type 1 and plexiform neurofibromas. Kim A, Dombi E, Tepas K, et al. *Pediatr Blood Cancer* 2013; 60: 396–401.

Children with NF1 and PNs did not tolerate sorafenib at doses substantially lower than the maximum tolerated dose in children and adults with solid tumors. No tumor shrinkage was observed.

Randomised controlled trial of simvastatin treatment for autism in young children with neurofibromatosis type 1 (SANTA). Stivaros S, Garg S, Tziraki M, et al. *Mol Autism* 2018; 9: 12.

A group of 30 children with NF1 and comorbid autism were randomized to receive simvastatin or placebo for 12 weeks. Results showed that 25% of simvastatin cases compared to the none in the placebo group met ‘clinical responder’ criteria for behavioral outcome.

Prolonged survival in adult neurofibromatosis type I patients with recurrent high-grade gliomas treated with bevacizumab. Theeler BJ, Ellezam B, Yust-Katz S, et al. *J Neurol* 2014; 261: 1559–64.

Five adult NF1 patients with recurrent high-grade gliomas were treated with a median of 20 cycles of bevacizumab. All experienced prolonged postrecurrence survival ranging from 10 to 72 months. The median overall survival from the time of glioma diagnosis was 72.6 months; 3/5 patients developed vascular complications leading to discontinuation of the drug.

Phase II trial of pegylated interferon alfa-2b in young patients with neurofibromatosis type 1 and unresectable plexiform neurofibromas. Jakacki RI, Dombi E, Steinberg SM, et al. *Neuro-Oncol* 2017; 19: 289–97.

A group of 82 patients with unresectable PNs were given pegylated interferon- α 2b for at least one year. Pegylated interferon resulted in more than doubling of the time to progression of PNs compared with placebo.

Quick and sustained clinical response to MEK inhibitor I in a NF1 patient with neurofibromas. Papalia H, Audic F, Rivi re GR, et al. *ecancer* 2018; 12: 1–5.

A 12-year-old boy who could not walk due to multiple cutaneous and paraspinal neurofibromas showed improved walking, reduction in size of a large neurofibroma on the hand, and reduced pain after 1 week of being treated with trametinib 1 mg/day.

Dramatic response to trametinib in a male child with neurofibromatosis type 1 and refractory astrocytoma. Knight T, Shatara M, Wang ZJ, et al. *Pediatr Blood Cancer* 2019; 66(1): e27474.

A child with neurofibromatosis 1 and a diffuse left temporal astrocytoma experienced progression on vinorelbine, vinblastine, a combination of sirolimus and erlotinib, and temozolomide. He experienced a dramatic improvement when switched to trametinib monotherapy.

Activity of selumetinib in neurofibromatosis type 1-related plexiform neurofibromas. Dombi E, Baldwin A, Widemann BC, et al. *N Engl J Med* 2016; 375: 2550–60.

In total, 24 children with inoperable PNs were given selumetinib twice daily at a dose of 20–30 mg per square meter of body surface area; 17/24 had decreases in neurofibroma volume compared to baseline.

Selumetinib for plexiform neurofibromas in neurofibromatosis type 1: a single-institution experience. Espirito Santo V, Passos J, Nzwalo H, et al. *J Neuro-Oncol* 2020; 147: 459–463.

Nineteen patients with PNs were treated with selumetinib and followed for a mean of 223 days. All but one had sustained clinical improvement, mainly within the first 60–90 days. There were no adverse effects leading to treatment cessation.

Selumetinib in children with inoperable plexiform neurofibromas. Gross AM, Wolters PL, Dombi E, et al. *N Engl J Med* 2020; 382:1430–1442.

A total of 50 children with inoperable PNs were treated with oral selumetinib twice daily, 25 mg/m², on a continuous dosing schedule (28-day cycles). The majority showed long-lasting tumor shrinkage and significant clinical benefit including reduced pain. Side effects included nausea, vomiting, or diarrhea; asymptomatic increase in creatine phosphokinase level; acneiform rash; and paronychia.

Selumetinib is now FDA-approved for the treatment of PNs.

Nevoid basal cell carcinoma syndrome (Gorlin syndrome)

Ervin H. Epstein Jr.



Courtesy of Maral Kibarian Skelsey, Gary L. Peck

Gorlin (nevoid basal cell nevus, Gorlin–Goltz) syndrome (GS) is an autosomal dominant syndrome characterized dermatologically, especially by the development of large numbers of basal cell carcinomas (BCCs). The age at which the first BCC is seen and the lifetime numbers of BCCs vary significantly – can start as early as childhood and in dozens to hundreds – likely due to varying exposure to ambient sunlight (e.g., earlier and in higher numbers in Australia than in England) and to genetic predisposition (e.g., many fewer BCCs in persons of East Asian or African descent than in those of European descent, factors that also affect the development of sporadic BCCs). In addition, Gorlin patients may have multiple systemic manifestations, including, among others, palmar or plantar pits, odontogenic keratocysts of the jaw, ectopic intracranial calcification (particularly of the falx cerebri), fused or bifid ribs, macrocephaly, cleft lip/palate, coarse facies, hypertelorism, medulloblastomas, cardiac and ovarian fibromas, lymphomesenteric cysts, pectus deformity, and syndactyly of the digits (Gorlin 2004).

Inactivating mutations in the Patched (PTCH1) tumor suppressor gene underlie most cases of GS but approximately 5% of patients' causative mutations inactivate the Suppressor of Fused (SUFU) gene. Both genes encode proteins that *inhibit* activation of the hedgehog (HH) signaling pathway, specifically activation of the smoothened protein (PTCH1) or of the more downstream SUFU. Therefore, drugs (e.g., vismodegib or sonidegib) that effectively block smoothened activity can replace the function of the defective PTCH1 protein and effectively block HH signaling but are less effective at blocking HH activation due to loss of SUFU protein. Of note, the development of childhood

medulloblastomas, a classic manifestation of GS, is approximately $\times 20$ more frequent in patients with SUFU mutations than in families with PTCH1 mutations. GS patients with SUFU mutations also are more likely to develop meningiomas and less likely to develop jaw cysts than are GS patients with PTCH1 mutations.

MANAGEMENT STRATEGY

Despite advances in molecular understanding, the diagnosis of GS currently generally depends on identification of clinical abnormalities, most commonly for those patients seen by dermatologists the development of multiple BCCs or of at least one BCC before the age of 20, the presence of three or more palmo-plantar pits, and by jaw cysts. Dermatologic management of GS patients focuses on patient education, tumor prevention, and treatment of BCCs while optimizing cosmesis and minimizing discomfort and cost.

Patient education should include information on avoidance of sun exposure and the necessity of avoiding unnecessary ionizing radiation (IR) exposure, as GS patients are especially susceptible to the development of BCCs in areas of IR, as well as genetic counseling. Patients who avoid sunlight should be tested regularly for vitamin D deficiency and given D₃ supplements as needed. Complete skin examinations should be performed at least annually and more frequently after the development of the first BCC. Dermatologists can advocate and provide resources including referrals to other specialists for diagnosis and treatment of extracutaneous manifestations of GS, e.g., annual ophthalmologic and dental examinations. Pediatric GS patients especially should be monitored for development, vision, speech, and hearing. A baseline echocardiogram can identify the rare cardiac fibroma. Pelvic ultrasound of girls who have reached puberty can assess for ovarian fibromas. Magnetic resonance imaging (MRI) is preferable when possible, e.g., for assessing for jaw cysts. An annual MRI of the head is recommended until the age of 8, when medulloblastoma becomes less common.

Genetic testing generally can be limited to the following situations: (1) when future prenatal testing is likely; (2) for establishing the diagnosis in patients whose clinical criteria are ambiguous; and (3) for screening an asymptomatic patient who is at risk because of an affected family member.

Patients with GS need emotional support as they undergo multiple treatments that may result in scarring and deformity. They may benefit from regular screening for depression and referral to a support network (e.g., <https://gorlinsyndrome.org>; <https://gorlingroup.org>).

The size and numbers of BCCs, especially in those with type I and II skin, the often young age at presentation, and the distribution on the head and neck, pose challenges greater than those associated with sporadic BCC. Nonetheless, with the notable exception of radiotherapy, which should be avoided, treatment generally is based on the same modalities as are used for sporadic BCCs including surgery; photodynamic therapy (PDT); and topical, injectable, and systemic therapy, including vismodegib and sonidegib, HH pathway inhibitors that bind SMO protein, and, if all else fails, chemotherapeutic drugs.

The role of chemoprevention (prophylactic therapy to reduce the incidence of new BCCs) is still unclear. Evidence for its efficacy in GS is inconclusive, except for vismodegib, which may be useful in severe cases, if patients tolerate its common side effects.

This chapter focuses largely on literature specific to GS; that on BCC gives a broader review of the management of this tumor. One difference is that in some GS patients much of the skin, at least near BCCs, has BCC-like budding from the base of the epidermis, making a 'clear surgical margin' essentially impossible.

Specific Investigations

- Radiologic studies
- Vitamin D level
- Genetic studies (in selected cases)

Nevoid basal cell carcinoma syndrome. Evans DG, Farndon PA. 2002 Jun 20 [Updated 2018 Mar 29]. In: Adan MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews [Internet]. Seattle: University of Washington, Seattle, 1993–2020.

This is a very extensive, highly authoritative review of GS with detailed suggestions for management.

Consensus statement from the first international colloquium on basal cell nevus syndrome (BCNS). Bree AF, Shah MR, BCNS Colloquium Group. Am J Med Genet A 2011; 155: 2091–7.

This is a multidisciplinary consensus group's statement on the diagnostic criteria for GS and protocols for evaluation and surveillance of pediatric and adult patients.

High prevalence of vitamin D deficiency in patients with basal cell nevus syndrome. Tang J, Wu A, Linos E, et al. Arch Dermatol 2010; 146: 1105–10.

GS patients participating in a trial of vismodegib were three times more likely to be vitamin D deficient than were matched controls (56% vs. 18%; $p < 0.001$).

First-Line Therapies

• Surgical management	B
• Mohs micrographic surgery	B
• Avoidance of ultraviolet light and radiotherapy	B
• Imiquimod, 5-FU, and PDT for superficial BCCs	B

Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines. Peris P, Fargnoli MC, Garbe C, et al. Eur J Cancer 2019; 118: 10–34.

This extensive, authoritative review of BCC management includes a section on BCCs in GS patients, among the 'hard to treat' patients, recommending that their BCC treatment mirror that of sporadic BCCs with an emphasis on educating the patient regarding non-BCC complications and the importance of sun avoidance/protection and frequent examinations to identify and treat BCCs when they are small rather than waiting for them to become larger, at which time the degree of scarring and recurrence becomes greater.

Guidelines of care for the management of basal cell carcinoma. Bichajian C, Armstrong A, Baum C, et al. J Amer Acad Dermatol 2018; 78: 540–59.

Reflecting different treatment approaches in Europe vs. America, this consensus statement focuses more on surgery and less on other treatment modalities. Its appraisal of current data leads to their conclusion that neither laser treatment nor retinoid prevention is recommended for BCCs.

Consensus for nonmelanoma skin cancer treatment: basal cell carcinoma, including a cost analysis of treatment methods. Kauvar AN, Cronin T, Roenigk R. Dermatol Surg 2015; 41: 550–71.

Tumor factors associated with increased recurrence rates of BCC include location on the 'mask' area of the midface, hands, feet, and genitalia; size over 20 cm on the torso or extremities and 10 mm or larger in the non-mask areas of the face; micronodular, infiltrative, sclerosing, morpheaform, or desmoplastic histologic subtypes; ill-defined margins; prior recurrence; and perineural invasion. Host factors linked to high-risk BCC include occurrence in a site of prior radiation or scar, immunosuppression, genetic syndrome, and age younger than 40.

The nevoid basal cell carcinoma syndrome: sensitivity to ultraviolet and x-ray irradiation. Frentz G, Munch-Petersen B, Wulf HC. J Am Acad Dermatol 1987; 17: 637–43.

Radiation therapy should be avoided in patients with GS because these patients frequently develop BCCs as a consequence of radiotherapy directed, for example, for medulloblastomas or BCCs, often within 6 months to 3 years, unlike the usual 20- to 30-year lag for IR-induced tumors seen in patients with sporadic BCC.

Five-year results of a randomized controlled trial comparing effectiveness of photodynamic therapy, topical imiquimod, and 5-fluorouracil in patients with superficial basal cell carcinoma. Jansen MHE, Mosterd K, Arits AHMM. J Invest Dermatol 2018; 138: 527–33.

This large, long-term study randomized 200 patients (85% monitored for 5 years), each with a sporadic, biopsy-confirmed superficial BCC, into each of three groups, using PDT (two treatments separated by 1 week with MAL-PDT), imiquimod (applied 6 weeks, daily 5×/week), or 5-FU (applied 4 weeks twice daily). The probability of recurrence-free survival was 63% for PDT, 70% for 5-FU, and 81% for imiquimod. The results of the latter two were statistically better than that for PDT; results for imiquimod were better than that for 5-FU, albeit not of formal statistical significance. Patients may choose different alternatives depending on cost, ease of treatment (e.g., some patients cannot apply topicals to their back), and their perception of the importance of these differences in the cure rates, but these data (although in sporadic patients) allow more authoritative counseling. These modalities treat nodular BCCs less successfully and hence generally are at best reserved for third-line treatment of deeper BCCs; they can be first-line treatments for superficial BCCs.

Second-Line Therapy

• Electrodesiccation and curettage	B

Basal cell and squamous cell skin cancers: clinical practice guidelines in oncology. Miller SJ, Alam M, Anderson J, et al. JNCCN 2010; 8: 836–64.

Excisional surgery results in the highest cure rate and lowest recurrence for BCC but electrodesiccation and curettage also is effective for low-risk tumors. Pathology should be obtained to exclude high-risk tumor type. Excisions with 4-mm clinical margins are usually adequate. High-risk tumors generally should be treated with microscopically controlled (e.g., Mohs) surgery.

Third-Line Therapies

• Photodynamic therapy (PDT)	A
• Imiquimod	A
• Cryosurgery	B
• 5-Fluorouracil (5FU)	B
• CO ₂ laser	B
• Pulsed dye laser (PDL)	C
• Alexandrite laser	E
• Interferon	B
• Bleomycin	B
• Electrochemotherapy	E
• Retinoids	C
• Interleukin-2 (IL-2)	C
• Paclitaxel	E
• Capecitabine	E
• Chemical peel	E
• Dermabrasion	E
• Vismodegib (in locally advanced or metastatic BCC)	A
• Sonidegib	B
• Ingenol mebutate	D
• Immune checkpoint inhibitors	D

Treatment of Gorlin syndrome (nevoid basal cell carcinoma syndrome) with methylaminolevulinate photodynamic therapy in seven patients, including two children: interest of tumescent anesthesia for pain control in children. Girard C, Debu A, Bessis D. *J Eur Acad Dermatol Venereol* 2013; 27: e171–5.

Seven patients with 41 BCCs had prior superficial curettage for superficial BCCs or debulking for nodular BCCs, then had methylaminolevulinic (MAL) acid applied topically to lesions 3 hours before illumination with 635 nm red light for 10 minutes. Overall clearance in patients was 60% after one session and 78% after three sessions. There were excellent cosmetic outcomes in all patients. Treatments were well tolerated in adults with moderate pain sensation during illumination, and a ropivacaine–lidocaine tumescent anesthesia was used on the youngest patient to ensure excellent pain tolerance.

Efficacy of photodynamic therapy as a treatment for Gorlin syndrome-related basal cell carcinomas. Lancaster J, Swindell R, Slevin F. *Clin Oncol* 2009; 21: 502–8.

The authors report that 33 NBCCS patients (138 lesions) were treated with PDT, and lesion thicknesses were assessed using ultrasound, both before treatment and during follow-up. Topical PDT was used to treat superficial lesions (<2 mm thick) and a systemic photosensitizer + light delivered by interstitially placed optical fibers, which extended the remit of PDT, allowed for thicker lesions (>2 mm) to be treated. Local control rates of 56.3% at 12 months were achieved overall.

Consensus recommendations for the treatment of basal cell carcinomas in Gorlin syndrome with topical methylaminolevulinate-photodynamic therapy. Basset-Seguín N, Bissonnette R, Girard C, et al. *J Eur Acad Dermatol Venereol* 2014; 28: 626–32.

Consensus recommendations (seven experts) based on personal experience and literature review: all superficial BCCs and nodular BCCs <2 mm in depth may be treated; periorificial superficial and nodular BCC may be considered for treatment. Multiple tumors may be treated simultaneously. Although MAL-PDT is not approved for pediatric use, the panel agreed, based on case studies and the experts' pediatric experience, that treatment of children may be considered.

Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update of the pivotal ERIVANCE BCC study. Sekulic A, Migden MR, Basset-Seguín N. *BMC Cancer* 2017; 17: 332.

Results after 5 years were little changed vs. the first report in this trial of the efficacy and safety of oral vismodegib, 150 mg daily – a positive response in approximately 48% of metastatic BCCs and 60% of locally advanced BCCs, median overall survivals 33 months and not yet reached, respectively. Side effects remained annoying and common, and only eight of the original 104 subjects remained on the drug.

Follow-up of patients with complete remission of locally advanced basal cell carcinoma after discontinuation: a multicenter French study of 116 patients. Herms F, Lambert J, Grob JJ, et al. *J Clin Oncol* 2019; 37: 3275–82.

Patients (18 of whom had GS) with vismodegib-induced complete response of a locally advanced BCC (median duration of treatment 8.4 months, 150 mg/day) and stopped treatment had a median remission-free period of 18.4 months. All GS patients experienced a relapse and/or developed a new BCC. Importantly, half of the patients experiencing relapse and treated again with vismodegib had an objective response.

Patient with Gorlin syndrome and metastatic basal cell carcinoma refractory to smoothened inhibitors. Zhu GA, Li AS, Chang AL. *J Am Acad Dermatol* 2014; 150: 877–9.

This and subsequent publications have documented the general experience that BCCs that are resistant to one of the approved oral HH inhibitors – vismodegib and sonidegib – are resistant to the other. Most of these resistant advanced BCCs have acquired mutations that, for example, interfere with binding of the drug to the protein. However, one report documented near contemporaneous development of drug resistance of normal hair follicles and BCC, suggesting the theoretical possibility that reduced circulating drug levels might underlie resistance of some BCCs.

The use of vismodegib to shrink keratocystic odontogenic tumors in patients with basal cell nevus syndrome. Ally MS, Tang JU, Joseph T, et al. *JAMA Dermatol* 2014; 150: 542–5.

Vismodegib may offer a non-surgical treatment option for jaw cysts in GS patients. In six patients with both GS and keratocystic odontogenic tumors (KCOTs), tumor size was reduced by 50% after vismodegib 150 mg/day, mean 18 months. No new KCOTs developed during therapy. Long-term efficacy is uncertain, and it is not clear why some patients did not respond.

An investigator-initiated open-label clinical trial of vismodegib as a neoadjuvant to surgery for high-risk basal cell carcinoma. Ally MS, Aasi S, Wysong A, et al. *J Am Acad Dermatol* 2014; 71: 904–11.

In this trial, 11 patients with advanced BCC were treated with vismodegib 150 mg/day, mean 4 months, which reduced the predicted surgical defect area by 27% (95% CI, 45.7%–7.9%; $p = 0.006$). Adverse side effects prevented 29% of patients from continuing vismodegib for more than 3 months. No effect was seen with treatment less than 3 months. Unfortunately, no larger study addressing the use of oral HH inhibitors as neoadjuvant therapy has yet been published.

Topical treatment of basal cell carcinomas in nevoid basal cell carcinoma syndrome with a smoothened inhibitor. Skavara H, Kalthoff F, Meingassner JG, et al. *J Invest Dermatol* 2011; 131: 1735–44.

Topical application of a cream containing sonidegib, an SMO inhibitor, with oral anti-BCC results similar to those of vismodegib, to 13 BCCs in 8 GS patients for 4 weeks caused complete response in three and partial response in nine tumors. One had no clinical response. Treatment was well tolerated. Although results were not monitored for an extended time and oral HH-inhibitor treatment discontinuation is generally followed by recurrence, suggesting that topical therapy also will produce remission but not cure, the therapeutic efficacy with lack of systemic adverse effects indicates a potential role for topical hedgehog inhibitor management for BCCs, including those in patients with GS.

PEP005 (ingenol mebutate) gel for the topical treatment of superficial basal cell carcinoma: results of a randomized phase IIa trial. Siller G, Rosen R, Freeman M. *Australas J Dermatol* 2010; 51: 99–105.

Although developed for treatment of actinic keratoses, topical ingenol mebutate gel 0.05% caused histologic clearance of superficial BCCs in 63% of patients ($n=8$). Side effects included local skin reactions, application-site pain, and headache.

Multiple reports, especially in the pre-HH inhibitor era, documented in relatively small case series a low-to-moderate response rate of advanced/metastatic BCCs to systemic chemotherapy with agents including platinum-based drug, paclitaxel; capecitabine (pro-5-fluorouracil); and electrochemotherapy, in which the drug is given systemically and the tumor is treated with electrical pulses to increase the drug's local efficacy. Judging by the numbers of publications, this approach is now confined mostly to patients whose BCCs have become resistant to HH-targeted drugs. Similarly, local injections of interferons and IL-2 and cryosurgery have been reported as helpful but appear to be less commonly used currently. By contrast, despite the European consensus statement that this modality today is not generally of use vs. BCCs, many publications document ongoing interest in laser treatment of BCCs, as primary therapy or as a means to enhance percutaneous absorption of anti-BCC molecules, suggesting that this modality may become more clinically relevant in the future.

Chemoprevention

• Retinoids	D
• Non-steroidal antiinflammatory drugs (NSAIDs)	A
• Vismodegib	A
• Sonidegib	B
• Nicotinamide	A

Treatment and prevention of basal cell carcinoma with oral isotretinoin. Peck GL, DiGiovanna JJ, Sarnoff DS, et al. *J Am Acad Dermatol* 1988; 19: 176–85.

Eight percent of 270 tumors due to GS, arsenic exposure, or sunlight exposure in 12 patients treated with a mean dose of 3.1 mg/kg/day for 8 months underwent complete clinical and histologic regression. Lower doses given to three patients for 3–8 years were effective for chemoprevention of new BCCs. Note, as per earlier, European consensus is that oral or topical retinoids are yet to be proven helpful in GS BCC management.

Basal cell carcinoma chemoprevention with nonsteroidal anti-inflammatory drugs in genetically predisposed PTCH1± humans and mice. Tang JY, Aszterbaum M, Athar M, et al. *Cancer Prev Res* 2010; 3: 253–4.

This 3-year, double-blind, randomized clinical trial in 60 PTCH1± patients with GS assessed the effects of oral celecoxib on

the development of BCCs. A trend toward reduced BCC burden was detected ($p=0.069$), most pronounced in patients with less severe disease. The study was discontinued because of concern over celecoxib-induced enhanced cardiovascular risks.

Inhibition of the hedgehog pathway in patients with the basal-cell nevus syndrome: final results from the multicenter, randomised, double-blind, placebo-controlled, phase 2 trial. Tang JY, Ally MS, Chanana AM. *Lancet Oncology* 2016; 17: 1720–31.

Approximately half of the 41 GS patients who continued oral vismodegib 150/day had complete clinical clearing of all non-locally advanced BCCs by month 15 and near immediate complete cessation of new surgically eligible BCCs. However, only three of the 18 eligible patients initially randomized to the active drug continued the treatment for the full 36 months of the trial. As experienced by patients with sporadic BCCs, these GS patients had the alopecia, taste loss, and muscle cramps that are characteristic side effects of this class of drugs. When the drug was stopped, BCCs that had been in complete remission clinically and, predicted from the results of multiple biopsies, histologically generally recurred. The time to recurrence of baseline surgically eligible BCC burden varied with the duration of vismodegib treatment – approximately a year in those taking the drug for 7 months or less, and several years in those taking the drug for 18 months. Few locally advanced BCCs were present in these patients.

Two intermittent vismodegib dosing regimens in patients with multiple basal-cell carcinomas (MIKIE): a randomized, regimen-controlled, double-blind, phase 2 trial. Dreno B, Kunstfeld R, Hauschild A, et al. *Lancet Oncology* 2017; 18: 404–12.

This trial compared the results of two intermittent dosing regimens in 229 patients, one-third with GS, with at least six non-locally advanced BCCs at baseline, approximately half of whom completed the planned 72 weeks of treatment. The reduction in the number of clinically evident BCCs was similar in both groups: 63% with cycles of 12 weeks of vismodegib, 150 mg/day, likely followed by 8 weeks of placebo, and 54% with 24 weeks of vismodegib followed by cycles of 8 weeks of placebo and 8 weeks of vismodegib. Although there was no head-to-head comparison, patients appeared to tolerate intermittent therapy better than those reported on continuous therapy, and there was no appreciable development of resistance in either group. This and other reports suggest that the best tolerated/most efficacious intermittent treatment schedule has yet to be identified but that intermittent treatment does not breed resistance, is considerably better tolerated, and likely is today's most used regimen.

Safety and efficacy of vismodegib in patients with basal cell carcinoma nevus syndrome: pooled analysis of two trials. Chang ALS, Arron ST, Migden MR. *Orphanet J Rare Dis* 2016; 11: 120.

Oral vismodegib treatment, 150 mg/day, of locally advanced BCCs in GS and sporadic patients is equally efficacious and free of serious side effects.

Efficacy and safety of sonidegib in adult patients with nevoid basal cell carcinoma syndrome (Gorlin syndrome): results from a phase 2, double blind, randomized trial. Lear JT, Hauschild A, Stockfleth E. *Clin Cosmet Investig Dermatol* 2020; 13: 117–21.

Nine subjects with GS with at least two non-advanced BCCs at baseline randomized to take oral sonidegib 400 mg/day, double the now-approved dose, or placebo for 16 weeks had efficacy and safety similar to those reported for oral vismodegib.

A phase 3 randomized trial of nicotinamide for skin cancer prevention. Chen AC, Martin AJ, Choy B, et al. *N Engl J Med* 2015; 373: 717.

Patients, excluding those with GS, with at least two non-melanoma skin cancers (NMSCs) in the previous 5 years, were randomized 1:1 to oral 500 mg nicotinamide or placebo twice daily. During this 1-year trial, subjects taking nicotinamide had 20% fewer new BCCs than did those taking placebo (mean 1.3 vs. 1.7, $p=0.12$). The protection appeared mainly to be vs. the superficial subtype. No significant adverse events were seen.

Prevention of basal and squamous cell carcinoma with a single course of fluorouracil, 5%, cream: A randomized clinical trial.

Weinstock MA, Thwin SS, Siegel JA, et al. *JAMA Dermatol* 2018; 154: 167–74.

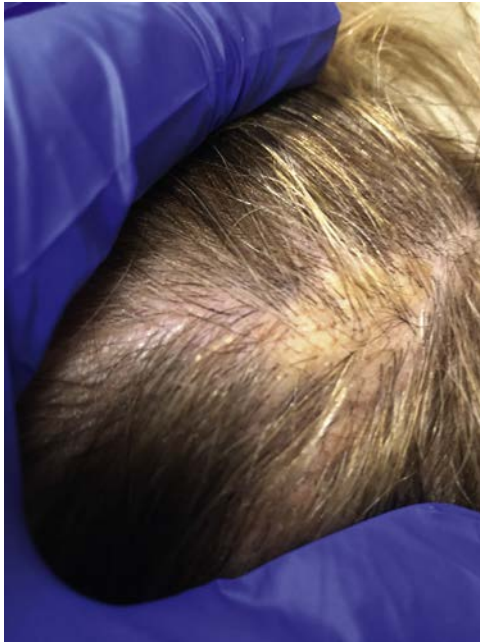
This trial randomized 932 US veterans, none of whom had GS and all of whom had at least two NMSCs during the previous 5 years, to active or placebo cream applied twice daily to the face and ears for 2–4 weeks. During the 3 years of observation, those applying active cream developed no more or fewer BCCs than did those who applied placebo cream. In contrast, there was a significant reduction in the number of squamous cell carcinomas (SCCs) during year 1 of observation.

Effective programmed death-1 therapy in a patient with Gorlin–Goltz syndrome. Morreira W, Kicheberger MC, Toussaint F, et al. *Br J Dermatol* 2018; 179: 747–9.

Several reports of small numbers of cases have documented disparate responses to this class of drugs in advanced BCCs. Larger trials are now underway.

Nevus sebaceus

Matthew Wynne, Ian H. Coulson



Nevus sebaceus (NS), first described by Jadassohn in 1895, is a term for a congenital hamartoma of the epidermis and adnexal structures typically involving the scalp and face. It results from the mosaic expression of HRAS and KRAS gene mutations. It presents at birth or appears in early childhood as a pink, orange, or yellow waxy plaque with a granular pitted surface that is often hairless. The size and configuration can be variable. During puberty the lesion thickens and becomes verrucous as glands enlarge within the dermis. Development of cutaneous and adnexal neoplasms has been reported in 10%–20% of lesions after puberty and in adulthood. These neoplasms are most commonly benign, although multiple benign and malignant neoplasms may arise concomitantly within a single lesion. Rarely, NS may occur as part of an epidermal nevus syndrome, such as phakomatosis pigmentokeratotic or Schimmelpenning syndrome, resulting in neurological, ophthalmological, and musculoskeletal abnormalities. Surgical treatment addresses cosmetic issues, as well as prophylaxis or treatment of neoplasms.

MANAGEMENT STRATEGY

For most lesions, clinical examination is sufficient to establish the diagnosis. A skin biopsy can confirm the clinical impression when indicated. Most neoplastic growths that arise in a NS do not develop until after the age of 16 years and the overwhelming majority are benign. These include syringocystadenoma; papilliferum; trichoblastoma; trichilemmoma; sebaceoma; nevocellular nevus; apocrine cystadenoma; and seborrheic keratosis. The most common malignancy that develops within a NS is a basal

cell carcinoma, but the absolute incidence is very rare. Isolated case reports describe rare patients who have developed sebaceous carcinoma, squamous cell carcinoma, trichilemmal carcinoma, or microcystic adnexal carcinoma within a NS.

In 2000, a case series established that trichoblastoma was the most common neoplasm arising in NS. With this evidence of minimal risk of malignant neoplastic transformation, prophylactic surgery is not justified. Conservative management with clinical observation and biopsy of any lesions suspicious for malignancy appear to be most prudent.

Tumors arising in nevus sebaceus: a study of 596 cases. Cribier B, Scrivener Y, Grosshans E. *J Am Acad Dermatol* 2000; 42: 263–8.

Retrospective case series of 596 cases demonstrating a 1.7% occurrence of benign tumors in childhood. Most tumors arising in NS occurred in adults over 40; in these adults, 2.1% of the neoplasms were basal cell carcinomas. The authors conclude that prophylactic surgery in children is of uncertain benefit.

Trichoblastoma is the most common neoplasm developed in nevus sebaceus of Jadassohn: a clinicopathologic study of a series of 155 cases. Jaqueti G, Requena L, Sánchez Yus E. *Am J Dermatopathol* 2000; 22: 108–18.

Retrospective case series of 155 cases failed to reveal any cases of basal cell carcinoma. Trichoblastoma was the most common (7.7%) basaloid tumor. It appears that histologic misinterpretation of trichoblastomas as basal cell carcinomas has been responsible for the erroneous reporting of an increased risk of basal cell carcinoma development within NS. The authors concluded that early prophylactic surgery seems inappropriate.

Secondary neoplasms associated with nevus sebaceus of Jadassohn: a study of 707 cases. Idriss MH, Elston DM. *J Am Acad Dermatol* 2014; 70: 332–7.

Retrospective case series of 706 cases demonstrating that most secondary neoplasms arising in association with NS are benign. Trichoblastoma and syringocystadenoma papilliferum were the most frequent benign tumors, occurring in 7.4% and 5.2% of cases, respectively. Malignant tumors were present in 2.5% of the cases, with basal cell carcinoma being most common, and almost all were seen in adults. The authors conclude that it is reasonable to delay surgical management until adolescence.

Specific Investigation

- Skin biopsy

A skin biopsy may be performed to confirm a clinical diagnosis. Clinical changes suggestive of neoplastic transformation may be investigated by skin biopsy.

First-Line Therapies

• Observation	D
• Surgical excision	E

Based on recent case series and histologic analyses that demonstrate the incidence of basal carcinoma is rare, particularly in children, clinical observation should be considered as the first option for any intervention. In addition, surgical outcomes on scalp lesions may have high rates of poor outcomes, which increase

with lesion size. Prophylactic surgical excision is therefore not warranted based on current data. Elective surgical excision may be considered if lesions become symptomatic or affect appearance. In instances of biopsy-confirmed neoplastic transformation, management should be dictated by the histology of the specific tumor.

Nevus sebaceous revisited. Moody MN, Landau JM, Goldberg LH. *Pediatr Dermatol* 2012; 29: 15–23.

A comprehensive review of reported NS outcomes, and recommendations for prophylactic excision are provided. It is recommended that all cases of NS be evaluated individually with a thorough medical history, physical examination, and review of therapeutic options in order to determine if prophylactic excision is warranted. Nevus sebaceous in cosmetically apparent regions in healthy children is recognized as a reasonable indication for consideration of prophylactic excision.

Sebaceous nevus of the scalp. Goel P, Wolfswinkel E, Fahradyan A, et al. *J Craniofac Surg* 2020; 31: 257–60.

An institutional retrospective review found 92 pediatric patients (average age 7.24 years) who had biopsy-proven NS of the scalp excised between 2004 and 2017. The average lesion size for those undergoing: (1) primary closure with undermining/galeal scoring (LTUGS) was 3.6 cm² ($n=78$); (2) rotational or transpositional flaps (RF/TF) was 4.3 cm² ($n=5$); (3) serial excision was 13.9 cm² ($n=3$); and (4) tissue expansion (TE) was 21 cm² ($n=6$). Poor outcomes were defined as: significant (>0.5 cm) scar widening; alopecia outside scar borders; wound infection; wound dehiscence; or unanticipated need for revision. Univariate binary regression analysis of patients who underwent LTUGS and RF/TF found that lesion size was a significant predictor of poor surgical outcomes, with an odds ratio of 1.24 ($p=0.012$) for every cm² increase in surface area. The predictive probability of poor outcomes in these groups was 38.5% (22.4–93.6, SD 15.1) for lesions measuring 3.66 cm² (0.04–18.50, SD 3.3) and this increased in linear fashion with surface area. In total, 3.3% ($n=3$) had recurrences. The authors developed a proposed treatment algorithm based on lesion size, location, and hair pattern. They concluded that to minimize scar widening in larger lesions, TE may be required to reduce wound tension. Authors recommend that most defects can be closed with a single-phase procedure but warn of increasing risk of poor outcomes with larger lesions and the importance of counseling for significant rates of poor outcomes even in smaller lesions.

Second-Line Therapies

- Curettage and cautery
- Cryotherapy
- Laser resurfacing
- Photodynamic therapy

E
E
E
E

A variety of destructive methods have been described for treatment of NS and provide an alternative to surgical excision. While data is limited, photodynamic therapy (PDT) may reduce lesion size with minimal complications. However, laser has high rates of recurrence and scarring.

Laser treatment of epidermal nevi: a multicenter retrospective study with long-term follow-up. Alkhalifah A, Fransen F, Le Duff F, et al. *J Am Acad Dermatol* 2020; 83: 1606–15.

A retrospective cohort of patients treated with laser for an epidermal nevus with >1 year follow-up identified 70 patients, 16 of whom were treated for nevus sebaceous of the face and neck. Ten received CO₂ laser and six Er:YAG. Of these 16 patients, 50% ($n=8$) had >50% initial improvement, but 88% ($n=14$) had partial or complete recurrence at mean follow-up of 45 months and 38% ($n=6$) developed permanent scarring, one of which was keloidal. Overall, 44% ($n=7$) were not satisfied with the outcome. The authors attributed the high rate of recurrence and scarring due to NS being a dermal lesion, which required deep treatment to prevent recurrence, but which will inevitably lead to scarring. The authors felt that laser therapy has limited long-term efficacy for NS and highlighted the importance of counseling for risks of recurrence and scarring.

Topical photodynamic therapy for nevus sebaceous on the face. In S-I, Lee JY, Kim YC. *Eur J Dermatol* 2010; 20: 590–2.

A total of 12 patients were treated with topical 20% aminolevulinic acid (ALA) or methyl-aminolevulinate (MAL) after CO₂ laser ablation. Lesions were irradiated with a light-emitting diode (LED) device. Treatment was repeated at 1- to 4-week intervals to each patient. All 12 patients responded with 3/12 (25%) mild (25%–50% improvement), 7/12 (58%) moderate (51%–75% improvement), and 2/12 (17%) marked (>75%) improvement. Two patients showed partial recurrences after completion of treatments. There were no significant side effects.

Nevus sebaceous on the face: experience with photodynamic therapy in adults and children. Moreno-Arrones O 1, Perez-Garcia B. *Indian J Dermatol Venereol Leprol* 2019; 85: 440.

As part of a retrospective study, six patients (mean age 16.8 years) with facial NS were treated with PDT. Topical methyl-aminolevulinate was applied, followed by irradiation with a 630 nm LED. Treatments were repeated at 3-weekly intervals. All six patients responded, with 5/6 (83.3%) achieving significant ($\geq 50\%$ reduction in size) improvement, two of whom achieved more than 80% reduction in size compared with baseline. The one patient with minor ($\geq 30\%$ reduction in size) improvement had lesions on the right eyelid. All those with significant improvement achieved this within three sessions. Two patients had transient adverse events, one with an urticarial reaction and the other developed hyperpigmentation. At mean follow-up of 55.8 months, there was no recurrence or malignancy identified. The authors concluded PDT offered good clinical responses with low risk of adverse reactions.

Notalgia paresthetica

Joanna Wallengren



Notalgia paresthetica is a unilateral sensory neuropathy characterized by pruritus, tingling, burning pain, or hyperesthesia to light touch at the medial border of the scapula. Accompanying pigmentation or mild lichenification is secondary to scratching. Occasionally the distribution may be bilateral, and a few hereditary cases have been described. Pruritus is believed to result from nerve impingement or chronic nerve trauma and often persists for years.

MANAGEMENT STRATEGY

Treatment aims to reduce the itch by altering peripheral or central nerve transmission. Topical corticosteroids are generally ineffective unless secondary inflammation is present.

Topical *capsaicin* 0.025% two times daily for 6 weeks depletes sensory nerve transmitters in the skin. In case of relapse, the treatment may be repeated for a few days or weeks until pruritus subsides. Capsaicin may be applied in higher concentrations, such as 0.075% or 0.1%; with increasing concentrations there is more burning, but the desensitization of the skin occurs sooner. High-dose (8%) capsaicin patch for 1 hour is associated with severe burning. It has shown considerable variability in efficacy, reducing pruritus for 2 days to 3 months.

Topical *tacrolimus* 0.1% twice daily for 6 weeks has reduced incidence of side effects and may be tried in less severe cases.

Local anesthesia with 5% lidocaine patch twice daily blocks peripheral nerve transmission, but there is a risk for contact allergy to the anesthetic.

Daily electrical stimulation for 20 min using *CFS* or *transcutaneous electrical nerve stimulation (TENS)* for 2–5 weeks has been tried with good results, with the pruritus relapsing gradually.

Deep intramuscular *acupuncture* to the paravertebral muscles in the T2–T6 dermatome once a week until the pruritus subsides, as well as spinal physiotherapy, has been reported in a few cases.

Despite several promising case reports on single treatments with *botulinum toxin*, a randomized clinical trial on 20 patients could not confirm the efficacy.

Anesthetic paravertebral block has been described in anecdotal case reports. The reduction of itch due to this treatment may last for months or years.

Oral therapy may be preferred in patients in whom repeated topical treatments may be difficult to perform. Anticonvulsants such as *gabapentin* or *oxcarbazepine* alter central nerve transmission. Low dose *gabapentin* (100–900 mg daily) or *oxcarbazepine* (600 mg daily) is often sufficient.

Most of these treatments offer only transient relief, and there is a considerable risk of relapse upon discontinuation of treatment.

Specific Investigations

- Skin biopsy
- Radiography of the thoracic spine
- Magnetic resonance imaging (MRI) of the thoracic spine

Notalgia paresthetica. Case reports and histologic appraisal.

Weber PJ, Poulos EG. *J Am Acad Dermatol* 1988; 18: 25–30.

Skin biopsies from 14 patients revealed necrotic keratinocytes. Melanin and melanophages in the upper and mid-dermis were found in biopsies of patients with pigmented lesions.

Symptoms of notalgia paresthetica may be explained by increased dermal innervation. Springall DR, Karanth SS, Kirkham N, et al. *J Invest Dermatol* 1991; 97(3): 555–61.

Skin biopsies using immunohistochemistry revealed a significant increase of sensory nerve fibers (PGP 9.5) in the dermis of five patients with notalgia paresthetica compared with the contralateral unaffected area and with 10 healthy controls.

Investigation of spinal pathology in notalgia paresthetica. Savk O, Savk E. *J Am Acad Dermatol* 2005; 52: 1085–7.

Forty-three patients with notalgia paresthetica underwent radiography of the spine. Thirty-seven skin lesions were accompanied by relevant degenerative spinal changes (60.7%).

Notalgia paresthetica associated with nerve root impingement. Eisenberg E, Barmeir E, Bergman R. *J Am Acad Dermatol* 1997; 37: 998–1000.

An impingement of the nerve root was confirmed by MRI in one patient.

Notalgia paresthetica is a clinical diagnosis, and none of the previously mentioned investigations are required in the clinical situation.

First-Line Therapies

• Capsaicin 0.025%	A
• Capsaicin 8% patch	C
• Tacrolimus 0.1%	D
• Lidocaine 5% patch	E

Successful treatment of notalgia paresthetica with topical capsaicin: vehicle-controlled, double-blind, crossover study. Wallengren J, Klinker M. *J Am Acad Dermatol* 1995; 32: 287–9.

This double-blind crossover comparison between capsaicin 0.025% and vehicle cream was performed in 20 patients for 10 weeks, with the 4-week treatments being followed by 2 weeks of washout. The group treated with capsaicin first had a reduction of VAS (visual analog scale) from 61% to 35% during the first period, whereas in the other group, VAS was reduced from 52% to 27%. Most patients relapsed within a month.

Cost-effectiveness of an 8% capsaicin patch in the treatment of brachioradial pruritus and notalgia paraesthetica, two forms of neuropathic pruritus. Steinke S, Gutknecht M, Zeidler C, et al. *Acta Derm Venereol* 2017 Jan 4; 97(1): 71–6.

After a single application of capsaicin 8% patch for 30–60 min in 20 patients with notalgia paresthetica, an improvement of pruritus ranging from 1 to 2.4 points on two 10-point scales was reported for up to 12 weeks.

Notalgia paresthetica: treatment with topical tacrolimus. Ochi H, Tan LX, Tey HL. *J Eur Acad Dermatol Venereol* 2016; 30(3): 452–4.

Retrospective report of six patients treated with tacrolimus 0.1% twice daily for 6 weeks where 70% improved.

Notalgia paraesthetica – report of three cases and their treatment. Layton AM, Cotterill JA. *Clin Exp Dermatol* 1991; 16: 197–8.

All three patients improved upon treatment with 2.5% lidocaine and 2.5% prilocaine; two patients relapsed, but pruritus was reduced.

Second-Line Therapies

• Cutaneous field stimulation (CFS)	D
• Transcutaneous electrical nerve stimulation (TENS)	D
• Gabapentin	C
• Oxcarbazepine	E

Cutaneous field stimulation (CFS) in treatment of severe localized itch. Wallengren J, Sundler F. *Arch Dermatol* 2001; 137: 1323–5.

Seventeen patients with different disorders of neuropathic pruritus completed the study. Four of five patients with notalgia paresthetica improved after daily use of CFS (20 min a day) for 5 weeks, with VAS reduced from 65% to 40%. Itch gradually relapsed after the discontinuation of CFS.

Transcutaneous electrical nerve stimulation offers partial relief in notalgia paresthetica patients with a relevant spinal pathology. Savk E, Savk O, Sendur F. *J Dermatol* 2007; 34: 315–9.

Nine of 15 patients treated with TENS (20 min a day) for 2 weeks improved substantially, with mean VAS being reduced from 100% to 45%.

Efficacy of gabapentin in the improvement of pruritus and quality of life of patients with notalgia paresthetica. Maciel AA, Cunha PR, Laraia IO, et al. *An Bras Dermatol* 2014; 89: 570–5.

A non-randomized study of 20 patients, where 10 patients were treated with gabapentin 300mg/day for 4 weeks. At the end of treatment, mean VAS for pruritus was decreased from 95% to 50% in the gabapentin group.

Open pilot study on oxcarbazepine for the treatment of notalgia paresthetica. Savk E, Bolukbasi O, Akyol A, et al. *J Am Acad Dermatol* 2001; 45: 630–2.

Five patients were treated with oxcarbazepine (300mg twice daily) for 6 months: four reported improvement but no resolution of symptoms.

Third-Line Therapies

• Spinal physiotherapy with ultrasound and manipulation	D
• Exercise of scapular and pectoral muscles	E
• Intradermal botulinum toxin A	C
• Acupuncture (deep stimulation of paravertebral muscles)	E
• Anesthetic block with bupivacaine 0.75%	E

Notalgia paresthetica: clinical, physiopathological and therapeutic aspects. A study of 12 cases. Raison-Peyron N, Meunier L, Acevedo M, et al. *J Eur Acad Dermatol Venereol* 1999; 12: 215–21.

Pruritus was reduced in four of six patients treated by spinal physiotherapy using ultrasound or manipulation. The improvement was sustained for 1–9 years.

Notalgia paresthetica: successful treatment with exercises. Fleischer AB, Meade TJ, Fleischer AB. *Acta Derm Venereol* 2011; 91(3): 356–7.

Itch resolved in two patients with notalgia paresthetica after 1 week of stretching and strengthening of rhomboid and pectoral muscles.

Botulinum toxin type A for neuropathic itch. Wallengren J, Bartosik J. *Br J Dermatol* 2010; 163: 424–6.

Four patients with notalgia paresthetica received a total of 18–100 U of botulinum toxin A (BTX-A) intradermally to the affected area. Mean VAS was reduced by 40% at 6-week follow-up. At follow-up after 18 months, pruritus relapsed.

Treatment of notalgia paresthetica with botulinum toxin A: a double-blind randomized controlled trial. Maari C, Marchessault P, Bissonnette R. *J Am Acad Dermatol* 2014; 70(6): 1139–41.

In this double-blind, randomized, placebo-controlled study on 20 patients with notalgia paresthetica, a total dose of up to 200 U BTX-A or saline was administered intradermally. After an observation of 12 weeks after the treatment, the placebo group received BTX-A, and both groups were evaluated at week 24. There was no statistically significant difference between the patients treated with BTX-A and placebo.

Neurogenic pruritus: an unrecognised problem? A retrospective case series of treatment by acupuncture. Stellon A. *Acupunct Med* 2002; 20: 186–90.

Sixteen patients with different disorders of neuropathic pruritus completed the study. Four patients with notalgia paresthetica resulted in VAS reduction from 73% to 0%.

Successful treatment of notalgia paresthetica with a paravertebral local anesthetic block. Goulden V, Toomey PJ, Highet AS. *J Am Acad Dermatol* 1998; 8: 114–6.

Two paravertebral blocks with bupivacaine 0.75% and methylprednisolone at dermatome T3–T6 in one patient resulted in clearing of pruritus within a few days, lasting for 1 year of follow-up.

Onchocerciasis

Michele E. Murdoch



Onchocerciasis is a major tropical parasitic infection caused by the filarial worm *Onchocerca volvulus* and is transmitted by blood-sucking *Simulium* spp. blackflies, which breed near fast-flowing rivers. The Global Burden of Disease Study 2017 estimated that 20.9 million people carry *O. volvulus*, most of whom live in Africa, and a total of 205 million people are considered at risk of infection because of where they live. The disease is endemic in 31 countries in sub-Saharan Africa, and in smaller foci in Latin America and Yemen. Mass ivermectin treatment has now eliminated or interrupted transmission in 11 of the previous 13 foci in the Americas and the two remaining foci in Brazil and Venezuela together form a single transmission unit along the border of these countries. The World Health Organization has verified elimination of transmission of infection in Colombia, Ecuador, Mexico, and Guatemala. The first manifestation of infection is usually intense pruritus, and subsequently a wide variety of acute and chronic skin and eye changes develop, including blindness. The socioeconomic consequences of onchocerciasis are most marked in hyperendemic areas in sub-Saharan Africa. A multicountry study in Africa revealed that 42% of the adult population in endemic villages suffered from pruritus, and 28% of the population had onchocercal skin lesions.

MANAGEMENT STRATEGY

The mainstay of treatment is *ivermectin*. Ivermectin is a safe, effective microfilaricide (i.e., it kills the immature larval stages of filarial worms), but it does not kill the adult worms. After a few months of dosing, the numbers of microfilariae in the skin gradually increase again toward pretreatment levels, and treatment must be repeated throughout the lifespan of the adult worm (10–14 years).

Wolbachia spp. symbiotic endobacteria have been identified as essential for the filarial worms' fertility and offer novel targets for

treatment. Additional treatment with *doxycycline* to sterilize the worms significantly enhances ivermectin-induced suppression of microfilaridemia.

The approach to treatment of onchocerciasis varies for (1) treatment of individuals outside of endemic areas; (2) treatment of individuals within endemic areas; and (3) mass treatment programs.

Treatment of Individuals Outside of Endemic Areas

Treatment of individuals living outside of areas with ongoing transmission consists of a single dose of ivermectin (150 mcg/kg), followed 1 week later by doxycycline (200 mg daily for 6 weeks). Alternative doxycycline regimens are doxycycline 200 mg daily for 4 weeks or 100 mg daily for 6 weeks. If the patient is pregnant or less than 9 years of age, doxycycline is contraindicated.

Treatment of Individuals Within Endemic Areas

Treatment of individuals within areas of ongoing transmission consists of a single dose of ivermectin 150 mcg/kg repeated every 3–6 months until the patient is asymptomatic. Treatment should be repeated if there is recurrence of pruritus, itchy papular rash, or eosinophilia. Treatment with ivermectin may be required for 10 years or more.

Mass Treatment Programs

Three regional programs have coordinated global control. The Onchocerciasis Control Program (OCP, 1974–2002) successfully used *aerial larviciding* of rivers in West Africa to control the vector blackfly, and more recently it distributed *ivermectin* to control any recrudescence.

The Onchocerciasis Elimination Program in the Americas (OEPA, 1991–present) uses 6-monthly mass ivermectin therapy and from its outset aimed to eliminate onchocerciasis from the region.

The largest program, the African Program for Onchocerciasis Control (APOC, 1995–2016) consisted of large-scale, annual, community-directed treatment of ivermectin in 15 non-OCP countries and four ex-OCP countries. Its original aim was to reduce onchocerciasis until it was no longer a public health problem, but this was revised in 2009 to aim for elimination in Africa where feasible by 2025. The current Expanded Special Project for Elimination of Neglected Tropical Diseases (ESPEN) is a public-private partnership among WHO (AFRO), member states, and Neglected Tropical Diseases (NTD) partners, which aims to mobilize resources to accelerate elimination of onchocerciasis alongside other neglected tropical diseases.

In forested areas of central Africa and Sudan, which are coendemic with loiasis, ivermectin can cause serious neurologic adverse reactions, including fatal encephalopathy, associated with the death of large numbers of *Loa loa* microfilariae. Whereas lengthy doxycycline regimens are deemed impractical for main large-scale treatment of onchocerciasis, in areas coendemic with loiasis, doxycycline is a safe alternative as, due to the absence of *Wolbachia*, doxycycline is inactive against *L. loa*. Alternatively, in these high risk coendemic areas, individuals may be prescreened for *L. loa* and those with high *L. loa* microfilarial loads can be excluded from ivermectin treatment.

Specific Investigations

- Skin snips
- Other parasitological forms of diagnosis:
 - Detection of intraocular microfilariae using a slit lamp
 - Demonstration of adult worms by collagenase digestion of excised nodules (not routine)
- Full blood count (for eosinophilia)
- Mazzotti test (only do if skin snips negative and hence patient likely to be lightly infected)
- Future investigative tools:
 - Serodiagnosis
 - Polymerase chain reaction
 - Antigen detection dipstick assay on urine

First-Line Therapies

• Ivermectin	A
• Ivermectin combined with doxycycline	A

The effects of ivermectin on onchocercal skin disease and severe itching: results of a multicentre trial. Brieger WR, Awedoba AK, Eneanya CI, et al. *Trop Med Int Health* 1998; 3: 951–61.

The effects of ivermectin were assessed in 3-monthly, 6-monthly, and annual doses in 4072 villagers in forest zones of Ghana, Nigeria, and Uganda who underwent interviews and clinical examinations at baseline and at five follow-up visits. Reactive skin lesions were categorized as acute papular onchodermatitis, chronic papular onchodermatitis, and lichenified onchodermatitis. From 6 months onwards there was a 40%–50% reduction in the prevalence of severe itching after ivermectin treatment compared with the placebo group. Also, a greater reduction in prevalence and severity of reactive skin lesions over time was seen in those receiving ivermectin. The differences between the various ivermectin treatment regimens were not significant.

The African Programme for Onchocerciasis Control: impact on onchocercal skin disease. Ozoh GA, Murdoch ME, Bissek A-C, et al. *Trop Med Int Health* 2011; 16: 875–83.

Seven study sites in Cameroon, Sudan, Nigeria, and Uganda participated in two cross-sectional surveys of 5193 individuals at baseline and 5180 people after 5 or 6 years of annual ivermectin therapy. At follow-up, significant ($p < 0.001$) reductions were found in the risk of itching (odds ratio [OR] 0.32) and acute papular onchodermatitis (OR 0.28), chronic papular onchodermatitis (OR 0.34), depigmentation (OR 0.31), and nodules (OR 0.37). Reduction in the odds ratio of lichenified onchodermatitis was also significant (OR 0.54, $p < 0.03$).

A trial of a three-dose regimen of ivermectin for the treatment of patients with onchocerciasis in the UK. Churchill DR, Godfrey-Faussett P, Birley HDL, et al. *Trans R Soc Trop Med Hyg* 1994; 88: 242.

As ivermectin is also thought to suppress embryogenesis in adult worms, the efficacy of three doses of ivermectin given at monthly intervals was studied to determine whether such a regimen could lead to a greater suppression of microfilaridermia. Thirty-three patients (of whom 27 were European) with onchocerciasis were treated with a single dose of 150–200 mcg/kg ivermectin and observed in hospital for 72 hours. Second and third doses were given as outpatient treatment, respectively, 1 and 2

months later. Patients were followed up at 3-, 6-, and 12-monthly intervals after the last dose of ivermectin. The patients with positive skin snips before treatment were compared with patients given a single dose of ivermectin in a previous study (Godfrey-Faussett P et al., 1991; see later). Relapses occurred slightly less frequently after three doses. In contrast to studies in West Africa, where reactions to ivermectin are rare, 17 patients (52%) had reactions. The authors therefore recommended that the first dose of ivermectin for lightly infected expatriates be given in hospital.

Ivermectin in the treatment of onchocerciasis in Britain. Godfrey-Faussett P, Dow C, Black ME, et al. *Trop Med Parasitol* 1991; 42: 82–4.

Thirty-one patients with early, light infection were treated with a single dose of 150–200 mcg/kg ivermectin. Those who relapsed were re-treated after an interval of not less than 5 months. Approximately two-thirds relapsed within 1 year. A similar pattern was seen after the second dose. A single dose of ivermectin, repeated every 3–6 months as necessary, was considered to be the treatment of choice for patients in non-endemic areas lightly infected with *O. volvulus*. One-third of such patients may be cured with each treatment.

Effects of standard and high doses of ivermectin on adult worms of *Onchocerca volvulus*: a randomized controlled trial. Gardon J, Boussinesq M, Kamgno J, et al. *Lancet* 2002; 360: 203–10.

Ivermectin 150 mcg/kg given at intervals of 0.5–3.0 months is known to cause slight but significant increased mortality of adult worms. In this randomized study of 657 Cameroonian patients with onchocerciasis, 3-monthly treatment with ivermectin killed more female adult worms than did annual treatment. There was no difference between standard (150 mcg/kg) and high-dose schedules (800 mcg/kg).

The feasibility of large-scale, 3-monthly ivermectin treatment in endemic areas and its likely greater effect in reducing transmission have still to be determined.

Endosymbiotic bacteria in worms as targets for a novel chemotherapy in filariasis. Hoerauf A, Volkmann L, Hamelmann C, et al. *Lancet* 2000; 355: 1242–3.

The activity of doxycycline against *Wolbachia* spp. and the fertility of adult female worms were assessed by examination of excised subcutaneous onchocercal nodules in 22 Ghanaian individuals treated with doxycycline 100 mg daily for 6 weeks and 14 untreated controls. Immunohistology with an antibody to bacterial heat shock protein-60 was used to assess the presence or absence of *Wolbachia* spp., and the morphology of female worms was examined. In addition, PCR reactions using, first, endobacterial primers, and second, nematode primers, were performed. None of the treated worms had usual bacterial loads, and there was total suppression of normal embryonic worm development during early oocyte/morula stages, whereas nodules from untreated controls showed normal embryogenesis.

Depletion of *Wolbachia* endobacteria in *Onchocerca volvulus* by doxycycline and microfilaridermia after ivermectin treatment. Hoerauf A, Mand S, Adjei O, et al. *Lancet* 2001; 357: 1415–6.

The Ghanaian participants in this study were not randomized because this was not acceptable to the village elders. Instead, the first 55 patients were allocated to ivermectin and doxycycline and the next 33 to ivermectin alone. Doxycycline 100 mg daily was given from the start of the study for 6 weeks. Subgroup A (31

doxycycline-treated and 24 controls) was given ivermectin 2.5 months after the start of the study, and subgroup B (24 doxycycline-treated and 9 controls) 6 months after the onset of the study. The results suggested a complete block in worm embryogenesis for at least 18 months after treatment with ivermectin and doxycycline.

The principle of targeting *Wolbachia* spp. with ivermectin in combination treatment offers the potential of interrupting transmission. Shorter anti-*Wolbachia* spp. regimens (either with other antibiotics or in combinations) are needed for mass treatment of endemic areas.

***Wolbachia* endobacteria depletion by doxycycline as antifilarial therapy has macrofilaricidal activity in onchocerciasis: a randomized placebo-controlled study.** Hoerauf A, Specht S, Büttner M, et al. *Med Microbiol Immunol* 2008; 197: 295–311.

In a randomized, placebo-controlled trial in Ghana, 67 onchocerciasis patients received 200mg/day doxycycline for 4 or 6 weeks, followed by ivermectin after 6 months. After 6, 20, and 27 months, efficacy was evaluated by onchocercoma histology, PCR, and microfilariae determination. Administration of doxycycline resulted in endobacteria depletion and female worm sterilization. The 6-week treatment was macrofilaricidal, with >60% of the female worms found dead.

Macrofilaricidal activity after doxycycline only treatment of *Onchocerca volvulus* in an area of *Loa loa* co-endemicity: a randomized controlled trial. Turner JD, Tendongfor N, Esum M, et al. *PLoS Negl Trop Dis* 2010; 4: e660.

Within a larger, double-blind, randomized trial, a group of 22 Cameroonian individuals coinfecting with *O. volvulus* and low-to-moderate intensities of *L. loa* infection were treated with a course of 6 weeks of doxycycline 200mg/day followed by ivermectin at 4 months. Doxycycline was well tolerated in patients coinfecting with moderate intensities of *L. loa* microfilariae. A 6-week course of doxycycline yielded macrofilaricidal and worm-sterilizing effects, which were not dependent on coadministration of ivermectin.

Long term impact of large scale community-directed delivery of doxycycline for the treatment of onchocerciasis. Tam-arozi F, Tendongfor N, Enyong PA, et al. *Parasites Vectors* 2012; 5: 53.

In an area coendemic for *O. volvulus* and *L. loa*, 375 Cameroonian individuals who had been treated 4 years previously with doxycycline 200mg daily for 6 weeks followed by one or two rounds of annual ivermectin mass drug treatment, plus 132 persons who had had one or two rounds of annual ivermectin alone, were evaluated. A statistically significant lower microfilarial prevalence and load were found in those who had received doxycycline followed by ivermectin compared with those who received ivermectin alone.

Second-Line Therapy

- Albendazole

A

Albendazole in the treatment of onchocerciasis: double-blind clinical trial in Venezuela. Cline BL, Hernandez JL, Mather FJ, et al. *Am J Trop Med Hyg* 1992; 47: 512–20.

Forty-nine individuals with onchocerciasis (26 treated and 23 controls) were treated with a 10-day course of albendazole (400mg daily) or placebo. Patients in the albendazole-treated group with baseline microfilarial densities over 5 microfilariae/mg skin showed a significant reduction in microfilarial densities at 12 months. Albendazole was well tolerated and is believed to interfere with embryogenesis in adult *O. volvulus* worms.

The co-administration of ivermectin and albendazole – safety, pharmacokinetics and efficacy against *Onchocerca volvulus*. Awadzi K, Edwards G, Duke BOL, et al. *Ann Trop Med Parasitol* 2003; 97: 165–78.

In a randomized, double-blind, placebo-controlled trial in 42 male patients with onchocerciasis in Ghana, the coadministration of ivermectin (200mcg/kg) with albendazole (400 mg) did not offer any advantage over ivermectin alone.

Onchocerciasis and lymphatic filariasis commonly coexist, and current integrated control programs use repeated annual mass treatment of coendemic communities with ivermectin and albendazole.

Future Therapies

- Moxidectin
- Future macrofilaricides

A

Single dose moxidectin versus ivermectin for *Onchocerca volvulus* infection in Ghana, Liberia, and the Democratic Republic of the Congo: a randomised, controlled, double-blind phase 3 trial. Opoku NO, Bakajika DK, Kanza EM, et al. *Lancet* 2018; 392: 1207–16.

Moxidectin is a macrofilaricidal drug with a higher and more prolonged efficacy than ivermectin. This phase III trial in subjects aged ≥ 12 years with at least 10 microfilariae/mg skin in four study sites in Ghana, Liberia, and the Democratic Republic of the Congo compared a single dose of 8 mg moxidectin with ivermectin (150 mcg/kg). The primary efficacy outcome analyses included 947 moxidectin and 480 ivermectin recipients. At 12 months, skin microfilarial load was lower in the moxidectin group than in the ivermectin group (adjusted geometric mean 0.6 [95% CI 0.3–1.0] vs. 4.5 [3.5–5.9]; difference 3.9 [3.2–4.9], *p* <0.0001; treatment difference 86%). There were no serious adverse events.

Annual moxidectin may prove just as effective as 6-monthly rounds of ivermectin and hence may accelerate progress toward elimination. Moxidectin has the same mode of action as ivermectin, so it is uncertain whether it could replace ivermectin in the event of resistance.

Future Macrofilaricides

A safe, single dose or short-course macrofilaricide remains an urgent need for both mass drug administration programs and for treatment of individual patients. In collaboration with several drug companies and academic institutions DNDi (Drugs for Neglected Diseases Initiative) is currently working on a translation portfolio of four potential treatments: (1) macrofilaricide CC6166; (2) oxfendazole; (3) TylAMac (ABBV-4083) (an oral anti-*Wolbachia* drug that is superior to doxycycline and is effective in a shorter dosing regime in in vivo models); and (4) emodepside.

Oral lichen planus

Drora Eisen



Oral lichen planus (OLP) is a common chronic inflammatory disorder affecting all areas of the oral mucosa that rarely undergoes complete remission, even with treatment.

MANAGEMENT STRATEGY

All treatment should be aimed at eliminating erythematous and ulcerative lesions, alleviating symptoms, and potentially reducing the risk of malignant transformation. Given the premalignant nature of OLP, it is important to monitor all patients carefully and long term.

Although the etiology of OLP is unknown, the possibility of a hypersensitivity reaction (oral lichenoid reaction) should be considered when lesions are confined to mucosa in close proximity to a dental restoration. In such cases, identifying allergies to dental materials by patch testing and then removing the fillings with positive reactions or empirically removing the fillings often results in resolution. Rarely, drugs induce lichenoid reactions. A thorough medication history with emphasis on non-steroidal antiinflammatory drugs (NSAIDs) is warranted, as drug-induced reactions are reversible when the implicated drug is withdrawn.

Exacerbating factors, including sharp dental restorations and poorly fitting dental appliances, should be eliminated. Stress, anxiety, and depression are increased in OLP patients and should be addressed. An optimal oral hygiene program that minimizes dental plaque and calculus can significantly improve gingival OLP.

All agents employed for the treatment of OLP are for off-label indications and lack adequate efficacy studies; thus, optimal dose, duration of treatment, safety, and their true efficacy remain unknown.

The most useful agents for the treatment of OLP are *potent topical corticosteroids*. Asymptomatic reticular lesions do not require therapy. For intractable erosive lesions, *intralesional corticosteroids* repeated every 2–4 weeks are highly effective.

Unresponsive OLP may benefit from *topical immunomodulators* (i.e., tacrolimus, pimecrolimus, and ciclosporin), which may be used as alternatives to, or in conjunction with, topical corticosteroids.

Relapses after cessation of therapy are to be expected. Their long-term safety for this chronic disease is unknown.

A number of *herbal preparations* have been reported anecdotally or in small clinical trials to benefit OLP, including curcuminoids (6000 mg/day), lycopene (8 mg/day), zinc acetate (50 mg/day), and topical preparations of hyaluronic acid (0.2%), propolis (5%), aloe vera (70% concentration), and chamomile gel (2%).

Photodynamic therapy has also been shown to be beneficial in alleviating OLP symptoms.

For patients with severe oral disease or with extraoral manifestations, the addition of *systemic immunosuppressives* is indicated. The author has found that *methotrexate* (12.5–20 mg/week), *azathioprine* (100–150 mg/day), *mycophenolate mofetil* (1–2 g/day), *acitretin* (25–50 mg/day), and *hydroxychloroquine* (400 mg/day) are the most useful systemic agents. *Ciclosporin*, *thalidomide*, and *tumor necrosis factor-alpha (TNF-α) inhibitors* may be used for refractory cases, but data are limited.

Systemic corticosteroids (30–80 mg of prednisone) should be reserved for acute flares and not as maintenance therapy. Secondary candidiasis frequently complicates all therapies and requires treatment with topical or systemic agents. All treatments for OLP are palliative and not curative, and patients should expect a chronic course with intermittent acute exacerbations.

Specific Investigations

- Biopsy for confirmation; direct immunofluorescence when indicated to exclude vesiculoerosive diseases
- Monitoring for malignant transformation
- Hepatitis serologies when risk factors are present
- Thyroid disease may constitute a comorbidity of OLP
- Consider contact and drug lichenoid reactions

Direct immunofluorescence in oral lichen planus. Buajebe W, Okuma N, Thanakun S, et al. JCDR 2015; 9: ZC34–7.

Biopsies of gingival OLP are often non-diagnostic. Immunofluorescence shows characteristic shaggy fibrinogen deposition at the basement membrane zone.

Malignant transformation risk of oral lichen planus: a systematic review and comprehensive meta-analysis. Gonzalez-Moles MA, Ruiz-Avila I, Gonzalez-Ruiz L, et al. Oral Oncol 2019; 96: 121–30.

Although the malignant potential of OLP remains controversial, the overall rate of transformation approximates 1%, requiring continued regular observation of patients.

Hepatitis C virus infections in oral lichen planus: a systematic review and meta-analysis. Alaizari NA, Al-Maweri SA, Al-Shamiri HM, et al. Aust Dent J 2016; 61: 282–7.

Routine hepatitis screening in northern European and American OLP patients without risk factors may not be warranted, but OLP is significantly associated with hepatitis C infections in southern Europe and Japan.

Association between oral lichenoid reactions and amalgam restorations. Pezelj-Ribarić S, Prpić J, Miletić I, et al. J Eur Acad Dermatol Venereol 2008; 22: 1163–7.

When patch test reactions to mercury compounds were positive, partial or complete replacement of amalgam fillings led to a significant improvement in nearly all patients.

Oral lichen planus and thyroid gland diseases: possible associations. Kats L, Goldman Y, Kahn A, et al. BMC Oral Health 2019; 19: 169.

Although several reports have shown a possible association between lichen planus (LP) and thyroid disease, these, and other, authors did not.

First-Line Therapies

- Topical corticosteroids **A**
- Intralesional corticosteroids **B**

Randomized, placebo-controlled, double-blind trial of clobetasol propionate 0.05% in the treatment of oral lichen planus. Arduino PG, Campolongo MG, Sciannameo V, et al. Oral Dis 2018; 24: 772–7.

A randomized triple-blind clinical trial to compare the effectiveness of topical triamcinolone acetonate (0.1%), clobetasol propionate (0.05%), and tacrolimus orabase (0.03%) in the management of oral lichen planus. Sivaraman S, Santham K, Nelson A, et al. J Pharm Bioallied Sci 2016; 8: S86–9.

High-potency preparations are more effective than mid-potency preparations. Once the disease becomes controlled, topical steroids may be used several times weekly to prevent flare-ups. Prednisone should be reserved only for acute exacerbations.

Efficacy of intralesional betamethasone for erosive oral lichen planus and evaluation of recurrence: a randomized, controlled trial. Liu C, Xie B, Yang Y, et al. Oral Surg Oral Med Oral Pathol Oral Radiol 2013; 116: 584–90.

Patients with erosive disease received either 1.4 mg intralesional betamethasone or 8 mg of intralesional triamcinolone acetonide once a week for 2 weeks. Both were effective but the more potent betamethasone more so and with a reduced recurrence rate.

Intralesional triamcinolone and betamethasone are highly efficacious for erosive lesions.

Second-Line Therapies

Topical immunosuppressants

- Tacrolimus **A**
- Pimecrolimus **A**
- Ciclosporin **A**

Systemic immunosuppressants

- Methotrexate **C**
- Mycophenolate mofetil **E**
- Azathioprine **E**
- Hydroxychloroquine sulfate **B**
- TNF- α inhibitors (adalimumab, etanercept) **E**
- Apremilast **E**

Comparison of topical tacrolimus and clobetasol in the management of symptomatic oral lichen planus: a double-blinded, randomized clinical trial in Sri Lanka. Hettiarachchi P, Hettiarachchi RM, Jayasinghe RD, et al. J Investig Clin Dent 2017; 8.

In a 3-week double-blind study with 68 OLP patients, tacrolimus was more effective than clobetasol.

Topical pimecrolimus versus betamethasone for oral lichen planus: a randomized clinical trial. Ezzatt OM, Helmy IM. Clin Oral Investig 2019; 23: 947–56.

In a 4-week double-blind study involving 30 patients, pimecrolimus resulted in a more rapid improvement and a lower recurrence rate than betamethasone.

Clinical and serologic efficacy of topical calcineurin inhibitors in oral lichen planus: a prospective randomized controlled trial. Vohra S, Singal A, Sharma SB. Int J Dermatol 2016; 55: 101–5.

In an 8-week study involving 40 patients, pimecrolimus and tacrolimus were equally effective.

Ciclosporin vs. clobetasol in the topical management of atrophic and erosive oral lichen planus: a double-blind, randomized controlled trial. Conrotto D, Carbone M, Carrozzo M, et al. Br J Dermatol 2006; 154: 139–45.

In this 2-month study, 40 patients (65%) improved with topical ciclosporin versus 95% with clobetasol.

Topical calcineurin inhibitors in the treatment of oral lichen planus: a systematic review and meta-analysis. Sun SL, Liu JJ, Zhong B, et al. Br J Dermatol 2019; 181: 1166–76.

Tacrolimus, pimecrolimus, and ciclosporin are similar in efficacy to topical steroids for the short-term treatment of OLP.

Tacrolimus, pimecrolimus, and ciclosporin are not always effective and, when discontinued, do not result in long-term benefits. Their safety for long-term use in the oral cavity remains unknown.

Treatment of erosive oral lichen planus with methotrexate. Lajevardi V, Ghodsi SZ, Hallaji Z, et al. J Dtsch Dermatol Ges 2016; 14: 286–93.

Over 80% of patients achieved pain reduction and overall improvement with methotrexate (15 mg/w), administered for 12 weeks in 18 patients with erosive disease.

Efficacy of mycophenolate mofetil in severe mucocutaneous lichen planus: a retrospective review of 10 patients. Wee JS, Shirlaw PJ, Challacombe SJ, et al. Br J Dermatol 2012; 167: 36–43.

A retrospective review of oral disease severity scores performed in 10 patients with recalcitrant, ulcerative, oral lichen planus (vulvovaginal-gingival, $n = 8$; penogingival, $n = 1$; oral, $n = 1$) before and after treatment with mycophenolate mofetil (MMF) therapy. The mean duration of MMF treatment was 3.7 (SD $\pm$ 2.4) years with a mean follow-up of 4.2 (SD $\pm$ 2.7) years. The mean baseline oral disease severity scores (39.1 ± 11.9) improved by 40% after 12–15 months (24.3 ± 11.9 , $n = 8$, $p = 0.01$) and by 43% after 21–24 months of MMF treatment (22.2 ± 10.4 , $n = 9$, $p = 0.01$). Of the 10 patients, six achieved remission, one had well-controlled disease, and three had partially controlled disease. Two patients who achieved remission successfully discontinued treatment. MMF was well tolerated in all patients.

A prospective study of findings and management in 214 patients with oral lichen planus. Silverman S Jr, Gorsky M, Lozada-Nur F, et al. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1991; 72: 665–70.

Azathioprine (50–150 mg/day) is effective but requires 3–6 months before maximal benefit is achieved.

Hydroxychloroquine sulphate therapy of erosive oral lichen planus. Yeshurun A, Bergman R, Bathish N, et al. Australas J Dermatol 2019; 60: e109–12.

More than 86% of the 21 patients with erosive disease treated with hydroxychloroquine (400 mg/day) achieved significant improvement after 2–4 months of therapy.

Adalimumab in the management of cutaneous and oral lichen planus. Chao TJ. *Cutis* 2009; 84: 325–8.

Etanercept for the management of oral lichen planus. Yarom N. *Am J Clin Dermatol* 2007; 8: 121.

Oral lichen planus treated with apremilast. Bettencourt MJ. *Drugs Dermatol* 2016; 15: 1026–8.

Three patients with recalcitrant OLP responded to apremilast, 30 mg BID.

Although systemic agents offer significantly better results than topicals, none produces long-term remission when discontinued. Clinical benefits are achieved and maintained with long-term administration, and topicals should be administered concomitantly.

Third-Line Therapies

• Topical and systemic retinoids	B
• Systemic ciclosporin	D
• Thalidomide	E
• Herbal preparations	C
• Systemic: curcuminoids, lycopene zinc	E
• Topical: aloe vera, hyaluronic acid, propolis, chamomile	B
• Photodynamic therapy	C

Topical retinoids in oral lichen planus treatment: an overview. Petruzzi M, Lucchese A, Lajolo C, et al. *Dermatology* 2013; 226: 61–7.

As a monotherapy, topical retinoids have limited value and should be used in combination with topical corticosteroids.

Treatment of lichen planus with acitretin: a double-blind, placebo-controlled study in 65 patients. Laurberg G, Geiger JM, Hjorth N, et al. *J Am Acad Dermatol* 1991; 24: 434–7.

In this 2-month study with 65 patients, some with OLP, acitretin (30 mg/day) resulted in remission or marked improvement in most cases. The majority of patients experienced adverse effects.

Efficacy and safety of oral alitretinoin in severe oral lichen planus – results of a prospective pilot study. Kunz M, Urošević-Maiwald M, Goldinger SM, et al. *JEADV* 2016; 30: 293–8.

In this study, 30 mg oral alitretinoin for 24 weeks in 10 refractory patients resulted in improvement in 40% of patients.

Severe lichen planus clears with very low-dose cyclosporine. Levell NJ, Munro CS, Marks JM. *Br J Dermatol* 1992; 127: 66–7.

In this study, ciclosporin 1–2.5 mg/kg/day was used in four patients with extensive disease until skin and oral disease clearance. Relapses could be then controlled with topical therapies on oral ciclosporin discontinuation.

Effective treatment of oral erosive lichen planus with thalidomide. Camisa C, Popovsky JL. *Arch Dermatol* 2000; 136: 1442–3.

A single report resolving with thalidomide (50–100 mg/day).

High-dose curcuminoids are efficacious in the reduction in symptoms and signs of oral lichen planus. Chainani-Wu N, Madden E, Lozada-Nur F, et al. *J Am Acad Dermatol* 2012; 66: 752–60.

In 20 patients in this double-blind placebo study, curcuminoids (6000 mg/day) produced modest benefits.

Lycopene in the management of oral lichen planus: a placebo-controlled study. Saawarn N, Shashikanth MC, Saawarn S, et al. *Indian J Dent Res* 2011; 22: 639–43.

In 15 patients taking lycopene (8 mg/day) for 6 weeks, 73% showed 70–100% benefit.

Zinc therapy in treatment of symptomatic oral lichen planus. Chaitanya NC, Chintada S, Kandi P, et al. *Indian Dermatol Online J* 2019; 10: 174–7.

Three patients with symptomatic OLP responded to oral zinc acetate 50 mg twice daily for 8 weeks.

Efficacy of topical aloe vera in patients with oral lichen planus: a randomized double-blind study. Salazar-Sánchez N, López-Jornet P, Camacho-Alonso F, et al. *J Oral Pathol Med* 2010; 39: 735–40.

In 32 patients taking a 70% concentration of aloe vera three times a day for 12 weeks, most improved modestly.

Topical hyaluronic acid in the management of oral lichen planus: a comparative study. Hashem AS, Issrani R, Elsayed TEE, et al. *J Investig Clin Dent* 2019; 10: e12385.

To evaluate the efficacy of topical propolis in the management of symptomatic oral lichen planus: a randomized controlled trial. Joshy A, Doggalli N, Patil K, et al. *Contemp Clin Dent* 2018; 9: 65–71.

Both hyaluronic acid and propolis were found to be as effective for OLP as triamcinolone cream 0.1%.

Efficacy of topical chamomile management vs. placebo in patients with oral lichen planus: a randomized double-blind study. Lopez Jornet P, Aznar-Cayuela CJ. *Eur Acad Dermatol Venereol* 2016; 30: 1783–6.

In a 60-patient double-blind study, 92% of patients treated with a 2% chamomile gel improved.

Clinical evaluation of photodynamic therapy for the treatment of refractory oral lichen planus – a case series. Rakesh N, Clint JB, Reddy SS, et al. *Photodiagnosis Photodyn Ther* 2018; 24: 280–5.

All 10 patients with erosive LP treated by 5-aminolevulinic acid mediated photodynamic therapy improved significantly.

Orf

Niraj Butala



Orf (ecthyma contagiosum) is a zoonotic cutaneous infection caused by the orf virus of the genus *Parapoxvirus*. Transmission occurs due to direct exposure to infected animals and fomites. The most commonly associated animals are sheep, goats, and deer. As such, it is predominantly an occupational disease affecting hunters, livestock owners, butchers, farmers, veterinarians, and shepherds. Human-to-human transmission remains very rare. Affected animals usually have lesions around the mouth, muzzle, and eyes, and humans are affected most commonly on the hands. Orf usually presents as a single lesion but lesions can be recalcitrant, giant, or multiple in immunosuppressed individuals. Classically, there are five described stages: maculopapular, targetoid, nodular, regenerative, and regressive. Clinicians should maintain a broad differential diagnosis including a milker's nodule, erysipeloid, pyogenic granuloma, sporotrichosis, atypical mycobacterial infection, anthrax, keratoacanthoma, and tularemia.

MANAGEMENT STRATEGY

Orf is a self-limiting infection, and *treatment is usually not necessary*. The immune response to the virus usually results in resolution of the disease within 2–7 weeks without any specific treatment. There is no available treatment that is specifically antiviral for the orf virus, and no human vaccine has been produced. Treatment is usually only indicated if there is secondary bacterial infection or immunosuppression. Erythema multiforme and id reactions have been reported as potential sequelae.

Preventive measures include vaccination of sheep before the lambing period to boost immune response and the wearing of non-porous gloves when handling animals with any sign of the disease.

Various treatments have been reported anecdotally. *Idoxuridine*, *surgery*, and *cryotherapy* have been suggested to reduce the time to healing. For persistent or more progressive cases, interventional treatment is warranted, and often treatments can be combined. Surgery may be performed to remove the bulk of the infected tissue. *Idoxuridine*, *cryotherapy*, *cidofovir*, *interferon*, and topical *imiquimod* cream have been reported to show benefit.

Specific Investigations

- Electron microscopy of scrapings from lesion
- Biopsy
- Polymerase chain reaction (PCR)

Diagnosis is usually clinical but can be confirmed by the noted investigations if required. Routine pathology with hematoxylin and eosin staining, electron microscopy, and PCR can all be used if needed.

The structure of the orf virus. Nagington J, Newton A, Horne RW. *Virology* 1964; 23: 4611–72.

The ultrastructural description of the orf virus.

Erythema multiforme after orf virus infection: a report of two cases and literature review. Joseph RH, Haddad, FA, Matthews AL, et al. *Epidemiol Infect.* 2015; 143: 385–90.

Polymerase chain reaction for laboratory diagnosis of orf virus infections. Torfason EG, Gunadottir S. *J Clin Virol* 2002; 24: 79–84.

Method for molecular diagnosis of orf initially used as a research tool but now used in the United States.

Ecthyma contagiosum (orf) – report of a human case from the United Arab Emirates and review of the literature. Al-Salam S, Nowotny N, Sohail MR, et al. *J Cutan Pathol* 2008; 35: 603–7.

More detailed method for molecular diagnosis of orf used in a clinical case.

First-Line Therapy

- No specific treatment usually necessary

Orf virus infection in humans: a review with a focus on advances in diagnosis and treatment. Caravaglio JV, Khachemoune A. *J Drugs Dermatol* 2017; 16: 684–9.

Literature review. Disease self-limited. Treatment options are limited with no widely accepted antiviral options available.

Orf. Report of 19 human cases with clinical and pathological observations. Leavell UW, McNamara MJ, Muelling R, et al. *JAMA* 1968; 204: 657–64.

Lymphangitis and lymphadenopathy occurred in three of 19 cases.

Awareness of the risk of secondary bacterial infection is important.

Second-Line Therapies

• Surgery	D
• Cryotherapy	D
• Idoxuridine	E
• Cidofovir	E
• Interferon	E
• Imiquimod	D

Giant orf with prolonged recovery in a patient with psoriatic arthritis treated with etanercept. Rørdam OM, Grimstad Ø, Spigset O, et al. *Acta Derm Venereol* 2013; 93: 487–8.

During long-term treatment with etanercept, a sheep farmer developed giant orf. He was treated successfully with debulking surgery followed by repeated cryotherapy and imiquimod for a total of 17 weeks.

Orf infection: a clinical study at the Royal Medical Services Hospitals. Tawara MJ, Obaidat NA. *J Roy Med Serv* 2010; 17: 41–6.

A review of 64 cases observed and treated over 5 years in Jordan. Eleven were treated with cryotherapy and 13 with antibiotics. Most were treated symptomatically only.

A case of ecthyma contagiosum (human orf) treated with idoxuridine. Hunskaar S. *Dermatologica* 1984; 168: 207.

The orf lesion of a healthy female was treated with 40% idoxuridine in dimethyl sulfoxide three times daily for 6 days. The lesion healed in less than 4 weeks.

Parapoxvirus orf in kidney transplantation. Peeters P, Senesaël J. *Nephrol Dial Transplant* 1998; 13: 531.

A large lesion on the thumb recurred after excisional surgery. After 40% idoxuridine topically, further surgery, and repeated cryotherapy, the lesion resolved.

Giant orf in a patient with chronic lymphocytic leukaemia. Hunskaar S. *Br J Dermatol* 1986; 114: 631–4.

A large palmar orf lesion was excised and small local recurrences treated with 40% idoxuridine.

A case of human orf in an immunocompromised patient treated successfully with cidofovir cream. Geerinck K, Lukito G, Snoeck R, et al. *J Med Virol* 2001; 64: 543–9.

An immunosuppressed renal transplant patient developed a persistent giant orf lesion. Treatment with 1% cidofovir cream daily for five cycles of 5 days of treatment alternating with 5 rest days plus debridement as necessary led to full resolution of the lesion.

Recurrent orf in an immunocompromised host. Tan ST, Blake GB, Chambers S. *Br J Plast Surg* 1991; 44: 465–7.

A tumorlike orf lesion in an immunosuppressed patient was unresponsive to surgery and idoxuridine. Temporary improvement occurred after 2 weeks of daily intralesional interferon of 1 million IU per injection with clearance after repeat surgery with subcutaneous interferon (1 million IU daily).

Rapid improvement of human orf (ecthyma contagiosum) with topical imiquimod cream; report of four complicated cases. Erbağcı Z, Erbağcı I, Almıla Tuncel A. *J Dermatolog Treat* 2005; 16: 353–6.

Treatment with imiquimod 5% applied twice daily for up to 10 days to orf lesions complicated by erythema multiforme, angioedema, or as giant orf possibly hastened clearance of the orf lesion and the secondary effects.

Progressive orf virus infection in a patient with lymphoma: successful treatment using imiquimod. Lederman ER, Green GM, DeGroot HE, et al. *Clin Infect Dis* 2007; 44: e100–3.

Giant and multifocal orf in a patient with non-Hodgkin lymphoma did not respond to debulking and topical cidofovir. Imiquimod 5% cream applied on alternate days led to improvement after a week and clearance within 2 months.

Palmoplantar keratoderma

Ravi Ratnavel



Palmoplantar keratodermas (PPKs) consist of a heterogeneous group of disorders characterized by thickening of the skin of the palms and soles. The condition may be subdivided into primary, hereditary keratodermas, acquired forms, and conditions in which PPK is an associated secondary feature of a specific dermatosis or underlying medical condition.

MANAGEMENT STRATEGY

PPK may be localized to the hands and feet or develop as part of a more generalized skin disorder. It is important when making a diagnosis to establish its morphology and the presence of any associated ectodermal disease at sites other than the palms and soles. Biopsy may be necessary to distinguish between some hereditary forms of PPK. PPK can be associated with infections (dermatophytes, human papillomavirus, HIV, syphilis, and scabies), drugs (arsenic exposure), and internal malignancy (paraneoplastic phenomenon) or may be a cutaneous manifestation of systemic disease (myxedema, diabetes mellitus). Hyperkeratosis of the palms and soles can also be a feature of eczema, psoriasis, and cutaneous T-cell lymphoma.

Treatment of PPK is challenging. Most therapeutic options produce only short-term improvement and are frequently complicated by unwanted adverse effects. Treatment options range from simple measures such as *saltwater soaks* with physical paring of the skin and use of *topical keratolytics*, through to *systemic retinoids* and *reconstructive surgery* with total excision of the hyperkeratotic skin followed by grafting.

In patients with limited disease, *topical keratolytics* containing salicylic acid, lactic acid, or urea in a suitable emollient base may be tried. Examples include 5–10% salicylic acid, 20–70% propylene glycol, or 10% lactic acid in aqueous cream or a combination therapy using 10% urea and 5% lactic acid in aqueous cream to be applied twice daily. These formulations can be made up on an individual basis or the closest proprietary product prescribed. The efficacy of these agents may be increased by occlusion at night.

Simple antiseptic soaks can prove helpful in reducing secondary dermatophyte and bacterial infections, which contribute to malodor affecting a significant number of PPK patients, as well as signs of skin maceration and fissuring.

Topical retinoids such as tretinoin (0.01% gel and 0.1% cream) may also be tried; treatment is, however, often limited by skin irritation. *Potent topical corticosteroids*, such as clobetasol propionate 0.05%, with or without keratolytics, are occasionally of value in the management of inflammatory PPK. *5-Fluorouracil* 5% has produced dramatic results in spiny keratoderma, but its use in other keratodermas has not been evaluated.

The efficacy of the *oral retinoids* in keratoderma is well established. Good responses have been seen in mal de Meleda, Papillon-Lefèvre syndrome, and erythrokeratoderma variabilis. In some types of PPKs, particularly epidermolytic forms, hyperesthesia may limit the usefulness or practicality of treatment with retinoids. The potential risk of bone toxicity should also be assessed in patients on long-term therapy, although the risks are small. Periodic radiologic bone monitoring and, when possible, prescription of pulsed (intermittent) therapy are recommended. The optimal dosage of oral acitretin is 25–35 mg daily in adults or 0.6 mg/kg daily in children, which may be adjusted after 4 weeks of therapy. Oral isotretinoin 0.5 mg/kg is a less effective option. Oral alitretinoin 30 mg/day is a further option with mixed clinical response.

Psoralen plus UVA (PUVA) therapy or *re-PUVA* (a synergistic combination of oral retinoids and PUVA) may be effective in PPK secondary to psoriasis or eczema. In oculocutaneous tyrosinemia (an autosomal recessive condition characterized by focal palmoplantar keratosis, corneal ulceration, and mental retardation), *dietary restriction of phenylalanine and tyrosine* has led to resolution of PPK. *Oral administration of 1 α ,25-dihydroxyvitamin D₃* and *topical calcipotriol* ointment has been reported to be effective.

Regular podiatry, careful selection of footwear, and treatment of secondary fungal infections are integral parts of management of all PPK. Regular intermittent use of terbinafine cream and other topical antifungals can reduce skin maceration and improve comfort. *Surgical or laser dermabrasion* is an option for some patients, with potential amelioration of symptoms and improved penetration of topical agents.

For severe refractory PPK *excision and skin grafting* may be considered. Excision should remove hyperkeratotic skin, including dermis, epidermis, and subcutis, to prevent any risk of recurrence. Establishing the genetic cause of various inherited PPKs has so far not translated into therapeutic advances.

Specific Investigations

- Scrapings for mycology
- Thyroid function tests

An epidemiologic investigation of dermatologic fungus infections in the northernmost county of Sweden (Norrbotten) 1977–81. Nielson PG. *Mycoses* 1984; 27: 203–10.

In a 5-year survey of dermatophyte infections in Norrbotten, Sweden, the frequency of dermatophytosis among patients with hereditary PPK was shown to be 35%, corresponding to a

prevalence of 36.7%. The predominant feature of dermatophytosis in patients with hereditary PPK was scaling and fissuring. Treatment improved the clinical signs after 2–3 months.

Hereditary palmoplantar keratoderma and dermatophytosis in the northernmost county of Sweden (Norrbotten). Nielson PG. Acta Derm Venereol Suppl (Stockh) 1994; 188: 1–60.

In relatives of the original case, dermatophytosis was found in 65% of men, 22% of women, and 21% of children, resulting in a total frequency of 36.2%. Statistically, it was proved that *Trichophyton mentagrophytes* occurred more often in patients with hereditary PPK. Vesicular eruptions along the hyperkeratotic border occurred significantly more often in patients with dermatophytosis and were considered pathognomonic of secondary dermatophytosis.

Palmoplantar keratoderma in association with myxedema. Hodak E, David M, Feuerman EJ. Acta Derm Venereol 1986; 66: 354–5.

A patient with myxedema and intractable PPK showed improvement after treatment with thyroid replacement therapy. The possibility of a causal relationship between hypothyroidism and PPK was questioned.

Severe palmar keratoderma with myxedema. Tan OT, Sarkany I. Clin Exp Derm 1977; 2: 287–8.

A patient with myxedema and PPK showed rapid improvement in PPK after thyroxine treatment.

First-Line Therapies

- Topical keratolytics **B**
- Topical retinoids **B**

Alleviation of the plantar discomfort caused by pachyonychia congenita with topical applications of aluminum chloride and salicylic acid ointments. Takayama M, Okuyama R, Sasaki Y, et al. Dermatology 2005; 211: 302.

Aluminum chloride solution 10% once daily was used to reduce plantar sweating, which may exacerbate blistering and hyperkeratosis in this condition.

Vitamin A acid in the treatment of palmoplantar keratoderma. Gunther SH. Arch Dermatol 1972; 106: 854–7.

Nine patients with PPK were treated with once-daily retinoic acid 0.1% in petroleum jelly, and all improved within 4 months. Permanent remission ensued in two patients. Recurrence was observed in the majority of cases 8 weeks after the withdrawal of treatment. This was avoided by the topical application of vitamin A acid once or twice weekly.

Topical treatment of keratosis palmaris et plantaris with tretinoin. Touraine R, Revuz J. Acta Derm Venereol Suppl (Stockh) 1975; 74: 152–3.

Six patients were treated for 2 months with either tretinoin 0.1% lotion or 0.05% cream once daily. Improvement was seen in most patients. Better results were achieved with the use of occlusive dressings, mechanical paring before topical application, and when a higher concentration of topical tretinoin was used (0.3%).

Second-Line Therapy

- Systemic retinoids **A**

The treatment of keratosis palmaris et plantaris with isotretinoin. A multicenter study. Bergfeld WF, Derbes VJ, Elias PM, et al. J Am Acad Dermatol 1982; 6: 727–31.

Five of six patients with PPK were safely and effectively treated with isotretinoin, with dramatic clearing of the keratoderma within the first 4 weeks of therapy. The mean dose was 1.95 mg/kg daily, and mean duration of therapy was 113 days.

Acitretin in the treatment of severe disorders of keratinisation. Results of an open study. Blanchet-Bardon C, Nazzaro VV, Rognin C, et al. J Am Acad Dermatol 1991; 24: 982–6.

An open, non-comparative study to evaluate the clinical response to acitretin in patients with non-psoriatic disorders of keratinization and to establish the optimal dosage for efficacy and tolerance. Thirty-three patients with ichthyoses, PPK, or Darier disease were treated for 4 months. Most showed a marked improvement. The optimal acitretin dosage providing the best efficacy with minimal side effects varied from patient to patient. The mean daily dose ($\pm$ SD) was 27 ± 11 mg in adults and 0.7 ± 0.2 mg/kg in children.

A controlled study of comparative efficacy of oral retinoids and topical betamethasone/salicylic acid for chronic hyperkeratotic palmoplantar dermatitis. Capella GL, Fracchiolla C, Frigerio E, et al. J Dermatolog Treat 2004; 15: 88–93.

A single-blind, matched-sample investigation was carried out in 42 patients with chronic hyperkeratotic palmoplantar dermatitis, who were administered acitretin 25–50 mg daily for 1 month controlled versus a conventional topical treatment (betamethasone/salicylic acid ointment). Acitretin was significantly better than the conventional treatment after 30 days (two-sided, $p < 0.0001$). The authors suggested that acitretin should be considered a first-choice treatment.

Acitretin in the treatment of mal de Meleda. Van de Kerkhof PC, Dooren-Greebe RJ, Steijlen PM. Br J Dermatol 1992; 127: 191–2.

Two patients with mal de Meleda treated with acitretin experienced a marked reduction of PPK. The optimal dosage was found to be 10–30 mg daily. Higher dosages resulted in hyperesthesia. Discontinuation of acitretin resulted in relapse within days.

Alitretinoin: a new treatment option for hereditary punctate palmoplantar keratoderma. Raone B, Raboni R, Patrizi P. J Am Acad Dermatol 2014; 71: e48–9.

A single patient case report demonstrating improvement of punctate keratoderma with alitretinoin 30 mg daily for 8 months.

Third-Line Therapies

- Reconstructive surgery with total excision of hyperkeratotic skin followed by grafting **C**
- Topical calcipotriol **E**
- Oral vitamin D₃ analogs **E**
- Topical corticosteroids with or without keratolytics **E**
- PUVA or re-PUVA **D**
- Dermabrasion **E**
- CO₂ laser **B**
- 5-Fluorouracil **E**
- Tyrosine-restricted diet in oculocutaneous keratoderma **E**

Plastic surgery in the management of palmoplantar keratoderma (palmoplantar neoplasty). Farina R. *Aesthet Plast Surg* 1987; 11: 249–53.

Five cases of PPK were treated successfully by grafting skin taken from the calves and thighs.

Palmoplantar keratoderma and skin grafting: postsurgical long-term follow-up of two cases with Olmsted syndrome. Bédard MS, Powell J, Laberge L, et al. *Pediatr Dermatol* 2008; 25: 223–9.

A 6- and 10-year follow-up of successful surgical correction of mutilating keratoderma.

Surgical correction of pseudoainhum in Vohwinkel syndrome. Pisoh T, Bhatia A, Oberlin C. *J Hand Surg [Br]* 1995; 20: 338–41.

Successful surgical correction of constricting rings in a patient with Vohwinkel syndrome.

Surgical correction of hyperkeratosis in the Papillon-Lefèvre syndrome. Peled IJ, Weinrauch L, Cohen HA, et al. *J Dermatol Surg Oncol* 1981; 7: 142–3.

A patient with Papillon-Lefèvre syndrome underwent successful surgical correction of hyperkeratosis of the palms.

Topical calcipotriol in the treatment of epidermolytic palmoplantar keratoderma of Vörner. Luckner GP, van de Kerkhof PC, Steijlen PM. *Br J Dermatol* 1994; 130: 543–5.

A patient with hereditary epidermolytic PPK of Vörner was successfully treated with topical calcipotriol.

Efficacy, tolerability, and safety of calcipotriol ointment in disorders of keratinisation. Results of a randomized, double blind vehicle-controlled, right/left comparative study. Kragballe K, Steijlen PM, Ibsen HH, et al. *Arch Dermatol* 1995; 131: 556–60.

Twenty patients with PPK showed no therapeutic benefit with topical calcipotriol.

Improvement of palmoplantar keratoderma of nonhereditary type (eczema tyloiticum) after oral administration of 1 alpha, 25-dihydroxyvitamin D₃. Katayama H, Yamane Y. *Arch Dermatol* 1989; 125: 1713.

A patient with acquired PPK was successfully treated with oral 1 α ,25-dihydroxyvitamin D₃ 0.5 mcg daily for 3 months, with no side effects.

Oral psoralen photochemotherapy (PUVA) of hyperkeratotic dermatitis of the palms. Mobacken H, Rosen K, Swanbeck G. *Br J Dermatol* 1983; 109: 205–8.

PUVA was found to be effective in five patients with chronic hyperkeratotic dermatitis of the palms.

Dermabrasion of the hyperkeratotic foot. Daoud MS, Randle HW, Yarborough JM. *Dermatol Surg* 1995; 21: 243–4.

A patient with acquired PPK treated with dermabrasion and then 2% crude coal tar and 5% salicylic acid in petrolatum showed no evidence of recurrence after 6 months. The indications for dermabrasion include dry, fissured hyperkeratotic heels; psoriatic keratoderma before PUVA therapy; punctate keratoderma; and generalized keratoderma.

Methods and effectiveness of surgical treatment of limited hyperkeratosis with CO₂ laser. Babaev OG, Bashilov VP, Zakharov AK. *Khirurgiia (Mosk)* 1993; 4: 74–9.

Five hundred and two patients with limited hyperkeratosis were treated, with a favorable clinical effect. Recurrences were noted in only 4% of cases

Dietary management of oculocutaneous tyrosinemia in an 11-year-old child. Ney D, Bay C, Schneider JA, et al. *Am J Dis Child* 1983; 137: 995–1000.

An 11-year-old girl with oculocutaneous tyrosinemia with plantar keratosis and keratitis demonstrated resolution of her keratitis and improvement of her plantar keratosis with dietary restriction of phenylalanine and tyrosine to less than 100 mg/kg.

Palmoplantar pustulosis

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Palmoplantar pustulosis (PPP) is an inflammatory skin disease characterized by chronic and relapsing pustular eruptions of palms and soles as the primary observed lesions. Although seen in combination with plaque psoriasis, gene expression microarray analysis suggests PPP and palmoplantar psoriasis (PP) are highly related diseases that appear to be distinct from psoriasis vulgaris. Limited rather than extensive plaque psoriasis involvement elsewhere is the norm for palmoplantar pustular psoriasis. There are currently no US Food and Drug Administration (FDA)–approved treatments with an indication for palmoplantar pustulosis.

MANAGEMENT STRATEGY

PPP is often refractory to treatment and shows a high recurrence rate. Unlike psoriasis, there are no reported associations with candidate genes within the PSORS1 locus, interleukin-36 receptor antagonist mutations, or tumor necrosis factor (TNF)- α promoter polymorphisms. It predominantly affects middle-aged women and has a higher prevalence in smokers. No single factor appears to cause PPP although streptococcal or *Helicobacter pylori* infection, diabetes mellitus, thyroid disease, celiac disease, inflammatory arthritis, and metal allergy have all been implicated. Cessation of smoking is important for the treatment course of PPP. *Tonsillectomy* can be helpful if a streptococcal focus and association are found. A *gluten-free diet* is recommended if gluten intolerance is proved.

In the remainder of this chapter, we will review in depth the treatment options available for palmoplantar pustulosis. The

allocation of each into first-, second- and third-line therapy is based on quality of study, efficacy, and treatment cost. In patients with milder symptoms of PPP, potent *topical corticosteroids* are the treatment of choice and are even more effective when used *under occlusion*. Studies on the vitamin D analog maxacalcitol show benefit compared with placebo for the topical treatment of PPP. *Psoralen and ultraviolet A light (PUVA)* therapy is also effective. Narrowband and broadband ultraviolet B (UVB) should not be considered. The retinoid *acitretin* (starting dose 0.3–0.5 mg/kg body weight) is of proven value, but its practical use in women and children is limited due to teratogenicity and premature closure of the epiphyseal growth plates. There is evidence that the combination of PUVA with systemic retinoids is superior to the individual treatments. Low-dose *ciclosporin* (1–4 mg/kg daily) and *methotrexate* (10–25 mg once weekly) can cause improvement of PPP but require careful clinical and laboratory monitoring. The oral phosphodiesterase-4 inhibitor apremilast showed mild to moderate improvement of disease.

Reports on *TNF- α antagonist* therapy in PPP show conflicting results, with many reports highlighting even induction or aggravation of the disease. Non-TNF- α -inhibiting biologic agents provide new therapeutic options, especially in recalcitrant cases. Controlled clinical trials on secukinumab (anti-IL-17A antibody), ustekinumab (anti-IL-12/23 p40 antibody), and guselkumab (IL-23 antibody) have shown efficacy in PPP. The effectiveness of other biologic therapies, such as brodalumab, an anti-IL-17RA antibody, as well as the oral Janus kinase inhibitor, is still unclear. More controlled clinical trials are needed to substantiate the evidence.

Specific Investigations

- Screen for infection with streptococci or *H. pylori*
- Gluten intolerance
- Thyroid disease
- Diabetes mellitus
- Osteoarthritis
- Metal allergy
- Exclude SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis)

Treatment outcome and prognostic factors of tonsillectomy for palmoplantar pustulosis and pustulotic arthro-osteitis: a retrospective subjective and objective quantitative analysis of 138 patients. Takahara M, Hirata Y, Nagato T, et al. *J Dermatol* 2018; 45: 812–23.

Tonsillectomy was performed on 80 patients with PPP, and an 80% or more improvement was seen in 71% of patients at 12 months and 95% of patients at 24 months. Complete clearance was seen in 38% of patients at 1 month and 66% of patients at 24 months.

Palmoplantar pustulosis associated with gastric *Helicobacter pylori* infection. Sáez-Rodríguez M, Noda-Cabrera A, García-Bustinduy M, et al. *Clin Exp Dermatol* 2002; 27: 720.

Clearing of PPP in a patient with gastric *H. pylori* infection after eradication treatment with amoxicillin and clarithromycin in combination with omeprazole. No relapse of PPP during a 4-year follow-up.

Palmoplantar pustulosis and gluten sensitivity: a study of serum antibodies against gliadin and tissue transglutaminase, the duodenal mucosa and effects of gluten-free diet.

Michaëlsson G, Kristjánsson G, Pihl Lundin I, et al. Br J Dermatol 2007; 156: 659–66.

Laboratory investigation of 123 patients with PPP showed immunoglobulin A (IgA) antibodies against gliadin in 18% and antibodies against tissue transglutaminase in 10% of cases. Celiac disease was found in 6% of patients. Gluten-free diet resulted in (nearly) total clearance of skin symptoms and decrease of antibody level.

Thyroid disease in pustulosis palmoplantaris. Agber T, Sindrup JH, Høier-Madsen M, et al. Br J Dermatol 1989; 121: 487–91.

In 53% of 32 patients with PPP, thyroid disease was detected compared with 16% in the control group.

Osteoarticular manifestations of pustulosis palmaris et plantaris and of psoriasis: two distinct entities. Mejjad O, Daragon A, Louvel JP, et al. Ann Rheum Dis 1996; 55: 177–80.

Comparison of 23 patients with PPP and 23 patients with psoriatic arthritis (PsoA). Clinical findings showed involvement of the anterior chest wall (e.g., sternoclavicular joints) in 19 out of 23 patients with PPP compared with 10 out of 23 with PsoA. Radiologic signs of arthropathy were demonstrated in 11 PPP patients and four PsoA patients.

SAPHO syndrome: a long-term follow-up study of 120 cases. Hayem G, Bouchaud-Chabot A, Benali K, et al. Semin Arthritis Rheum 1999; 29: 159–71.

Significant association of PPP with axial osteitis in 120 reported cases with SAPHO syndrome.

Palmoplantar pustulosis and allergies: a systematic review. Vernetti AMB, Puntoni M, Massone C. Dermatol Pract Concept 2019; 105–10.

This study reviewed 16 publications that examined contact allergy in a total of 519 patients. Results showed that 122 PPP patients also had contact allergy, 84% of which involved metals. In 65.1% of patients with metal allergies, the PPP improved after withdrawal of the metal involved.

First-Line Therapies

• Oral retinoids	A
• PUVA	B
• PUVA plus oral retinoids	B
• Topical corticosteroids	C

Interventions for chronic palmoplantar pustulosis. Marsland AM, Chalmers RJ, Hollis S, et al. Cochrane Database Syst Rev 2006; 1: CD001433.

An extensive review of literature concerning PPP treatment showed proven evidence of PUVA and systemic retinoids alone or in combination; effectiveness of topical corticosteroids under occlusion; and probable benefit of low-dose ciclosporin, tetracycline antibiotics, and grenz ray therapy.

A detailed survey of evidence-based PPP treatment options, including the classical publications regarding PUVA and systemic retinoids.

A retrospective analysis of treatment responses of palmoplantar psoriasis in 114 patients. Adışen E, Tekin O, Gülekon A, et al. J Eur Acad Dermatol Venereol 2009; 23: 814–9.

A retrospective study comprised 62 PP and 52 PPP patients. In the PP group, 17 of 62 patients showed marked improvement to topical agents, while the remaining patients required systemic

agents including oral retinoids ($n=24$), local PUVA ($n=12$), methotrexate ($n=9$), and ciclosporin ($n=2$). Marked improvement was achieved in 53%, 45%, 47%, and 100%, respectively. In the PPP group, 18 of 52 patients achieved marked improvement by topical agents. Patients that required systemic agents were treated with colchicum ($n=19$), local PUVA ($n=8$), methotrexate ($n=4$), oral retinoids ($n=3$), and ciclosporin ($n=2$). These treatments achieved a marked improvement in 60%, 33%, 57%, 83%, and 50% of the patients, respectively.

A hydrocolloid occlusive dressing plus triamcinolone acetonide cream is superior to clobetasol cream in palmoplantar pustulosis. Kragballe K, Larsen FG. Acta Derm Venereol 1991; 71: 540–2.

Complete clearance of PPP with use of a medium-strength topical corticosteroid under hydrocolloid occlusion in 13 out of 19 patients in a left–right comparison with a highly potent topical corticosteroid alone (complete remission only in 3 out of 19 patients).

Second-Line Therapies

• Secukinumab	A
• Guselkumab	A
• Ciclosporin	A
• Ustekinumab	B
• Apremilast	A
• Methotrexate	B
• Excimer light (308 nm)	C

Dermatologic adverse reactions during anti-TNF treatments: focus on inflammatory bowel disease. Mocci G, Marzo M, Papa A, et al. J Crohns Colitis 2013; 7: 769–79.

Review about the potential skin side effects of anti-TNF blockade, including psoriasiform lesions and PPP.

Benefit of TNF- α antagonist use in PPP is conflicting, with therapeutic efficacy, PPP initiation, or aggravation occurring.

Secukinumab shows significant efficacy in palmoplantar psoriasis: results from GESTURE, a randomized controlled trial. Gottlieb A, Sullivan J, Doorn MV, et al. J Am Acad Dermatol 2017; 76: 70–80.

A double-blinded, controlled trial with 205 subjects randomized 1:1:1 to secukinumab 300 mg, 150 mg, or placebo. At week 16, 33.3% of subjects with secukinumab 300 mg and 22.1% with 150 mg achieved clear or almost clear palms and soles compared with 1.5% with placebo.

Sustained efficacy of secukinumab in patients with moderate-to-severe palmoplantar psoriasis: 2.5-year results from GESTURE, a randomized, double-blind, placebo-controlled trial. Gottlieb A, Kubanov A, Doorn M, et al. Br J Dermatol 2020; 182: 889–899.

A randomized, double-blind, placebo-controlled, multicenter, phase IIIb trial conducted across 15 countries. Sustained clearance of palms and soles over 2.5 years was achieved on 59% [95% confidence interval (CI) 43.5–74.1] and 53% (95% CI 35.1–69.6) of patients in the secukinumab 300 mg and 150 mg groups, respectively.

Secukinumab for moderate-to-severe palmoplantar pustular psoriasis: results of the 2PRECISE study. Mrowietz U, Bachelerz H, Burden AD, et al. J Am Acad Dermatol 2019; 80: 1344–52.

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study randomly assigned patients to secukinumab 300 mg ($n=79$), secukinumab 150 mg ($n=80$), and placebo ($n=78$). At 16 weeks, 26.6% of patients treated with 300 mg of secukinumab achieved 75% clearance versus 14.1% of those who received placebo. And at 52 weeks 41.8% of patients treated with secukinumab 300 mg achieved 75% clearance.

Efficacy and safety of guselkumab, an anti-interleukin 23 monoclonal antibody, for palmoplantar pustulosis: a randomized clinical trial. Terui T, Kobayashi S, Okubo Y. *JAMA Dermatol* 2018; 154: 309–16.

A 24-week randomized clinical trial including 49 patients showed superiority of guselkumab 200 mg over placebo. Treatment was given on weeks 0 and 4, with the primary end point for statistical analysis at week 16.

Efficacy and safety of guselkumab in Japanese patients with palmoplantar pustulosis. Terui T, Kobayashi S, Okubo Y, et al. *JAMA Dermatol* 2019; 155: 1153.

A 60-week phase 3, randomized, double-blind, multicenter, placebo-controlled trial including 159 patients showed significant PPP Area and Severity Index (PPASI) improvement after subcutaneous injection of guselkumab (100 mg or 200 mg) when compared with placebo. Treatment was given on weeks 0, 4, and 12, with the primary end point for statistical analysis at week 16.

Double-blind placebo-controlled study of long-term low-dose cyclosporine in the treatment of palmoplantar pustulosis. Erkkö P, Granlund H, Remitz A, et al. *Br J Dermatol* 1998; 139: 997–1004.

In this study, 58 PPP patients were treated with ciclosporin in a daily dose of 1–4 mg/kg body weight or placebo for 12 months. Low-dose treatment showed improvement in 13 of 27 patients compared with 6 of 31 in the placebo group. Benefit of long-term use only supposed.

Effects of cyclosporine on palmoplantar pustulosis and serum expression of IL-17, IL-23, and TNF- α . Jin X-H, Chen X, Mou Y, et al. *Dermatol Ther* 2019; 9: 547–52.

Of 48 patients treated with ciclosporin 3 mg/kg/day twice daily, 45 showed improvement.

Efficacy of ustekinumab in refractory palmoplantar pustular psoriasis. Morales-Múnera C, Vilarrasa E, Puig L. *Br J Dermatol* 2013; 168: 820–4.

Five PPP patients treated with ustekinumab responded.

Investigator-initiated, open-label trial of ustekinumab for the treatment of moderate-to-severe palmoplantar psoriasis. Au SC, Goldminz AM, Kim N, et al. *J Dermatolog Treat* 2013; 24: 179–87.

Patients treated with ustekinumab 45 mg did not show a statistically significant difference in achieving a 50% improvement in

their palmoplantar pustular area and severity index (PPASI-50) compared with patients treated with placebo.

Eight-patient case series of palmoplantar pustulosis treated successfully with apremilast. Mikhailitchenko A, Crowley E, Gooderham M. *J Psoriasis Psoriatic Arthritis* 2018; 4: 7–10.

A retrospective review of eight patients with PPP who were treated with apremilast showed complete clearance in two patients, near-complete clearance in four patients, moderate improvement in one patient, and mild improvement in one patient.

Pustulosis palmaris et plantaris treated with methotrexate. Thomsen K. *Acta Derm Venereol* 1971; 51: 397–400.

Satisfactory response in eight out of 25 patients receiving weekly oral doses of 25 mg methotrexate for 2 months.

Efficacy of excimer light therapy (308 nm) for palmoplantar pustulosis with the induction of circulating regulatory T cells. Furuhashi T, Torii K, Kato H, et al. *Exp Dermatol* 2011; 20: 768–70.

Significant improvement of PPASI score after 20–30 treatments with excimer light therapy in 17 patients.

Third-Line Therapies

• Maxacalcitol	A
• Brodalumab	E
• Tofacitinib	E

Phase III clinical study of maxacalcitol ointment in patients with palmoplantar pustulosis: a randomized, double-blind, placebo-controlled trial. Umezawa Y, Nakagawa H, Tamaki K. *J Dermatol* 2016; 43: 288–93.

Significant improvement in PPP patients treated topically with the vitamin D analog 22-oxacalcitriol twice daily for 8 weeks compared with placebo.

Interleukin-17 receptor A blockade with brodalumab in palmoplantar pustular psoriasis: report on four cases. Pinter A, Wilsmann-Theis D, Peitsch WK, et al. *J Dermatol* 2019; 46: 426–30.

Three patients treated with brodalumab did not respond to treatment and one had a partial response but discontinued therapy due to adverse effects.

Successful treatment of palmoplantar pustulosis with rheumatoid arthritis, with tofacitinib: impact of this JAK inhibitor on T-cell differentiation. Koga T, Sato T, Umeda M, et al. *Clin Immunol* 2016; 173: 147–8.

A rheumatoid arthritis patient with adalimumab-induced PPP had lesion improvement with tofacitinib.

Panniculitis

Zunaira Naeem, Kiana Malta, Carrie Ann R. Cusack



Panniculitis is a term describing the inflammatory diseases of subcutaneous fat. Embryologically, the subcutaneous fat derives from mesenchymal cells, which differentiate into adipocytes, or fat cells. A collection of adipocytes is termed a *microlobule*, and groups of microlobules make up individual lobules in the subcutaneous fat layer of the skin. Lobules are separated from each other by fibrous septae, which contain the main arteries and veins that nourish fatty tissue. Knowledge of the basic subcutaneous architecture allows for classification of the different types of panniculitides, which relies on identifying inflammation predominantly in lobules or fibrous septae. Using this classification, we can better separate the individual disease processes.

Erythema nodosum, the characteristic septal panniculitis, is the most common panniculitis. Most other panniculitides are predominantly lobular. However, some rarer panniculitides have predominantly septal inflammation, such as subacute nodular migratory panniculitis, panniculitis of morphea/scleroderma, and α 1-antitrypsin deficiency panniculitis. Within the lobular panniculitides, a further division can be made based on the presence of vasculitis.

The main lobular panniculitis with vasculitis is erythema induratum, or more aptly termed, *nodular vasculitis*. Rarer vasculitic panniculitides occur in the setting of leprosy with erythema nodosum leprosum and Lucio phenomenon.

The remaining lobular panniculitides are not associated with vasculitis but often associated with systemic disease. Subtypes include lupus panniculitis, pancreatic panniculitis, cytophagic histiocytic panniculitis, panniculitis of dermatomyositis,

infectious panniculitis, sclerosing panniculitis/lipodermatosclerosis, oxalosis, sclerema neonatorum, and subcutaneous fat necrosis of the newborn.

Previously the term *Weber-Christian disease (WCD)* encompassed lobular panniculitides without vasculitis with non-specific systemic features. This diagnosis of exclusion has since fallen out of favor, as most cases classified as WCD have been reclassified into newer and more specific diseases. Therefore, this terminology will not be used.

MANAGEMENT STRATEGY

A skin biopsy is paramount in evaluating panniculitides. It is mandatory the biopsy includes a substantial portion of the subcutaneous fat. A punch biopsy alone is insufficient. Although a double punch biopsy technique is better, the best approach to sample subcutaneous tissue is an excisional biopsy, extending through the subcutis, or a narrow incisional biopsy including a significant amount of fatty tissue. If an infectious cause is suspected, a portion of this biopsy should be sent for Gram staining along with culture for bacteria, mycobacteria, and fungi. If a mycobacterial infection is considered, the specimen should be grown at 24°, 30°, 37°, and 42°C.

Lupus panniculitis, *lupus profundus*, comprises a small portion of cutaneous lupus erythematosus (CLE), only 2%–3%. Often, it is the first sign of CLE. Mainly associated with discoid lupus erythematosus (DLE), it occurs in more than one-third of cases of DLE. Lesions of DLE often are present in the skin overlying the lesions of lupus profundus (see figure). Lupus panniculitis occurs in 10%–15% of patients with systemic lupus erythematosus (SLE), having a chronic course with few systemic manifestations, usually arthralgias. Lesional distribution aids in diagnosis, as lesions are typically located on the face, trunk, and proximal extremities, in contrast to erythema nodosum. Laboratory studies should include ANA, dsDNA, ssDNA, SSA, SSB, complement levels, complete blood count (CBC), and a chemistry panel. Biopsy shows a predominantly lobular infiltrate of T lymphocytes and macrophages. Direct immunofluorescence (DIF) should be performed in cases where the histopathology is non-specific. Linear deposition of C3 and immunoglobulin M (IgM) is often present along the dermoepidermal junction in the overlying skin. First-line therapy for lupus profundus consists of systemic *antimalarial agents* and sunscreen. Adding a second antimalarial agent can benefit patients resistant to one agent. *Systemic corticosteroids* can be used first line; however, they are usually effective only in the early phases of disease.

Nodular vasculitis includes both tuberculous and non-tuberculous causes. The tuberculous form is known as *erythema induratum (of Bazin)*. Non-tuberculous etiologies include other infectious agents, such as *Nocardia* or hepatitis C virus, and medications such as propylthiouracil. The non-tuberculous form, *erythema induratum of Whitfield*, presents as painful, erythematous nodules on the posterior legs of middle-aged women. Mycobacterial culture and polymerase chain reaction (PCR) of mycobacterial DNA should be used for diagnosis. Purified protein derivative and QuantiFERON-TB Gold test help confirm the diagnosis caused by tuberculosis. Histopathologically, there is a lobular panniculitis with mixed inflammation of lymphocytes and neutrophils. The key is identifying vasculitis, as the majority of cases show inflammation of either arteries or veins. Treatment includes *multidrug antituberculous* agents in cases caused by tuberculosis, and other antibiotics in cases of other infectious etiologies. Effective therapies include *potassium iodide*, *colchicine*, and *corticosteroids*.

Pancreatic panniculitis occurs in many different pancreatic disorders causing tissue necrosis, including acute or chronic pancreatitis, pancreatic carcinoma (mostly acinar cell type), pancreas divisum, and pancreatic pseudocysts. It occurs in 2%–3% of all cases of pancreatic diseases. The presence of panniculitis may precede the detection of pancreatic disease and warrants an investigation. It may be a harbinger of metastasis in cases of pancreatic carcinoma. Lesions consist of subcutaneous nodules, usually on the ankles and knees, but can occur in any location. Nodules may or may not be painful, but most of the lesions ulcerate, discharging an oily brown substance. Histopathology shows fat necrosis, and formation of ‘ghost cells’ is classic. Amylase and lipase, elevated in pancreatic panniculitis, should be ordered along with a CBC, as eosinophilia may be present in 60% of cases. Magnetic resonance imaging (MRI) can identify a pancreatic malignancy. Treatment involves addressing the underlying pancreatic inflammation. Octreotide has also been helpful.

Cytophagic histiocytic panniculitis (CHP) is defined based on the presence of hemophagocytosis on histopathology with the characteristic ‘bean-bag cells’ – macrophages that engulf lymphocytes, neutrophils, and erythrocytes. The disorder occurs in immunocompromised patients, often triggered by a herpesvirus infection; however, lymphoma may be an underlying cause. The main types are Epstein–Barr virus–associated extranodal NK/T-cell lymphoma and primary cutaneous gamma/delta T-cell lymphoma. Clinically, painful subcutaneous nodules are present. Patients may have a prolonged clinical course with fever, hepatosplenomegaly, and pancytopenia secondary to hemophagocytosis of the bone marrow. Many cases of CHP are now being classified on a spectrum with subcutaneous panniculitis–like T-cell lymphoma (SPTCL) as the two diseases share many clinical and histopathologic characteristics. Treatment of CHP consists of treating any underlying malignancy, possibly with bone marrow transplantation. In cases where lymphoma has not been identified, ciclosporin has been effective.

α_1 -Antitrypsin deficiency panniculitis occurs in patients with a severe deficiency of this protease inhibitor enzyme. Many different alleles of the gene encode this protein, with the most common being the M allele. The most common phenotype for the protease inhibitor (Pi) is PiMM. Patients with the S or Z allele may exhibit a mild deficiency in the enzyme. Patients with the phenotype PiZZ have the most severe enzyme deficiency, and typically these patients manifest the panniculitis. Inflammation in the subcutaneous fat occurs because lipase, elastase, and other enzymes are not neutralized, causing painful, often purpuric, nodules that ulcerate and drain. Histopathologically, there is focal necrosis of the fat lobules with a predominantly neutrophilic infiltrate in the septae. An elastin stain demonstrates reduced elastic tissue, and gene phenotyping can reveal an enzyme mutation. The most effective treatment is enzyme replacement through intravenous injections. Other treatments include dapsone, colchicine, and liver transplantation.

Panniculitis can also occur in infants as sclerema neonatorum and subcutaneous fat necrosis of the newborn. Both are characterized histologically by needle-shaped clefts within lipocytes. In sclerema neonatorum, an extremely rare condition, the skin becomes hardened on the buttocks or thighs and rapidly spreads in the first few days of life, causing immobility and then death. Treatment for this condition is disappointing, involving supportive care, treating any underlying condition, and exchange transfusions. However, the prognosis for subcutaneous fat necrosis of the newborn is good. Seen in full-term infants in contrast to premature newborns in sclerema neonatorum, this condition consists of localized, indurated plaques involving the trunk that appear

during the first few weeks of life. Most lesions resolve spontaneously with supportive treatment. Hypercalcemia may occur, requiring serial monitoring of calcium levels for at least 4 months after resolution. Treatment of hypercalcemia may be required.

Lipodermatosclerosis, or sclerosing panniculitis, usually develops in patients with chronic venous insufficiency. It is classically located on the medial lower legs in middle-aged women, described as looking like an ‘inverted champagne bottle.’ Histologically, there are ischemia and necrosis of the central fat lobule, leading to characteristic lipomembranous changes. Treatment involves correcting the venous insufficiency with compression stockings and leg elevation. Stanazolol and pentoxifylline have also been helpful.

Panniculitis can also occur in the setting of other connective tissue diseases such as dermatomyositis and morphea/scleroderma. In morphea, a septal panniculitis with a plasma-lymphocytic cell infiltrate, indurated plaques appear on the trunk and extremities. In dermatomyositis, the panniculitis is more lobular, and the inflammation is primarily lymphocytic. Clinically, there are tender, indurated plaques that may ulcerate, healing with atrophy. Treatment of both conditions involves treating the underlying connective tissue disease.

The physical forms of panniculitis, such as those resulting from cold exposure, foreign body, or factitious causes, usually resolve by removal of the offending trigger or surgical removal of the foreign body. This is similar to panniculitis caused by silicone or paraffin that has been used for cosmetic purposes. Other forms of panniculitis are associated with chronic renal failure, mainly calciphylaxis and oxalosis. Calciphylaxis can cause large areas of necrosis. Treatment involves parathyroidectomy, sodium thiosulfate, binding agents, or renal transplantation. Oxalosis is a crystalline deposit panniculitis, with calcium oxalate crystals often deposited on the palmar fingers. Treatment is renal transplantation.

Finally, panniculitis may be drug induced. Thirty cases of panniculitis are attributed to vemurafenib, used in the treatment of unresectable or metastatic melanoma harboring the BRAF-V600E mutation. Lesions are multiple, located on the lower limbs, and often of the lobular type. Withdrawal of the drug can result in resolution.

Specific Investigations

- Skin biopsy for routine microscopy (most important)
- Skin biopsy for culture and sensitivity (routine, mycobacterial, fungal)
- Skin biopsy for PCR
- Skin biopsy for immunoperoxidase and gene rearrangement studies
- ANA and other rheumatologic serologic tests
- Serum α_1 -antitrypsin levels
- Serum lipase and amylase
- Abdominal MRI
- CBC with differential
- Chemistry panel

LUPUS PANNICULITIS

First-Line Therapies

- Antimalarials
- Systemic corticosteroids

E
E

Connective tissue panniculitis: lupus panniculitis, dermatomyositis, morphea/scleroderma. Hansen CB, Callen JP. *Dermatol Ther* 2010; 23: 341–9.

A review article that touts oral antimalarials and sunscreen as first-line treatment for lupus profundus. Hydroxychloroquine is recommended at 200 mg twice a day with a maximum dose of 6.5 mg/kg/day. Onset of action is around 4–8 weeks but requires 6 months for optimal benefit. Chloroquine is also recommended at 250–500 mg/day but has a higher risk of ophthalmologic toxicity.

Connective tissue panniculitis. Winkelmann RK, Padilha-Goncalves A. *Arch Dermatol* 1980; 116: 291–4.

Case report of a patient in remission with hydroxychloroquine 200 mg twice daily and systemic corticosteroids. A second patient on hydroxychloroquine was cleared after failing to respond to non-steroidal antiinflammatory drugs (NSAIDs), potassium iodide, and corticosteroids.

Lupus panniculitis as an initial manifestation of systemic lupus erythematosus. Patel RM, Marfatia YS. *Indian J Dermatol* 2010;55(1):99–101.

Case report of a patient diagnosed with SLE by ANA, anti-dsDNA, whose lesions healed completely with systemic corticosteroids, hydroxychloroquine, and topical antibacterial.

Antimalarials for treatment of lupus panniculitis. Fraga J, Garcia-Diez A. *Dermatol Clin* 2008; 26: 453–63.

In this review article regarding lupus panniculitis, antimalarials were described as the classic and first choice treatment. The most commonly used antimalarial was hydroxychloroquine at a dose of 200–400 mg/day, as monotherapy or in combination with quinacrine when monotherapy is ineffective

Second-Line Therapies

• Topical corticosteroids under occlusion	E
• Second antimalarial agent	D
• Methotrexate	E

Lupus erythematosus profundus treated with clobetasol propionate under a hydrocolloid dressing. Yell JA, Burge SM. *Br J Dermatol* 1993; 128: 103.

A single case of a cure with clobetasol under hydrocolloid dressing occlusion, changed weekly. The patient responded after 1 month.

Quinacrine in the treatment of cutaneous lupus erythematosus. Gonzalez-Sixto B, Garcia-Doval I, Oliveira R, et al. *Actas Dermosifiliogr* 2010; 101(1): 54–8.

A case series reporting the benefit of quinacrine for patients with preexisting eye problems. Eight patients with cutaneous lupus received quinacrine in monotherapy or in combination with other antimalarials. Lesions resolved in five and improved in three while one treatment was withdrawn due to exacerbation of psoriasis.

Sustained drug free remission of lupus panniculitis with methotrexate. Vaidya B, Baral R, Nakarmi S. *J Nepal Med Assoc* 2018; 56(214): 963–6.

A 22-year-old female with lupus panniculitis showing negative autoantibody titers responded well to methotrexate with no residual skin atrophy or scarring. The lesions went into drug-free remission in 1 year and did not recur upon 1 year follow-up.

Third-Line Therapies

• Intravenous immunoglobulin (IVIG)	E
• Rituximab	E
• Ciclosporin	E
• Dapsone	E
• Mycophenolate mofetil	E
• Infliximab	E

Intravenous immunoglobulin in lupus panniculitis. Santo JE, Gomes MF, Gomes MJ, et al. *Clin Rev Allergy Immunol* 2010; 38: 307–18.

A 51-year-old Caucasian female developed nodular lesions on the abdomen and limbs, consistent with lupus panniculitis. She was initially treated with hydroxychloroquine but developed transaminitis. After decades of failing different therapies, she was started on intravenous immunoglobulin (IVIG) once monthly for 6 months with complete regression of the subcutaneous nodules. The patient remained in remission with Q3 month dosing.

Rituximab for the treatment of lupus erythematosus panniculitis. Moreno-Suarez F, Pulpillo-Ruiz A. *Dermatol Ther* 2013; 26: 415–8.

Two patients with lupus profundus, refractory to several therapies, demonstrated brisk improvement after infusion of rituximab at a dosage of 375 mg/m²/week. Painful lesions resolved after the first infusion, and no further lesions appeared.

A case of 'refractory' lupus erythematosus profundus responsive to rituximab. McArdle A, Baker JF. *Clin Rheumatol* 2009; 28: 745–6.

A 22-year-old African American female with painful nodules on the buttocks, consistent with lupus panniculitis. The patient started prednisolone 1 mg/kg and hydroxychloroquine but continued to worsen and could not tolerate mycophenolate mofetil. Rituximab, an anti-CD20 monoclonal antibody, was then administered 1000 mg 2 weeks apart. Over a 1-month period, the patient had complete resolution.

The dynamism of cutaneous lupus erythematosus: mild discoid lupus erythematosus evolving into SLE and SCLE and treatment-resistant lupus panniculitis. Wozniacka A, Salamon M, Lesiak A, et al. *Clin Rheumatol* 2007; 26: 1176–9.

A 47-year-old woman with biopsy-proven lupus panniculitis responded to ciclosporin at a dose of 4 mg/kg/day in addition to methylprednisolone. The patient had previously failed antimalarials, systemic steroids, azathioprine, cyclophosphamide, methotrexate, and pulse doses of methylprednisolone.

Lupus erythematosus profundus successfully treated with dapsone: review of the literature. Ujiie H, Shimizu T, Ito M, et al. *Arch Dermatol* 2006; 142: 399–401.

A 56-year-old woman with ulcerated, biopsy-proven lupus profundus responded to dapsone at a dose of 75 mg/day after 6 weeks.

Intractable ulceration in a patient with erythematosus profundus successfully treated with cyclosporine. Ishiguro N, Iwasaki T, Kawashima M, et al. *Int J Dermatol* 2012; 51: 1131–44.

A case report of a 23-year-old female with skin lesions diagnosed as lupus erythematosus profundus who was treated with prednisolone and ciclosporin with no further ulceration.

Mycophenolate mofetil and hydroxychloroquine: an effective treatment for recalcitrant cutaneous lupus erythematosus. Sadlier M, Kirby B, Lally A. *J Am Acad Dermatol* 2012; 66: 160–1.

This study presents three patients with antimalarial-resistant CLE who responded to combination treatment of mycophenolate mofetil and hydroxychloroquine. Patients had a mean clinical response time of 5.6 weeks on a maximum dose of 1500 mg/day.

Infliximab for treatment of lupus erythematosus profundus. Gunther C, Aringer M, Lochno M, et al. *Acta Derm Venereol* 2012; 92: 401–3.

A 36-year-old female was diagnosed with severe lupus erythematosus profundus. Prior treatment with antimalarials, methotrexate, and IVIG were unsuccessful. Patient was unable to tolerate rituximab, cyclophosphamide, and mycophenolate mofetil. She was initiated on infliximab and showed near complete epithelialization of the lesions in 18 months.

Fourth-Line Therapy

- Thalidomide

D

Efficacy and tolerance profile of thalidomide in cutaneous lupus erythematosus. Chasset F, Tounsi T, Cebon E, et al. *JAAD* 2018; 78(2): 342–50.

A meta-analysis of studies between 1965 and 2017, showing 548 patients of 21 studies had an overall response of 90% to thalidomide. There was a 24% adverse rate indicating thalidomide should be restricted to patients with severely refractory lupus erythematosus.

NODULAR VASCULITIS

First-Line Therapies

- Potassium iodide
- Treat underlying tuberculosis

D

B

Erythema induratum of Bazin. Cho KH, Lee DY, Kim CW. *Int J Dermatol* 1996; 35: 802–8.

A retrospective study of 32 patients with erythema induratum of Bazin. All improved with triple antituberculous therapy, but four relapsed and subsequently cleared.

Supersaturated potassium iodide (SSKI) for treatment of erythema nodosum. Sterling JB, Heyman WR. *J Am Acad Dermatol* 2000; 43: 691–7.

This review article reported that supersaturated potassium iodide solution (SSKI) is among the first-line therapies for treatment of erythema nodosum. SSKI can be used in the form of drops mixed in water or juice 2–10 drops (1 drop = 0.03 mL = 30 mg) TID.

Use of QuantiFERON-TB Gold to determine aetiology of idiopathic erythema induratum. Brandon A, Mufti A, Sibbald GR. *JCMS Case Reports* 2018; 6: 1–3.

A 73-year-old male diagnosed with idiopathic erythema induratum, previously treated with isoniazid for 9 months with no improvement. After a positive QuantiFERON-TB Gold test, the patient was treated successfully with ethambutol 1.6 g for 1

month; pyrazinamide 2 g for 2 months; and isoniazid 300 mg, vitamin B6 25 mg, and rifampin 600 mg for 6 months.

Successful treatment of erythema induratum with topical application of antituberculous drugs. Mei X, Zhai J. *Medicine* 2017; 96(49): e9010.

A 73-year-old woman diagnosed with erythema induratum presented with painful ulcerations to lower extremities. Topical anti-TB treatment was initiated due to severe side effects from systemic therapy. Patient showed improvement in lesions after 6 months of applying compounded 3.75% isoniazid cream twice daily.

Second-Line Therapies

- NSAIDs
- Antimalarials
- Colchicine
- Methotrexate

E

E

E

E

Neutrophilic vascular reactions. Jorizzo JL, Solomon AR, Zanolli MD, et al. *J Am Acad Dermatol* 1988; 19: 983–1005.

A review article in which nodular vasculitis is one of the causes of necrotizing vasculitis. NSAIDs may benefit serum sickness-like features but do not help cutaneous lesions.

Chloroquine-induced remission of nodular panniculitis present for 15 years. Shelley WB. *J Am Acad Dermatol* 1981; 5: 168–70.

One patient with nodular panniculitis responded within 1 month to chloroquine 250 mg/day after failing to respond to corticosteroids, NSAIDs, and tetracycline.

Cutaneous necrotizing vasculitis. Lotti T, Comacchi C, Gherstich I. *Int J Dermatol* 1996; 35: 457–74.

By inhibiting neutrophil chemotaxis, oral colchicine in doses of 0.6 mg twice daily may be helpful in chronic forms of the disease.

Treatment of nodular vasculitis with colchicine. Wee E, Kelly R. *Australasian Journal of Dermatology* 2017; 58: 79–82.

A case report of three patients with nodular vasculitis previously unsuccessful with anti-TB therapy, steroid sparing agents, and prednisolone began successful progress with added colchicine 500 mg BID.

Methotrexate in treatment of recalcitrant nodular vasculitis. Parajuli S, Dhital K. *J Nepal Med Assoc* 2015; 53(200): 298–300.

Case study of a 23-year-old male previously treated with anti-TB treatment. This case report highlights the efficacy of methotrexate in the treatment of recalcitrant nodular vasculitis.

Third-Line Therapy

- Mycophenolate mofetil

E

Case reports: nodular vasculitis responsive to mycophenolate mofetil. Taverna JA, Radfar A, Pentland A, et al. *J Drugs Dermatol* 2006; 5: 992–3.

A 70-year-old woman was treated with 1 g of mycophenolate mofetil twice daily. She slowly responded over a 1-year period.

PANCREATIC PANNICULITIS

First-Line Therapies

• Treat underlying pancreatic condition	E
• Resection of metastases of pancreatic cancer	E
• FOLFIRINOX chemotherapy	E

Resolution of panniculitis after placement of pancreatic duct stent in chronic pancreatitis. Lambiase P. *Am J Gastroenterol* 1996; 91: 1835–7.

One patient with pancreatitis secondary to alcohol presented with chest pain and tender skin nodules on the shins. A skin biopsy showed panniculitis, and he was diagnosed with pancreatitis. A stent was placed to correct a stricture in the pancreatic duct, leading to resolution of the symptoms and the skin lesions within 1 month.

Panniculitis caused by acinous pancreatic carcinoma. Heykants B, Anseeuw M, Degreef H. *Dermatology* 1999; 198: 182–3.

One patient with skin nodules was found to have acinar pancreatic carcinoma upon surgical resection. Initially unresponsive to high-dose corticosteroids and methotrexate, the skin lesions resolved slowly after resection. Subsequently, metastases were found in the right liver and the patient failed to respond.

Resolution of pancreatic panniculitis following metastasectomy. Banfill KE, Oliphant TJ, Prasad KR. *Clin Exp Dermatol* 2012; 37: 440–1.

A 69-year-old man presented with a 6-month history of painful skin lesions. Three months after developing the skin lesions, a computed tomography (CT) scan revealed a large necrotic mass in the liver consistent with a metastasis. The patient underwent resection of a solitary liver metastasis, which resulted in complete resolution of his panniculitis.

FOLFIRINOX chemotherapy for treatment of pancreatic acinar cell carcinoma and panniculitis. Callata-Carhuapoma HR, Pato Cour E, Garcia-Paredes B, et al. *Pancreatol* 2015; 15: 440–4.

A 36-year-old female diagnosed with pancreatic acinar cell carcinoma and associated panniculitis was treated with FOLFIRINOX regimen (FOL: folinic acid (leucovorin), F: fluorouracil (5-FU), IRIN: irinotecan, OX: oxaliplatin). Disease stabilization and clinical benefit were noted with initiation of chemotherapy.

Second-Line Therapies

• Octreotide	E
• Plasmapheresis	E

Liquefying panniculitis associated with acinous carcinoma of the pancreas responding to octreotide. Hudson-Peacock MJ, Regnard CF, Farr PM. *J R Soc Med* 1994; 87: 361–2.

One patient presented with increasing numbers of painful leg nodules secondary to poorly differentiated adenocarcinoma. She failed to respond to prednisolone, but octreotide 50 mcg twice daily subcutaneously halted progression of the skin nodules. Despite therapy, the patient died 3 weeks later.

Plasmapheresis for treatment of panniculitis associated with pancreatitis. Francombe J, Kingsnorth AN, Tunn E. *Br J Rheumatol* 1995; 34: 680–3.

A 41-year-old man with a history of recurrent acute pancreatitis associated with alcohol abuse developed panniculitis. He was treated with plasmapheresis with resolution of the lesions.

CYTOPHAGIC HISTIOCYTIC PANNICULITIS

First-Line Therapies

• Treat underlying T-cell lymphoma (chemotherapy)	E
• Prednisone	E
• Cyclosporin	E

Cytophagic histiocytic panniculitis and subcutaneous panniculitis-like T-cell lymphoma: report of 7 cases. Marzano AV, Berti E, Paulli M, et al. *Arch Dermatol* 2000; 136: 889–96.

A report of seven cases of CHP. Five patients had subcutaneous T-cell lymphoma and died after failing to respond to various chemotherapeutic agents. One patient improved with prednisone for 13 months, and the other living patient improved with systemic corticosteroids, cyclophosphamide, and dapsone for 36 years.

Successful treatment of cytophagic histiocytic panniculitis with modified CHOP-E: cyclophosphamide, Adriamycin, vincristine, prednisone, and etoposide. Matsue K, Itoh M, Tsukuda K, et al. *Am J Clin Oncol* 1994; 17: 470–4.

One patient with CHP received eight courses of modified CHOP-E every 3 weeks and obtained a remission that has lasted 2 years.

Cytophagic histiocytic panniculitis – a syndrome associated with benign and malignant panniculitis: case comparison and review of the literature. Craig AJ, Cualing H, Thomas G, et al. *J Am Acad Dermatol* 1998; 39: 721–36.

Case report of two patients with CHP. One patient responded to prednisone plus cyclosporin 15 mg/kg/day. The other patient died during treatment with chemotherapy for T-cell lymphoma.

Subcutaneous panniculitic T-cell lymphoma in children: response to combination therapy with cyclosporine and chemotherapy. Shani-Adir A, Lucky AW, Prendiville J, et al. *J Am Acad Dermatol* 2004; 50: S18–22.

A case report of two adolescents with CHP. Both responded symptomatically to cyclosporin, and complete remission was obtained in one with chemotherapy.

Combination therapy for treatment of cytophagic histiocytic panniculitis. Hasegawa H, Mizoguchi F, Kohsaka H, et al. *Lupus* 2013; 22: 316–9.

A 37-year-old female presented with fever, subcutaneous indurations, anemia, thrombocytopenia, and hyperferritinemia. She was diagnosed with SLE and CHP. She was treated with high-dose glucocorticoids and cyclosporin A. Remission of SLE and CHP was achieved with this regimen.

Cytophagic histiocytic panniculitis in children treated with cyclosporine A. Bader-Meunier B, Fraitag S, Janssen C, et al. *Pediatrics* 2013; 132: e545–9.

This article reports two cases, a 6-month-old boy and a 16-month-old girl who developed multiple infiltrating skin

lesions after a viral illness. They were diagnosed with CHP. Ciclosporin A treatment resulted in complete remission of the disease manifestations in both patients.

Second-Line Therapies

• Tacrolimus	E
• Bone marrow transplantation	E
• Potassium iodide	E
• Dapsone	E
• Cyclophosphamide	E
• Irradiation	E
• Anakinra	E

Successful treatment of cyclosporine-A-resistant cytophagic histiocytic panniculitis with tacrolimus. Miyabe Y, Murata Y, Baba Y, et al. *Mod Rheumatol* 2011; 21: 553–6.

A 34-year-old female with CHP initially failed treatment with high-dose prednisolone with ciclosporin. After changing ciclosporin to tacrolimus, the CHP responded.

Effective high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation in a patient with the aggressive form of cytophagic histiocytic panniculitis. Koizumi K, Sawada K, Nishio M, et al. *Bone Marrow Transplant* 1997; 20: 171–3.

One patient with CHP was treated with CHOP-E and GM-CSF and achieved remission. He was subsequently treated with bone marrow transplant and remained disease free for 1 year.

Cytophagic histiocytic panniculitis is not always fatal. White JW Jr, Winkelmann RK. *J Cutan Pathol* 1989; 16: 137–44.

One patient with CHP was treated with potassium iodide and achieved remission for 15 years.

Successful treatment of a patient with subcutaneous panniculitis-like T-cell lymphoma with high-dose chemotherapy and total body irradiation. Mukai HY, Okoshi Y, Shimizu S, et al. *Eur J Haematol* 2003; 70: 413–6.

One patient with CHP and T-cell lymphoma achieved remission after three courses of CHOP followed by total body irradiation and autologous stem cell transplant.

Interleukin 1 receptor antagonist to treat cytophagic histiocytic panniculitis with secondary hemophagocytic lymphohistiocytosis. Behrens EM, Kreiger PA, Cherian S, et al. *J Rheumatol* 2006; 33: 2081–4.

A 14-year-old girl with CHP who failed ciclosporin and etoposide responded to methylprednisolone and anakinra.

α_1 -ANTITRYPSIN DEFICIENCY PANNICULITIS

First-Line Therapies

• Doxycycline	E
• Dapsone	D
• α_1 -Antitrypsin concentrate	E
• Liver transplant	E

Clinical and pathologic correlations in 96 patients with panniculitis including 15 patients with deficient levels of

α_1 -antitrypsin. Smith KC, Su Pittelkow MR, Winkelmann RK. *J Am Acad Dermatol* 1989; 21: 1192–6.

Fifteen patients had α_1 -antitrypsin (A1AT) panniculitis. Out of six treated with dapsone, five responded.

Unusual acute sequelae of α_1 -antitrypsin deficiency: a myriad of symptoms with one common cure. Franciosi AN, McCarthy C, Carroll TP, et al. *Chest* 2015; 148: 136–8.

A single case of biopsy-proven A1AT panniculitis that cleared after one dose of IV A1AT at a dose of 120 mg/kg.

α_1 -Antitrypsin deficiency-associated panniculitis: resolution with intravenous alpha 1-antitrypsin administration and liver transplantation. O’Riordan K, Blei A, Rao MS, et al. *Transplantation* 1997; 63: 480–2.

Two patients with homozygous deficiency had panniculitis. One received cure with liver transplant, whereas the other received intravenous A1AT and was clear while on this medicine.

Severe panniculitis caused by homozygous ZZ α_1 -antitrypsin deficiency treated successfully with human purified enzyme (Prolastin). Chowdhury MM, Williams EJ, Morris JS, et al. *Br J Dermatol* 2002; 147: 1258–61.

Life-threatening panniculitis and skin necrosis was cleared with Prolastin and prednisolone. The female patient was put on a dose of 100 mg/kg every 6 days.

Suppurative panniculitis associated with alpha 1-antitrypsin deficiency (PiSZ phenotype) treated with doxycycline. Chng WJ, Henderson CA. *Br J Dermatol* 2001; 144: 1282–3.

A 16-year-old college student was diagnosed with suppurative panniculitis due to α_1 -antitrypsin deficiency after developing painful lesions on the feet and shins. He did not tolerate dapsone. He was then treated with doxycycline 200 mg daily with complete response.

Efficacy of alpha1-antitrypsin augmentation therapy in conditions other than pulmonary emphysema. Blanco I, Lara B, de Serres F, Orphanet J Rare Dis 2011; 6: 14.

In this review article, A1AT augmentation therapy was associated with complete response for A1AT deficiency-associated panniculitis when conventional therapies had failed. A1AT infusions for panniculitis are dosed at 60 mg/kg, a few times weekly.

Second-Line Therapies

• Plasmapheresis	E
• Cyclophosphamide	E
• Colchicine	E
• Prednisone	E

Cyclophosphamide therapy for Weber–Christian disease associated with α_1 -antitrypsin deficiency. Strunk RW, Scheld WM. *South Med J* 1986; 79: 1425–7.

One patient with A1AT-deficiency panniculitis failed to respond to prednisone and heparin. Cyclophosphamide was added with good response.

Necrotic panniculitis with alpha-1 antitrypsin deficiency. Viraben R, Massip P, Dicostanzo B, et al. *J Am Acad Dermatol* 1986; 14: 684–7.

A patient with A1AT-deficiency panniculitis failed to respond to prednisolone, lincomycin, colchicine, and cyclophosphamide.

Rapid improvement occurred after plasma exchange transfusions once daily for 8 weeks.

Familial occurrence of alpha 1-antitrypsin deficiency and Weber–Christian disease. Breit SN, Clark P, Robinson JP, et al. Arch Dermatol 1983; 119: 198–202.

A report of two cases of A1AT-deficiency panniculitis. One patient responded once cyclophosphamide was added to the initial treatment with dexamethasone. The other received colchicine and dicloxacillin, inducing resolution.

Papular urticaria

Aakaash Varma, Hee J. Kim, Jacob O. Levitt



Papular urticaria is a common disease characterized by chronic or recurrent eruptions of 3- to 10-mm pruritic papules, wheals, vesicles, or bullae with central pallor caused by hypersensitivity to the bites of arthropods. Not all individuals who are bitten by an offending arthropod develop a reaction. However, when a bite results in a pruritic papular eruption more persistent than typical urticaria, such dermatologic manifestation is described as papular urticaria. These papules characteristically present as clusters on the extensor surfaces of arms and legs; however, location is largely dependent on the offending arthropod. In the case of bed bugs, lesions classically appear in a linear array of three bites, cutely termed 'breakfast, lunch, and dinner.' Eruptions are less often found on the face, neck, trunk, buttocks, or thighs and typically spare the genital, perianal, and axillary regions. Individual lesions may last for 2–10 days and rarely longer. Intense pruritus associated with papular urticaria often leads to excoriations, lichenification, and secondary infection. Cases have been reported in infants as young as 2 weeks old but are generally seen in children 2–7 years old and in adult males. There is a predilection for the spring and summer months when insect populations peak.

MANAGEMENT STRATEGY

The exact cause of papular urticaria is often unidentified; hence, it is a diagnosis of exclusion. Initial evaluation should include complete blood count with differential, serum IgE, scratch test for dermatographism, environmental evaluation, and even skin biopsy if considering systemic treatment.

Given the lack of evidence-based treatments for papular urticaria, we have suggested a therapeutic ladder that addresses (1) a presumed arthropod assault; (2) the pathophysiology of the allergic and inflammatory response; and (3) the severity of the inflammation at presentation.

The most effective treatment for papular urticaria is the *identification and removal of the offending arthropod*. This may require intense investigation by both physician and patient. *Empiric therapy for scabies* should be given because benefits outweigh the risks. This can be achieved with application of permethrin cream 5% or malathion lotion 0.5% once and reapplication 3–7 days later. In the case of suspected bed bugs and fleas, *fumigation of the home* is required using professional services. Fumigation of the home should also be considered in recurrent cases of papular urticaria. Clothes and bedding should be laundered before and after treatment; specifically, they should be placed in a dryer at 60°C for 10 min to dehydrate and kill scabies and bed bugs. In persistent cases, application of diethyl-m-toluamide (DEET) before bed may help. If there are pets in the home, *aggressive flea control* and veterinary evaluation may be necessary. If the exposure is thought to be from the outdoors, prevention can be achieved through *protective clothing and insect repellents*.

While the cause of papular urticaria is being investigated and treated, symptomatic therapy should be implemented immediately for patient comfort. The goal of symptomatic therapy is to reduce and prevent inflammation. The degree of aggressiveness in therapy depends on the degree of inflammation at presentation. For milder cases, *topical steroids* should be prescribed, with choice of class depending on the severity of lesions. For individual refractory or severe lesion, *intralesional triamcinolone* is often helpful. If these are ineffective or if the inflammatory response is severe on initial presentation, proceed to systemic immunosuppression – for example, a 10-day *oral prednisone* taper starting at 1 mg/kg or 1 mg/kg of intramuscular triamcinolone. Systemic corticosteroids will often permanently blunt the inflammatory reaction, provided the antigenic stimulus has been removed. If papular urticaria becomes chronic in the context of two failed courses of systemic steroids and negative pest control investigations, a biopsy and consideration of a broadened differential diagnosis could precede other systemic immunosuppressants, such as *phototherapy*, *ciclosporin*, *methotrexate*, or *biologic agents* (i.e., *dupilumab* and *omalizumab*).

Pruritus control is often achieved with antihistamines. In milder cases, *non-sedating antihistamines* such as loratadine, desloratadine, fexofenadine, cetirizine, or levocetirizine can help alleviate symptoms. Doses above those given on the product labeling may be necessary. With more severe itching, *diphenhydramine* and *hydroxyzine* are favored. In chronic or recurrent cases, T-cell-mediated lesions, in contrast to the histamine-mediated lesions of early papular urticaria, may render antihistamines ineffective. In that case, topical agents, such as *camphor/menthol*, *calamine lotion*, *crotamiton*, *lidocaine*, and *pramoxine* can help.

Careful attention should be paid to any signs of infection secondary to scratching, and appropriate *topical or oral antibiotics* should be used.

Infrequently, cases of papular urticaria persist without the offending arthropod ultimately being identified. Although rare, hospitalizing the patient for a period of 3–7 days, while simultaneously treating for scabies on admission, results in resolution as reexposure to arthropod antigenic stimuli ceases in the hospital environment. In refractory cases, eruptions will continue until the patient is naturally hyposensitized over time. Hyposensitization can take years to develop, and the concept can be especially confusing to those who have no pets in the home or for those where only one family member is affected.

Specific Investigations

- Environmental evaluation
- Complete blood count with differential
- Serum IgE
- Scratch test for dermatographism
- Skin biopsy (if systemic treatment is being given)

First-Line Therapies

- Elimination of arthropod **D**
- Antihistamines **A**
- Topical steroids **D**
- Topical antipruritics (e.g., camphor/menthol, calamine lotion, croton oil, lidocaine, and pramoxine) **E**

Bed bugs (*Cimex lectularius*) tend to live in wallpaper, mattress seams, couches, and headboards but can also be found in luggage, vehicles, and clothing. Importantly, they can live away from a host for up to 1 year after just one blood meal and can be spread via used furniture as well as travelers (clothing, baggage). They feed at night every 4–12 min and typically cause a painless bite of which the host is unaware. In vitro, bed bugs have been found to transmit hepatitis B, but there is no evidence for human transmission. Bed bugs are detected by human inspection, bed bug-sniffing dogs, and carbon dioxide-emitting monitoring systems.

Papular urticaria: a histopathologic study of 30 patients.

Jordaan HE, Schneider JW. *Am J Dermatopathol* 1997; 19: 119–26. More than half of cases reported mild acanthosis, mild spongiosis, exocytosis of lymphocytes, mild subepidermal edema, extravasation of erythrocytes, and a superficial and deep mixed inflammatory cell infiltrate of moderate intensity with interstitial eosinophils. Four subtypes are described: lymphocytic, eosinophilic, neutrophilic, and mixed. The authors conclude that type I hypersensitivity reaction is part of the pathogenesis of papular urticaria based on immunohistochemical evidence.

Differential Th1/Th2 balance in peripheral blood lymphocytes from patients suffering from flea bite-induced papular urticaria.

Cuellar A, Rodríguez A, Rojas F, et al. *Allergol Immunopathol* 2009; 37: 7–10. Compared with age-matched healthy controls, 18 pediatric patients with papular urticaria had a lower frequency of interferon- γ -producing CD4+ T cells and a higher frequency of IL-4-producing CD4+ T cells.

This suggests that dupilumab, a monoclonal antibody against the IL-4 receptor alpha, may be useful in treating patients with refractory papular urticaria. This has not yet been documented in any published studies.

Specific pattern of flea antigen recognition by IgG subclass and IgE during the progression of papular urticaria caused by flea bite.

Cuellar A, Rodríguez A, Halpert E, et al. *Allergol Immunopathol* 2010; 38: 197–202. Among children clinically diagnosed with papular urticaria caused by flea bites, those who had 2–5 years of symptoms responded to flea antigen with higher IgE bands than those who had a shorter or longer duration of symptoms. In addition, healthy controls responded to flea antigen with IgG1 and IgG3 rather than IgE.

Both immediate and delayed-type hypersensitivity reactions are thought to be involved.

This suggests that omalizumab, a monoclonal antibody against IgE, may play a role in the treatment of refractory papular urticaria. This has not been documented in any studies to date.

Papular urticaria in children.

Howard R, Frieden IJ. *Pediatr Dermatol* 1996; 13: 246–9. Definitive treatment is elimination of the arthropod source. Pets must be treated with insecticidal shampoos and be well groomed. Carpets, rugs, and cloth furniture should be thoroughly vacuumed, and the vacuum bag disposed of, as eggs could fall off the pet onto these surfaces. Fumigation of fleas should include outdoor areas that the pet frequents. Veterinarians and professional exterminators should be called upon when necessary.

Dermatologic infestations.

Shmidt E, Levitt J. *Int J Dermatol* 2012; 51: 131–41. Removal and avoidance of the offending arthropod is the best treatment. Preventive measures include use of insect repellents such as DEET and control of parasites infesting indoor pets. Empiric therapy with permethrin cream 5% or malathion lotion 0.5% is recommended. Antiinflammatory therapy with topical steroids and control of pruritus with topical or oral antihistamines are discussed. A topical antibiotic such as mupirocin is recommended for impetiginized lesions.

Zoonoses of dermatologic interest.

Parish LC, Schwartzman RM. *Semin Dermatol* 1993; 12: 57–64. Animal fleas not only infest the pet but also live in the rugs and floors, visiting the pet for blood meals; therefore, the pet should be treated with insecticides, and the house should be fumigated.

Tropical rat mite dermatitis.

Theis J, Lavoipierre MM, LaPerriere R, et al. *Arch Dermatol* 1981; 117: 341–3. Six cases of papular urticaria caused by the tropical rat mite (*Ornithonyssus bacoti*) are presented. Rodents were present in or around the home in most cases.

Effectiveness of bed bug monitors for detecting and trapping bed bugs in apartments.

Wang C, Tsai WT, Cooper R, et al. *J Econ Entomol* 2011; 104: 274–8. Authors compared the effectiveness of three bed bug-monitoring devices containing CO₂ as an attractant. A homemade dry ice trap was most effective, followed by the Cimex Detection Case (CDC3000) and then NightWatch; however, when NightWatch was used on consecutive nights, its efficacy increased. This study also confirmed the efficacy of Interceptor, an attractant-less monitoring system.

Evaluation of four bed bug traps for surveillance of the brown dog tick (*Acari ixodidae*).

Carnohan LP, Kaufman PE, Allan SA, et al. *J Med Entomol* 2015; 52: 260–8. NightWatch and CO₂-baited ClimbUp traps were more effective than other trapping systems in capturing brown dog ticks.

Ability of bed bug-detecting canines to locate live bed bugs and viable bed bug eggs.

Pfiester M, Koehler PG, Pereira RM. *J Econ Entomol* 2008; 101: 1389–96.

In a controlled experiment set-up in hotel rooms, the dogs were able to detect bed bugs with 98% accuracy.

Lethal effects of heat and use of localized heat treatment for control of bed bug infestations. Pereira RM, Koehler PG, Pfister M, et al. *J Econ Entomol* 2009; 102: 1182–8.

Heat treatment of furniture for 2–7 hours at 49 °C using equipment that costs less than \$400 can successfully disinfect furniture.

Efficacy of three different steamers for control of bed bugs (*Cimex lectularius* L). Wang D, Wang C, Wang G, et al. *Pest Manag Sci* 2018; 74: 2030–7.

Both consumer-grade and professional-grade steamers are able to kill bed bugs at all stages of life, including those on mattresses, behind fabric materials, and in cracks.

Gaseous chlorine dioxide as an alternative for bedbug control. Gibbs SG, Lowe JJ, Smith PW, et al. *Infect Control Hosp Epidemiol* 2012; 33: 495–9.

At all concentrations tested (362, 724, and 1086 ppm), chlorine dioxide resulted in 100% mortality of bedbugs 18 hours after the exposure. These concentrations can be safely achieved in a hospital room.

In conjunction with chemical treatment of the home, the following strategies can be used to prevent further infestation: a sealed plastic cover for the mattress; moving the mattress away from the wall; keeping blankets off the floor; petrolatum applied to the legs of the bed; plastic cups with or without water under the legs of the beds; white sheets to make the bed bugs or blood more visible; removing loose wallpaper; and filling in cracks in the floorboards, furniture, walls, and windowsills. To prevent infection while traveling, travelers should examine the bed and area around the bed, avoid using hotel drawers, keep suitcases zipped, and launder clothes with heated drying upon return.

Comparison of cetirizine, ebastine and loratadine in the treatment of immediate mosquito-bite allergy. Karppinen A, Kautiainen H, Petman L, et al. *Allergy* 2002; 57: 534–7.

A double-blind, placebo-controlled, crossover study compared prophylactic administration of daily cetirizine 10 mg, ebastine 10 mg, and loratadine 10 mg in 29 adults with mosquito bites. Cetirizine and ebastine significantly reduced pruritus and the size of wheals. Cetirizine was found to be most effective against pruritus but more sedative than ebastine and loratadine.

Levocetirizine for treatment of immediate and delayed mosquito bite reactions. Karppinen A, Brummer-Korvenkontio H, Petman L, et al. *Acta Derm Venereol* 2006; 86: 329–31.

A double-blind, placebo-controlled, crossover study with levocetirizine 5 mg daily in 28 adults sensitive to mosquito bites. Patients were given the study drug for 4 days and exposed to mosquito bites on day 3. Levocetirizine reduced the size of wheals by 60% and pruritus by 62% compared with placebo.

Papular urticaria. Millikan LE. *Semin Dermatol* 1993; 12: 53–6.

Prevent papular urticaria by using repellents containing DEET if repeated exposure is suspected. Use antipruritics, including menthol, camphor, and pramoxine, for pruritus.

Second-Line Therapies

- Intralesional steroids E
- Oral steroids E
- Insect repellents, e.g., DEET E

Insect bite-induced hypersensitivity and the SCRATCH principles: a new approach to papular urticaria. Hernandez RG, Cohen BA. *Pediatrics* 2006; 118: 189–96.

Authors advocate the use of intralesional steroids in older children and adults to suppress pruritus if more conservative measures fail.

The role of dexamethasone in papular urticaria. El-Nasr NS. *J Egypt Med Assoc* 1961; 44: 340–1.

Dexamethasone 0.25 mg PO twice or three times daily for 1–2 weeks was used with good results. Pruritus resolved within 48 hours.

Comparative activity of three repellents against bedbugs *Cimex hemipterus* (Fabr). Kumar S, Prakash S, Rao KM. *Indian J Med Res* 1995; 102: 20–3.

N,N-diethyl-meta-toluamide (DEET), diethyl phenyl-acetamide (DEPA), and dimethyl phthalate (DMP) were tested against bedbugs on the shaven skin of rabbits. DEET was superior to the other two repellents at all concentrations tested. At 75% concentration, DEET showed 85% repellency for up to 2 hours and 52% repellency 6 hours after treatment.

Insect repellents: an overview. Brown M, Hebert AA. *J Am Acad Dermatol* 1997; 36: 243–9.

DEET was highly effective at repelling mosquitoes, biting fleas, gnats, chiggers, and ticks. Permethrin works as both an insecticide and a repellent against lice, ticks, fleas, mites, mosquitoes, and black flies.

Third-Line Therapies

- Phototherapy E
- Ciclosporin E
- Hospitalization E
- Biologic therapies (i.e., omalizumab and dupilumab) E

Papular dermatitis in adults: subacute prurigo, American style? Sherertz EF. *J Am Acad Dermatol* 1991; 24: 697–702.

Twelve patients with pruritic papular eruptions were followed, and the majority were refractory to conservative symptomatic management but showed some control with oral steroids, ultraviolet B (UVB), or psoralen and ultraviolet A radiation (PUVA) treatment.

Papular urticaria and transfer of allergy following bone marrow transplantation. Smith SR, Macfarlane AW, Lewis Jones MS. *Clin Exp Dermatol* 1988; 13: 260–2.

A 20-year-old male who underwent allogeneic bone marrow transplant developed papular urticaria as a result of transfer of allergy from the donor. Upon withdrawal of ciclosporin, the patient developed a papular eruption. This suggests a suppressive effect of ciclosporin on papular urticaria.

Anecdotally, the authors have noted an instance of rheumatoid arthritis-associated papular urticaria that resolved with ciclosporin therapy.

Papular urticaria. Rook A, Frain-Bell W. *Arch Dis Child* 1953; 28: 304–10.

Multiple cases of papular urticaria are reported where the eruption cleared when patients were hospitalized. Hospitalization removes the patient from the arthropod source of papular urticaria and allows for sufficient time to rid the home of the arthropods before the patient returns home.

Paracoccidioidomycosis

Wanda S. Robles, Mahreen Ameen



Courtesy of Douglas Altchek, MD

Paracoccidioidomycosis (PCM) is a chronic, progressive granulomatous infection caused by the dimorphic fungus *Paracoccidioides brasiliensis*. It primarily affects the lungs after inhalation of the fungus that resides in soil and plants of endemic regions. PCM is restricted to Latin America, where it is the most prevalent systemic endemic mycosis. It has been reported in nearly all countries from Mexico to Argentina, with exception of the Caribbean Islands and Chile. Eighty percent of cases occur in Brazil, with the highest incidence in the state of São Paulo. This is followed by Venezuela, Colombia, Ecuador, and Argentina. PCM characteristically affects those working in agriculture and in rural areas. Because of the long latency period, the disease may appear many years after a person has left the endemic region. Untreated PCM has one of the highest mortality rates of all the systemic mycoses.

There are two main clinical forms: an acute or subacute form, and a unifocal or multifocal chronic form. The acute form affects young people of both sexes and mainly involves the reticuloendothelial system. This form of infection is often severe and carries a worse prognosis. The chronic form most commonly affects adult males and causes pulmonary and/or mucocutaneous disease. Most cases of pulmonary infection have an indolent course. Only 2% of those infected develop the disseminated form of disease. Dissemination occurs most commonly to the mucosae of the upper airways and upper gastrointestinal tract. Cutaneous and lymph node involvement is common; other organ systems may be involved, such as the adrenal glands (causing Addison syndrome), bones, and central nervous system. Oral lesions affect the gingivae, hard palate, lips, and tongue. Nasal and pharyngeal ulcers can give rise to dysphonia and dysphagia. Ulcerative lesions can be painful and are characterized by a punctate vascular pattern over a granulomatous base. Cutaneous lesions are highly polymorphic, consisting of verrucous and ulcerative papules, plaques, and nodules. Centrifacial localization is typical and usually a result of dissemination of oral lesions. PCM is also characterized by massive and visible cervical and submandibular lymphadenopathy, which may progress to form abscesses with draining sinuses. Other lymph glands may also become enlarged. Primary mucocutaneous infection is rare but may occur

after direct inoculation of the skin and mucous membranes. It can arise from using twigs to clean the teeth, which is practiced in rural Brazil.

Disseminated infection is severe in the immunocompromised, including those coinfecting with HIV. The mortality rate with HIV infection is high, ranging from 30% to 45%. However, the incidence of PCM in patients with AIDS in Latin America is low, and this has been attributed to the widespread use of trimethoprim-sulfamethoxazole (TMP-SMX) as prophylaxis for *Pneumocystis carinii* pneumonia.

MANAGEMENT STRATEGY

P. brasiliensis is highly sensitive to antifungal drugs, and therefore a large therapeutic armamentarium exists to treat PCM. Itraconazole is the drug of choice for the treatment of mild-to-moderate acute and chronic clinical forms of PCM. It is given at a dose of 100–200 mg daily for a mean period of 6 months (range 3–12 months) depending on clinical response. It gives a cure rate of 90% and recurrence rates of 0%–15% have been reported, after a median of 12 months depending on comorbidities such as alcoholism, malnutrition, and AIDS. *Sulfonamides* (sulfadiazine, sulfamethoxypyridazine, sulfadimethoxine, TMP-SMX) were an attractive option in view of their low cost and good tolerance. However, therapy duration is characteristically long (2–3 years) and compliance becomes an issue. Currently, as the efficacy of the TMP-SMX combination (cotrimoxazole [CMX]) has been demonstrated, both azoles and CMX may be used on a course of treatment. New guidance from the Brazilian experts now divides the treatment into two phases: initial and follow-up periods. During the initial treatment period, patients are submitted to a number of evaluations once monthly: clinical, serological, hematologic, biochemical, and radiological, until they achieve clinical cure and normal erythrocyte sedimentation rate. At this point the follow-up or complementary treatment begins and patients are submitted to clinical, serological, and radiological evaluations every 3 months until 1 year after serological cure has been achieved. Parenteral *amphotericin B* (AmB; cumulative dose of 1–2 g based on clinical response) is the drug of choice for severe or refractory infection. The cure rate is only 60% but consideration must be given to the fact that is usually given to the most severely ill patients. The relapse rate with AmB is generally higher than with *itraconazole* occurring in 20%–30% of cases. Long-term maintenance therapy with an azole or sulfonamide is therefore required. In case of central nervous system (CNS) PCM, sulfadiazine appears to be equally effective as AmB. It is recommended that drugs via the oral route should be avoided in patients with abdominal lymphadenopathy. *Ketoconazole* (KTC; 200–400 mg daily) is also highly effective, with 90% of patients responding after 6–12 months of treatment with only a 10% relapse rate. However, adverse effects are common, especially with long-term treatment.

Pharmacologic management of paracoccidioidomycosis. Yasuda MA. Expert Opin Pharmacother 2005; 6: 385–97.

This article emphasizes the long duration of drug therapy required for both the treatment and maintenance of patients with severe infection. It explores the possibility of finding novel therapies among new classes of drugs, drug combinations, or agents capable of modulating the immune response, such as a peptide derived from the 43 kDa *P. brasiliensis* glycoprotein.

Central nervous system paracoccidioidomycosis: an overview. De Almeida SM. Braz J Infect Dis 2005; 9: 126–33.

CNS involvement with paracoccidioidomycosis has been found in 13% of patients with systemic disease. This review article covers the clinical presentation, diagnostic test, and treatment for CNS infection. Sulfas are considered the drugs of choice, with TMP-SMX (160/800 mg three times daily) being mostly used. AmB is only used in cases of resistance or intolerance to sulfonamides. Of the azoles, itraconazole and, particularly, ketoconazole penetrate the blood-brain barrier poorly. Fluconazole, however, has excellent CNS penetration, making it a potentially suitable alternative to the other drug therapies.

Drugs for treating paracoccidioidomycosis. Menezes VM, Soares BG, Fontes CJ. *Cochrane Database Syst Rev* 2006; 19: CD004967.

This is a critical evaluation of the current therapeutic armamentarium for the treatment of paracoccidioidomycosis. On the basis of straight selection criteria, including randomized controlled trials, only a single study could be included for analysis (Shikanai-Yasuda MA et al., 2002) with a brief mention of other studies.

Treatment options for paracoccidioidomycosis and new strategies investigated. Travassos LR, Taborda CP, Colombo AL. *Expert Rev Anti Infect Ther* 2008; 6: 251–62.

This article highlights the significant and unresolved burden of relapses despite the use of long courses of drug therapies, which include TMP-SMX, itraconazole, and AmB. A peptide vaccine aimed at immunotherapy of paracoccidioidomycosis is being studied, and the authors suggest that it could be used as a vaccine to reduce the duration of chemotherapy and the risk of relapse.

Paracoccidioidomycosis. Ramos-E-Silva M, Saraiva Ldo E. *Dermatol Clin* 2008; 26: 257–69.

This review is written with dermatologists in mind, with a focus on the features of mucocutaneous presentation.

Paracoccidioidomycosis due to *Paracoccidioides brasiliensis* S1 plus HIV co-infection. Marquez de Macedo P, Almeida-Paes R, de Abreu Almeida M, et al. *Mem Inst Oswaldo Cruz* 2018; 113(3): 167–72.

A recent review on paracoccidioidomycosis, which highlights the importance of the inclusion of HIV screening diagnostic tests routinely for patients with PCM. Their advice is based on the finding of 17.9% positive results in a cohort of patients diagnosed with PCM. Additionally, these patients were considered to have severe forms of the condition and a high rate of complications requiring combination therapy.

First-Line Therapies

• Itraconazole	B
• Sulfonamides	B
• Amphotericin B	B

Treatment of paracoccidioidomycosis with itraconazole. Naranjo MS, Trujillo M, Munera MI, et al. *J Med Vet Mycol* 1990; 28: 67–76.

Forty-seven patients with mainly the chronic adult form of infection were treated with itraconazole 100 mg daily for a mean treatment period of 6 months (range 3–24 months). There was marked clinical improvement in 43 patients (89%) and complete resolution of disease in only one patient. The mycologic tests (direct microscopy and cultures) became negative during the first month of treatment in 87% of patients, and by the end of

treatment there was a decline in specific antibody titers in 72% of patients. There was no clinical relapse in 15 patients during a 12-month follow-up period.

Randomized trial with itraconazole, ketoconazole and sulfadiazine in paracoccidioidomycosis. Shikanai-Yasuda MA, Bernard G, et al. *Med Mycol* 2002; 40: 411–7.

This study from Brazil included 42 patients with moderately severe paracoccidioidomycosis. They were randomized to receive itraconazole 50–100 mg daily ($n=14$), ketoconazole 200–400 mg daily ($n=14$), or sulfadiazine 150 mg/kg daily ($n=14$) for an induction period of 4–6 months. This was followed by slow-release sulfa (sulfamethoxy-pyridazine) until negative serologic results were obtained. The majority of patients in all arms were reported as cured after 6 months of treatment, and antibody levels reduced significantly by 10 months of treatment for all three drugs.

This study demonstrated that both sulfadiazine and the azoles were equally effective, and the cure rates for the individual drugs were similar to previous studies.

Paracoccidioidomycosis in children: clinical presentation, follow-up and outcome. Pereira RM, Bucarety F, Barison Ede M, et al. *Rev Inst Med Trop Sao Paulo* 2004; 46: 127–31.

This study from Brazil investigated 70 episodes of infection in 63 children under the age of 15 years (range 2–15 years). The juvenile and disseminated form of paracoccidioidomycosis was seen in 70% of episodes, most of them presenting with a febrile lymphoproliferative syndrome. The diagnosis was confirmed by lymph node biopsy (84%), bone biopsy (9%), and skin biopsy (7%). Treatment consisted of either TMP-SMX monotherapy ($n=50$), TMP-SMX combined with AmB ($n=9$), or ketoconazole ($n=5$). Follow-up revealed significant sequential improvement 1 and 6 months later. However, six patients died (9.3%) and four developed sequelae: portal hypertension in three and hypersplenism in one (6.3%). The authors attribute the deaths to the severity of disseminated infection in the context of profound immunosuppression caused by paracoccidioidomycosis as well as malnutrition. A long period of drug treatment, up to 2 years, is required in order to prevent any risk of relapse.

The authors suggest TMP-SMX as first-line therapy in children because of its efficacy, low cost, and easy route of oral administration. It may also be infused intravenously for severe infection. They attributed therapy failure largely to noncompliance.

Paracoccidioidomycosis: epidemiological, clinical, diagnostic and treatment up-dating. Marques SA. *An Bras Dermatol* 2013; 88: 700–11.

A very good review article that outlines the treatment of paracoccidioidomycosis with itraconazole, TMP-SMX, and AmB as first-line interventions.

Paracoccidioidomycosis in Mexico: clinical and epidemiological data from 93 cases (1972–2012). López-Martínez R, Hernández-Hernández F, Méndez-Tovar LJ, et al. *Mycoses* 2014; 57: 525–30.

This very good review article reports itraconazole alone and the combination of itraconazole with TMP-SMX as the most effective treatment.

Amphotericin B lipid complex in the treatment of severe paracoccidioidomycosis: a case series. Peçanha PM, de Souza S, Falqueto A, et al. *Int J Antimicrob Agents*. 2016; 48: 428–30.

First report on AmB lipid complex (ABLC) used in the treatment of paracoccidioidomycosis with a cure rate of 100% in 28 patients.

Therapeutic response in adult patients with nonsevere chronic paracoccidioidomycosis treated with sulfamethoxazole-trimethoprim: a retrospective study. Nery AE, Crepaldi NP, Rossi SBRS, et al. *Am J Trop Med Hyg* 2017; 97(2): 556–62.

This retrospective study highlights PCM as a major public health problem in South America. The Brazilian Consensus on PCM considers itraconazole as the drug of choice for treatment. This study considers the therapeutic value of TMP-SMX in the light of its higher availability in the public health services. The median treatment duration was 21 months. The most common factors associated with therapeutic failure were non-adherence and HIV coinfection.

Paracoccidioidomycosis: current perspectives from Brazil. Poncio Mendes R, de Souza Cavalcante R, Alençar Marques S, et al. *Open Microbiol J* 2017; 11: 224–82.

A very good and comprehensive recent review on paracoccidioidomycosis regarding the clinical spectrum and variability of the condition, diagnostic tools, and differences in serologic responses, probably related to the different species of the *Paracoccidioides* 'complex' in different regions of Brazil and the basis on which they recommend itraconazole as the first choice in the treatment of paracoccidioidomycosis.

Second-Line Therapies

• Ketoconazole	B
• Fluconazole	B
• Voriconazole	B

Treatment of paracoccidioidomycosis with ketoconazole: a three-year experience. Restrepo A, Gómez I, Arango MD, et al. *Am J Med* 1983; 74: 48–52.

Thirty-eight patients with active infection were treated with itraconazole 200 mg daily for 6 months. Treatment was well tolerated. There was complete resolution of infection in 13 patients (34%) and significant improvement in the majority of the rest of the patients.

In a subsequent study 24 of these patients were followed up for a 1- to 2-year period. Relapse was detected in only two patients. There are no recent studies evaluating ketoconazole for PCM, as its use has declined with the advent of newer antifungals.

A pan-American 5-year study of fluconazole therapy for deep mycoses in the immunocompetent host. Pan-American

Study Group. Diaz M, Negroni R, Montero-Gei F, et al. *Clin Infect Dis* 1992; 14 (Suppl 1): S68–76.

Twenty-seven of 28 patients responded to treatment with fluconazole 200–400 mg daily given for at least 6 months. Treatment was well tolerated. However, relapse was noted in one patient within the first year.

This is the only reported study of fluconazole therapy for PCM. A longer period of follow-up is required in order to evaluate drug efficacy.

An open-label comparative pilot study of oral voriconazole and itraconazole for long term treatment of paracoccidioidomycosis. Queiroz-Telles F, Goldani LZ, Schlamm HT, et al. *Clin Infect Dis* 2007; 45: 1462–9.

This multicenter study from Brazil investigated the efficacy, safety, and tolerability of voriconazole for the long-term treatment of acute or chronic paracoccidioidomycosis, with itraconazole as the control treatment. Patients were randomized (at a 2:1 ratio) to receive voriconazole ($n=35$) or itraconazole ($n=18$) for 6–12 months. Voriconazole was given at an initial loading dose of 800 mg on divided doses on day 1, followed by 200 mg twice daily. The dose of itraconazole was 100 mg twice daily. There was a satisfactory response rate in 88.6% of the voriconazole group and 94.4% of the itraconazole group. The response rate among treatment-evaluable patients was 100% for both treatment groups. No relapses were observed after 8 weeks of follow-up. Both drugs were well tolerated, although liver function test values were slightly higher in patients receiving voriconazole, necessitating the withdrawal of voriconazole from two patients.

This study has demonstrated equal efficacy and tolerability of oral voriconazole and itraconazole for the long-term treatment of paracoccidioidomycosis. This study also included a case of CNS paracoccidioidomycosis that responded to treatment. Voriconazole demonstrated good CNS penetration, having been successfully used in the treatment of other mycotic CNS infections. On the basis of these results, the authors suggested that intravenous voriconazole should be evaluated as an alternative to AmB for the initial treatment of severe paracoccidioidomycosis, given the high relapse rate and toxicity associated with AmB therapy.

Isavuconazole treatment of cryptococcosis and dimorphic mycoses. Thompson GR 3rd, Rendon A, Ribeiro Dos Santos R, et al. *Clin Infect Dis* 2016; 63: 356–62.

An open-label, non-randomized, phase III trial to evaluate efficacy and safety of isavuconazole, a novel, broad-spectrum triazole antifungal agent in the management of invasive fungal infections. A group of 38 patients, of whom 10 had paracoccidioidomycosis, received this treatment. The study reports that 63% of the total of patients had an overall successful response.

Parapsoriasis

Koen D. Quint, Maarten H. Vermeer



The use of the description parapsoriasis or *parapsoriasis en plaque*, even as an umbrella term, remains controversial, and debate remains whether the variants described in this chapter are, in fact, precursors of cutaneous T-cell lymphoma (CTCL). This chapter covers small plaque parapsoriasis (SPP), which includes the synonyms chronic superficial scaly dermatitis, persistent superficial dermatitis, digitate dermatosis, xanthoerythroderma perstans and hypopigmented parapsoriasis en plaque, and large plaque parapsoriasis (LPP), which includes the synonyms parakeratosis variegata, retiform parapsoriasis, atrophic parapsoriasis, and poikilodermatous parapsoriasis.

Parapsoriasis is often grouped with other cutaneous lymphocytic disorders (including pityriasis lichenoides et varioliformis acuta and pityriasis lichenoides chronica) and cutaneous lymphomas (including lymphomatoid papulosis and mycosis fungoides), all of which are the subjects of separate chapters.

MANAGEMENT STRATEGY

Although the diagnosis of parapsoriasis is initially considered on clinical grounds, histopathologic examination, including immunohistochemical staining, is essential to exclude CTCL (i.e., early-stage mycosis fungoides or lymphomatoid papulosis). Sometimes T-cell receptor gene rearrangement might help to differentiate between parapsoriasis and CTCL. Monoclonality has been identified in SPP and (more often) in LPP. The presence of a T-cell clone does not appear to predict the risk of progression to CTCL. Regular repeat skin biopsies are recommended if a clinical or histologic progression to CTCL is suspected.

Although topical therapy is appropriate in mild or early cases, the potential for progression to cutaneous lymphoma in patients with parapsoriasis can justify the use of phototherapy in symptomatic or advanced cases.

Furthermore, recent studies suggest an increased risk for vascular events, including venous thromboembolism, stroke, and acute myocardial infarction. Therefore, risk assessment for vascular events is recommended.

Specific Investigations

- The diagnosis is initially suspected on clinical findings
- Histology is non-specific with an acanthotic epidermis, patchy parakeratosis, and a perivascular infiltrate of small lymphocytes, sometimes with single cell epidermotropism
- Immunophenotyping of the lymphocytic infiltrate shows mainly CD4+ CD8- and CD45RO+ T-cells intermingled with a few CD8+ T-cells
- T-cell receptor (TCR) gene rearrangement studies can identify T-cell clones

Hypopigmented parapsoriasis en plaque, a new, overlooked member of the parapsoriasis family: a report of 34 patients and a 7-year experience. El Darouti MA, Fawzy MM, Hegazy RA, et al. J Am Acad Dermatol 2012; 67: 1182–8.

The authors describe a new variant of hypopigmented parapsoriasis that phenotypically showed most features of SPP. Immunohistochemically, the T-cell infiltrate was mostly CD8+, in contrast to the regular parapsoriasis with a CD4+ infiltrate in most cases; 14% developed a hypopigmented mycosis fungoides.

Skin microbiome in small- and large-plaque parapsoriasis. Salava A, Pereira P, Aho V, et al. Acta Derm Venereol 2017; 97: 685–91.

The study described the microbiome in patients with SPP and LPP. No difference in microbiome was observed between the lesional skin microbiome and contralateral healthy skin microbiome. No difference in SPP and LPP could be made although interpersonal variation was demonstrated. Overall, the results suggest that parapsoriasis is not associated with significant alterations in the cutaneous bacterial microbiome.

Clonal T cell receptor gamma-chain gene rearrangement by PCR-based GeneScan analysis in the skin and blood of patients with parapsoriasis and early-stage mycosis fungoides. Klemke CD, Dippel E, Dembinski A, et al. J Pathol 2002; 197: 348–54.

Although the authors of this paper concede that studies have shown T-cell clonality in both skin and peripheral blood, they argue that monoclonality is neither easily demonstrable nor a prerequisite for diagnosis.

The role of immunohistochemical analysis in the diagnosis of parapsoriasis. Bordignon M, Belloni-Fortina A, Pigozzi B, et al. Acta Histochem 2011; 113: 92–5.

Given the lack of clinical and histologic markers of distinction between parapsoriasis and early CTCL, the use of immunohistochemical techniques has been explored to try to establish a more definitive diagnosis. However, these techniques, including CD4/CD8 ratio, expression of T-cell antigens, and expression of proliferation markers, have been found unhelpful in distinguishing between parapsoriasis and early CTCL.

SMALL PLAQUE PARAPSORIASIS

SPP consists of fixed, scaly erythematous plaques less than 5 cm in diameter. They are predominantly asymptomatic but can be mildly pruritic and occur mainly on the trunk and proximal extremities. The lesions sometimes appear to run in fingerlike lines parallel to the ribs (hence the synonym digitate dermatosis). The histology is only supportive for SPP and shows mild acanthosis with focal parakeratosis and small areas of perivascular lymphocytic infiltrate within the papillary dermis. Single cell epidermotropism can be present. Nevertheless, Pautrier microabscesses, a prominent feature of mycosis fungoides, are usually absent. SPP runs a chronic, indolent, and usually benign course.

First-Line Therapies

• Emollients, tar, topical corticosteroids	E
• Psoralen ultraviolet A treatment	C
• Narrowband ultraviolet B	C
• Hydrogen-water bathing	D

Treatments with emollients, topical tar, and topical corticosteroid are widely used, but evidence is anecdotal, and these treatments are therefore unreferenced.

Narrowband UVB phototherapy for small plaque parapsoriasis. Aydoğan K, Karadogan SK, Tunali S, et al. *J Eur Acad Dermatol Venereol* 2006; 20: 573–7.

Forty-five patients were treated with narrowband UVB therapy three to four times weekly. There was a complete response in 33 patients with a mean cumulative dose of 14.3 J/cm² after a mean number of 29 exposures. There was a partial response in 12 of the 45. Relapses occurred in six of the 45 patients within a mean of 7.5 months.

Treatment of small plaque parapsoriasis with narrow-band (311 nm) ultraviolet B: a retrospective study. Herzinger T, Degitz K, Plewig G, et al. *Clin Exp Dermatol* 2005; 30: 379–81.

Sixteen patients had complete remission after a mean number of 33 exposures and a mean total dose of 35.4 J/cm². Relapse occurred after an average of 29 weeks, showing similarity with the study by Aydoğan et al.

Retrospective study of 24 patients with large or small plaque parapsoriasis treated with ultraviolet B therapy. Arai R, Horiguchi Y. *J Dermatol* 2012; 39: 674–6.

A retrospective study of 24 patients given UVB for both SPP and LPP. Five patients resolved with treatment over a median duration of 3.5 years. Eighteen continued with active disease, although this cohort had a median duration of 2 years of treatment. The findings suggest longer treatment is required to cause remission, although the values were not significant. One patient progressed from LPP to CTCL. The study suggests long-term phototherapy is of clinical benefit.

Positive effects of hydrogen-water bathing in patients of psoriasis and parapsoriasis en plaques. Zhu Q, Wu Y, Li Y, et al. *Scientific Reports* 2018; 8: 8051.

In a parallel, controlled trial including six patients with parapsoriasis (besides psoriasis), a complete response was observed in two patients after 8 weeks of treatment and a partial response in 4/6 patients.

Treatment of parapsoriasis and mycosis fungoides: the role of psoralen and long-wave ultraviolet light A (PUVA). Powell FC, Spiegel GT, Muller SA. *Mayo Clin Proc* 1984; 59: 538–46.

Seven patients with SPP had complete clearance with as few as 15 treatments (84 J/cm²) of standard PUVA. Three patients reported recurrence at follow-up (mean of 13 months), and one of these was then successfully treated with topical corticosteroid.

Second-Line Therapy

• Topical nitrogen mustard	C

Topical nitrogen mustard therapy in patients with mycosis fungoides or parapsoriasis. Lindahl LM, Fenger-Gron M, Iversen L. *J Eur Acad Dermatol Venereol* 2013; 27: 163–8.

Seventy-one patients with parapsoriasis (no information on numbers of LPP and SPP) were treated with mechlorethamine hydrochloride between 1991 and 2009. A dose of 20 mg was dissolved in 40 mL water and applied daily to affected skin for a 14-day induction period. Maintenance therapy of two treatments every 4–8 weeks occurred until clear, insufficient response, or side effects developed. The 'overall' response was 90%, with a 'complete' response of 41%. Relapse (no time given) was 62%. The main side effect was contact dermatitis resulting in withdrawal of treatment in 14% of patients.

LARGE PLAQUE PARAPSORIASIS

This is clinically similar to SPP but lesions are larger than 5 cm, irregularly shaped, and often atrophic or poikilodermatous. Lesions typically occur over the lower trunk and thighs.

Specific Investigations

- | |
|--------------------------|
| • Skin biopsy |
| • TCR gene rearrangement |

Like SPP, the diagnosis of LPP is based on clinical observation. The (immuno)histology is compatible with SPP, although some authors suggest that the histopathological features of LPP are moving more toward an early-stage mycosis fungoides.

Progression of LPP to CTCL is reported, with one retrospective study demonstrating a figure of 35%. This same study also reported 10% of patients with SPP progressing to CTCL.

A retrospective study of the probability of the evolution of parapsoriasis en plaques into mycosis fungoides. Väkevä L, Sarna S, Vaalasti A, et al. *Acta Derm Venereol* 2005; 85: 318–23.

A 26-year retrospective analysis of 105 patients with SPP and LPP reported that 10% of patients with SPP and 35% of patients with LPP progressed to histologically confirmed CTCL over a median time of 10 and 6 years, respectively.

Subsequent cancers, mortality and causes of death in patients with mycosis fungoides and parapsoriasis: a Danish nationwide, population-based cohort study. Lindahl LM, Fenger-Gron M, Iversen L. *J Am Acad Dermatol* 2014; 71: 529.

Using the Danish nationwide population-based registry, 368 mycosis fungoides and 582 parapsoriasis patients were compared with the general population for subsequent cancers, mortality, and causes of death. Subsequent cancers were significantly increased in the parapsoriasis group, including non-Hodgkin lymphoma (NHL),

hematologic cancers other than NHL, and non-hematologic cancers, with the highest incidence being in the gastrointestinal (GI) tract. Interestingly, the incidence of these malignancies was significantly higher within the first 5 years of diagnosis. In the mycosis fungoides group the only significantly increased cancer was NHL. Both groups had a significantly increased mortality compared with the general Danish population, with the mycosis fungoides group being more pronounced with the first 5 years of diagnosis.

Risk of venous thromboembolism in patients with mycosis fungoides and parapsoriasis: a Danish nationwide population-based cohort study. Lindahl LM, Schmidt M, Farkas DK, et al. *J. Am Acad Dermatol* 2017; 78: 1077–83.

Same database as described above. Patients with parapsoriasis had a 2.7-fold increased RR (95% CI, 1.32–5.40) of venous thromboembolism in the absence of other established risk factors.

Risk of acute myocardial infarction or stroke in patients with mycosis fungoides and parapsoriasis. Lindahl LM, Heide-Jorgensen U, Pedersen L, et al. *Acta Derm Venereol* 2016; 96: 530–4.

In men with parapsoriasis, the RR of acute myocardial infarction or stroke was 1.7 (95% CI 1.1–2.7) within the first 5 years of follow-up.

First-Line Therapies

• Topical corticosteroids, emollients	E
• Ultraviolet A with 5-methoxypsoralen	C
• Topical nitrogen mustard	B

The use of topical steroids has not been evaluated in clinical trials, but its benefit has been observed in early-stage CTCL.

Photochemotherapy in cutaneous T cell lymphoma and parapsoriasis en plaque. Long-term follow-up in forty-three patients. Rosenbaum MM, Roenigk HH Jr, Caro WA, et al. *J Am Acad Dermatol* 1985; 13: 613–22.

Of the 43 patients included in the study, seven patients had LPP treated with oral psoralen and UVA (PUVA). A complete response was achieved in all seven, though the total dosages of PUVA are not stated. Average follow-up for all 43 patients was 38.4 months (range 4–67 months) and, during that time, relapse was observed in five out of the seven patients with LPP.

The authors argue that because CTCL is in the differential diagnosis of LPP, and PUVA is effective for both conditions, it may be useful in patients in whom it is difficult to distinguish between the two conditions.

Topical nitrogen mustard therapy in patients with mycosis or parapsoriasis. Lindahl LM, Fenger-Gron M, Iversen L. *J Eur Acad Dermatol Venereol* 2013; 27: 163–8.

Seventy-one patients with parapsoriasis (no information on numbers of LPP and SPP) were treated with mechlorethamine hydrochloride between 1991 and 2009. A dose of 20 mg was dissolved in 40 mL water and applied daily to affected skin for a 14-day induction period. Maintenance therapy of two treatments every 4–8 weeks occurred until clear, insufficient response, or side effects developed. The 'overall' response was 90%, with a 'complete' response of 41%. Relapse (no time given) was 62%. The main side effect was contact dermatitis resulting in withdrawal of treatment in 14% of patients.

Evaluation of a 1-hour exposure time to mechlorethamine (chlormethine) in patients undergoing topical treatment. Foulc P, Evrard V, Dalac S, et al. *Br J Dermatol* 2002; 147: 926–30.

Three patients with LPP were included in this study. One patient stopped treatment because of the side effects, and two of the three resulted in complete remission. The mechlorethamine regimen, however, varied between the four centers included in the study and is not specified for the individual patient.

Paronychia

Richard B. Mallett, Cedric C. Banfield,
Peter K.C. Goon



Paronychia is characterized by inflammation of the proximal and/or lateral nailfolds, with the fingers being more commonly affected than the toes. Acute paronychia usually involves single digits, is a painful pyogenic infection that usually occurs after injury or minor trauma, and is characteristically caused by *Staphylococcus aureus*, although other aerobic and anaerobic bacteria and herpetic viruses are also found. Polymicrobial infection is also commonly found. Greenish-gray-black discoloration in the nail bed may help identify *Pseudomonas* dominant infections.

Chronic paronychia (typically polydigital) is one of the most common inflammatory nail disorders and presents as tender erythema of the nailfolds with thickening of the tissues, loss of the cuticle, and subsequent dystrophy of the nail plate. The causative factors are repetitive microtrauma and exposure to water, irritants, and allergens, causing a contact dermatitis with subsequent colonization by yeasts and bacteria. Other less common causes of chronic paronychia include retronychia, characterized by the disruption of the longitudinal growth of a nail due to acute traumatic injury or repetitive microtrauma, with resultant embedding of the old nail in the ventral surface of the proximal nailfold as the new nail regenerates. Also, cutaneous leishmaniasis may rarely present as an unusual chronic paronychia in endemic areas. Pemphigus vulgaris may present with either acute or chronic paronychia.

Drug-induced paronychia with pseudopyogenic granuloma is increasingly recognized and may occur with systemic retinoids; antiretroviral drugs such as indinavir; epidermal growth factor (EGF) receptor inhibitors, including gefitinib and cetuximab; and the novel anticancer mechanistic target of rapamycin (mTOR) inhibitors, such as everolimus.

Tumors, including Bowen disease, keratoacanthomas, squamous cell carcinoma, enchondroma, and amelanotic melanoma, may masquerade as chronic paronychia. Dermoscopy has been used to diagnose periungual Bowen disease mimicking chronic paronychia.

MANAGEMENT STRATEGY

Acute paronychia requires urgent effective treatment to prevent damage to the nail matrix. If the infection is superficial and pointing, then *incision and drainage* may be appropriate. Infection is often due to *S. aureus*, but β -hemolytic streptococci and anaerobic

organisms may also be found. A swab should be taken for bacterial culture and antibiotic sensitivity and a *broad-spectrum antibiotic* covering both aerobic and anaerobic organisms given. *Warm compresses with an astringent* (e.g., aluminum acetate solution, if available) can help reduce edema and provide a hostile environment for bacteria. For deeper infections, if there has been no marked clinical improvement after 48 hours of antibiotic therapy, *surgical treatment* may be undertaken. Under local anesthesia, the proximal third of the nail plate is removed, and a gauze wick is laid under the proximal nailfold to allow drainage. Cases of antibiotic-resistant acute paronychia may be due to herpetic viruses, fungi, or non-infectious causes.

Chronic paronychia is usually due to dermatitis and often associated with wet work (e.g., in domestic workers, cooks, bartenders, fishmongers, etc.) and may be exacerbated by contact irritants or allergens. Immediate sensitivity to fresh foods can be a factor. In children, thumb sucking may initiate the condition. Eczema or psoriasis may predispose to chronic paronychia, as may poor peripheral circulation and rarely pemphigus vulgaris. Microtrauma, including overzealous manicuring of the cuticle, is also important. The middle and index fingers of the right hand and the middle finger of the left hand are most commonly affected, but any finger may be involved. Inflammation with bolstering of the nailfold and loss of the cuticle opens a space between the nailfold and the nail plate, which commonly becomes colonized with yeast, especially *Candida* species, and a wide range of other microorganisms. Acute exacerbations due to bacterial infection may occur.

Successful treatment relies on protection of the affected fingers from water, irritants, allergens, and trauma, together with anti-inflammatory treatment using moderately potent or potent *topical corticosteroids*. *Tacrolimus* 0.1% ointment applied twice daily may also be effective. Swabs for yeast and bacteria should be taken, *anticandidal preparations* can be useful, and antibiotic preparations may also be needed. Treatment should be continued until the inflammation has subsided and the cuticle reformed and reattached to the nail plate (3 months or more). For repeated acute episodes, *intralesional or systemic corticosteroids plus systemic antibiotics* for a week may be useful. In cases where conservative management fails, surgery or *low-dose superficial radiotherapy* has been tried. For cases due to retronychia, simple avulsion of the nail plate is normally curative but conservative treatment using taping can be tried.

Drug-induced pseudopyogenic granulomatous paronychia responds to daily topical 2% *mupirocin* with *clobetasol propionate* ointment. Additionally, for patients on EGF or mTOR inhibitors, oral *doxycycline* 100 mg twice daily or dose reduction may be useful.

Specific Investigations

- Skin swabs $\pm$ abscess fluid (for microscopy, culture, and sensitivities)
- Open patch tests against fresh foods

Anaerobic paronychia. Whitehead SM, Eykyn SJ, Phillips I. *Br J Surg* 1981; 68: 420–2.

Swabs were taken from 116 acute paronychias. Anaerobes or mixed aerobes and anaerobes were isolated in 30%. Of 81 paronychias with aerobic organisms only, *S. aureus* was isolated in 69%.

Clinical and cytologic features of antibiotic-resistant acute paronychia. Durdu M, Ruocco V. *J Am Acad Dermatol* 2014; 70: 120–6.

Antibiotic-resistant paronychia may be infectious or non-infectious. Cytologic examination may be useful diagnostically and may prevent unnecessary use of antibiotics and surgical drainage procedures.

Refractory purulent paronychia in a young girl. Pediatric dermatology photoquiz. Diagnosis paronychia cutaneous leishmaniasis. Topal I, Duman H, Baz V, et al. *Pediatr Dermatol* 2016; 33: 93–4.

Case report and successful treatment with complete resolution using intralesional meglumine antimoniate once a week for 5 weeks.

Chronic paronychia. Short review of 590 cases. Frain-Bell W. *Trans St John's. Hosp Dermatol Soc* 1957; 38: 29–35.

On culture, *Candida albicans* was grown in 70% and bacteria, including *S. aureus*, in 10%.

An excellent overview.

Role of foods in the pathogenesis of chronic paronychia. Tosti A, Guerra L, Morelli R, et al. *J Am Acad Dermatol* 1992; 27: 706–10.

Nine of 20 food handlers with chronic paronychia had positive reactions to 20-minute open patch tests with suspected fresh foods, including wheat flour, egg, chicory, and tomatoes.

First-Line Therapies

Acute

- Amoxicillin with clavulanic acid **E**
- Surgical drainage **E**

Chronic

- Topical corticosteroid preparations **B**
- Topical tacrolimus 0.1% ointment **B**
- Topical clotrimazole drops **E**
- Topical clindamycin solution **E**

Due to retronychia

- Avulsion of nail plate **E**

Drug-induced paronychia/periungual granuloma

- Mupirocin and clobetasol propionate **E**
- Mupirocin, clobetasol, and acetic acid soaks **E**

EGF- or mTOR inhibitor-induced paronychia

- Doxycycline **E**
- Dose reduction **E**
- Topical β -blockers, i.e., timolol or propranolol **D**

Acute and chronic paronychia. Leggit JC. *Am Fam Physician* 2017; 96(1): 44–51

Successful drainage of acute paronychia/abscesses do not usually require oral antibiotic therapy postdrainage. Warm compresses or soaks with aluminum acetate solution or acetic acid 1–3% usually suffice.

Paronychia: a mixed infection, microbiology, and management. Brook I. *J Hand Surg [Br]* 1993; 18: 358–9.

Culture from 61 patients with paronychia showed a mixture of both aerobic and anaerobic bacteria in 49%. The combination

of amoxicillin with clavulanic acid is suggested as first-line treatment for acute bacterial paronychia, together with appropriate surgical drainage.

Nail surgery and traumatic abnormalities. Thomas L, Zook E, Rosio T, et al. In: Baran R, de Berker DAR, Holzberg M, et al., eds. *Baran and Dawber's Diseases of the Nails and Their Management*, 4th edn. Chichester: Wiley-Blackwell, 2012; 623–4.

For acute paronychia, under local anesthesia the proximal third of the nail plate is removed and a wick laid under the proximal nailfold.

Topical steroids versus systemic antifungals in the treatment of chronic paronychia: an open, randomized double-blind and double dummy study. Tosti A, Piraccini BM, Ghetti E. *J Am Acad Dermatol* 2002; 47: 73–6.

An open, randomized, double-blind trial of oral itraconazole, oral terbinafine, and topical methylprednisolone aceponate. Patients were treated for 3 weeks and observed for a further 6 weeks. Of 48 nails treated with methylprednisolone aceponate, 41 (85%) were improved or cured at the end of the study, compared with only 30 of 57 (53%) with itraconazole and 29 of 64 (45%) with terbinafine.

Efficacy and safety of tacrolimus ointment 0.1% vs. betamethasone 17-valerate 0.1% in the treatment of chronic paronychia: an unblinded randomized study. Rigopoulos D, Gregoriou S, Belyayeva E, et al. *Br J Dermatol* 2009; 160: 858–60.

This open study showed that both topical tacrolimus 0.1% and betamethasone 17-valerate 0.1% ointments applied twice daily to the affected perionychium gave statistically significantly better cure or improved rates compared with placebo. Also, in this study, tacrolimus 0.1% ointment appeared to be more effective than betamethasone 17-valerate 0.1% ointment.

The management of superficial candidiasis. Hay RJ. *J Am Acad Dermatol* 1999; 40: S35–42.

The central role of *Candida* in chronic paronychia is debatable, and other factors such as an irritant or allergic dermatitis may play a role. Therefore, in addition to polyenes or imidazoles, concomitant use of a topical corticosteroid is a logical approach.

Diseases of the nails in infants and children: paronychia. Silverman RA. In: Callen JP, Dahl MV, et al., eds. *Advances in Dermatology*, Vol. 5. Chicago: Mosby Year Book, 1990; 164–5.

Clotrimazole drops several times a day should inhibit fungal growth. Topical clindamycin solution applied to the fingers several times daily kills bacteria, has a bitter taste to discourage finger sucking, and has an alcohol-propylene glycol vehicle that dries out residual moisture. Side effects from oral absorption of these medications have not been reported.

Retronychia – clinical and pathophysiological aspects. Ventura F, Correia O, Duarte A, et al. *JEADV* 2016; 30: 16–9.

Review of 20 cases of retronychia. Avulsion of the nail confirms the diagnosis and is the curative treatment.

Paronychia associated with antiretroviral therapy. Tosti A, Piraccini BM, D'Antuono A, et al. *Br J Dermatol* 1999; 140: 1165–8.

Six cases of periungual pseudopyogenic granuloma induced by indinavir, lamivudine, and zidovudine responded to daily applications of clobetasol propionate and mupirocin.

Paronychia associated with ledipasvir/sofosbuvir for hepatitis C treatment. Sampson B, Lewis BKH. *J Clin Aesthet Dermatol* 2019; 12(1): 35–7 [Epub 1 Jan 2019].

Case report on a patient developing chronic paronychia in multiple digits during treatment with ledipasvir/sofosbuvir for chronic genotype 1a HCV infection. He was treated conservatively with mupirocin 2% ointment OD, clobetasol 0.05% ointment OD, and acetic acid soaks BD, with improvement on this regimen, but complete resolution only occurred after completion of HCV treatment.

Doxycycline for the treatment of paronychia induced by the epidermal growth factor receptor inhibitor cetuximab. Suh K-Y, Kindler HL, Medenica M, et al. *Br J Dermatol* 2006; 154: 191–2.

During treatment with cetuximab a patient developed painful paronychia, refractory to topical mupirocin and cephalexin, but improved after treatment with doxycycline 100 mg twice daily.

Paronychia and pyogenic granuloma induced by new anti-cancer mTOR inhibitors. Sibaud V, Dalenc F, Mourey L, et al. *Acta Derm Venereol* 2011; 91: 584–5.

Seven patients treated with mTOR inhibitors presenting with chronic paronychia were treated variously with topical steroids, silver nitrate, topical antibiotics, and oral doxycycline and pristinamycin; three patients required dose reduction.

Efficacy of topical beta-blockers in the management of EGFR-inhibitor induced paronychia and pyogenic granuloma-like lesions: case series and review of the literature. Sollena P, Mannino M, Tassone F, et al. *Drugs Context* 2019; 8: 212613.

Study with 25 cases of EGFR-inhibitor-induced periungual pyogenic granuloma or paronychia treated with topical timolol 0.5% gel, applied twice daily, under occlusion for 30 days. Of the 25, 22 demonstrated at least partial response or better, with 13 showing complete response, and three with no response.

Second-Line Therapies

Chronic

- Nystatin ointment **E**
- Intralesional or systemic corticosteroids and antibiotics **E**

Treatment of chronic paronychia. Vickers HR. *Br Med J* 1979; 2: 1588.

A nystatin-containing ointment should be worked into the affected nailfold every time the patient is going to get the hands wet, for at least 6 weeks.

Fungal (onychomycosis) and other infections involving the nail apparatus. Hay RJ, Baran R. In: Baran R, de Berker D, Holzberg M, et al., eds. *Baran and Dawber's Diseases of the Nails and Their Management*, 4th edn. Chichester: Wiley-Blackwell, 2012; 239.

For frequent acute exacerbations of chronic paronychia, intralesional or systemic corticosteroids plus either erythromycin 1 g daily or tetracycline 1 g daily for a week is recommended.

Third-Line Therapies

Acute

- Leeches **E**

Chronic

- Eponychial marsupialization **C**
- Excision of nailfold **E**
- Superficial low-dose radiotherapy **E**

Thumb paronychia treated with leeches. Graham CE. *Med J Aust* 1992; 156: 512.

Acute paronychia successfully treated with leeches while trekking in Tasmania.

Eponychial marsupialization and nail removal for surgical treatment of chronic paronychia. Bednar MS, Lane LB. *J Hand Surg [Am]* 1991; 16: 314–7.

Twenty-eight fingers with chronic paronychia were treated with marsupialization of the dorsal roof of the proximal nailfold plus complete or partial removal of the nail in those patients with associated nail abnormality. Postoperative treatment was with hydrogen peroxide soaks and oral antibiotics for 5–14 days: 27 of 28 fingers were cured.

Surgical treatment of recalcitrant chronic paronychia of the fingers. Baran R, Bureau H. *J Dermatol Surg Oncol* 1981; 7: 106–7.

Description of the technique of simple excision of the affected nailfold without the need for marsupialization.

How we treat paronychia. Fliegelman MT, Lafayette GO. *Postgrad Med* 1970; 48: 267–8.

For recalcitrant cases of chronic paronychia, triamcinolone can be injected into the affected nailfold. For the most severe cases, a course of low-dose superficial radiotherapy may be given.

Periungual Bowen disease mimicking chronic paronychia and diagnosed by dermoscopy. Giacomel J, Lallas A, Zalaudek I, et al. *J Am Acad Dermatol* 2014; 71: e65–7.

Parvovirus infection

Andrea L. Zaenglein, Lindsay C. Bacik



Infection with human parvovirus B19 (HPB19), a member of the *Erythrovirus* genus, causes a variety of well-described exanthems and can result in a spectrum of systemic illnesses. Erythema infectiosum, also known as fifth disease, is the classic and most common eruption associated with HPB19 infection. Purpuric eruptions, including papular purpuric gloves-and-socks syndrome (PPGSS), are also reported in association with HPB19. Extracutaneous manifestations are common, particularly arthropathy and red cell dyscrasia. Primary infection during pregnancy may place the fetus at risk for hydrops fetalis and intrauterine fetal demise, while perinatal infection is a cause of 'blueberry muffin' lesions in neonates.

MANAGEMENT STRATEGY

Erythema infectiosum is typically a self-resolving exanthema transmitted via respiratory droplets. Outbreaks occur in the winter and spring and typically affect school-aged children between 5 and 15 years of age. After a short variable prodrome of fever, malaise, diarrhea, and pharyngitis, the classic features of the exanthem appear. Bright pink macular erythema of the cheeks ('slapped cheek' sign) together with nasal bridge and circumoral pallor precedes an evanescent macular, reticulated, or 'lacy' rash over the trunk and proximal limbs. The rash may last for up to weeks to months (rarely years) and subsequently recurs after exposure to sun, warm temperature, and intense physical activity. In the majority of cases, *supportive care and reassurance* are all that is required. The rash of erythema infectiosum is immune complex-mediated so patients are no longer infectious by the time it appears and HPB19 IgG is detectable in the blood once the

eruption occurs. Patients can be reassured and advised on simple supportive measures such as antipyretics, fluids, and bland emollients for the rash.

Parvovirus should be suspected with all petechial rashes whose origin is undetermined. PPGSS is the most common, presenting with pruritic to painful edema, erythema, and petechiae of the hands and feet with a classic sharp demarcation at the wrist and ankles. The 'slapped cheek' sign and an enanthem (palatal, pharyngeal, labial, and lingual erythema, petechiae, and ulcerations) may accompany the rash along with fever, and other non-specific viral symptoms. PPGSS typically occurs in spring and summer and in adolescents and young adults. Unlike erythema infectiosum, patients with PPGSS are viremic while the rash is present and are thus contagious. The eruption typically resolves within 1–2 weeks with non-specific supportive measures. The acropetechial syndrome involves the perioral skin in addition to the hand and foot involvement classically seen in PPGSS. A petechial eruption in a bathing trunk distribution, sometimes associated with pustules, as well as a cellulitis-like presentation, has also been described. Postviral disorders, including asymmetric periflexural exanthema (unilateral lateral thoracic syndrome), papular acrodermatitis of childhood (Gianotti-Crosti syndrome), and Kawasaki disease, have occurred after HPB19 infection. HPB19 is also in the differential diagnosis of the 'blueberry muffin' baby and TORCH infections, and should be considered in any newborn with multiple blue to purple cutaneous lesions. Other secondary associations include erythema nodosum, erythema multiforme, livedo reticularis, vasculitis, and Sweet syndrome.

HPVB19 infection may cause a symmetric arthropathy in up to 50% of adults, most commonly women, and in up to 10% of children. It is similar to rheumatoid arthritis involving the wrists, ankles, knees, and metacarpophalangeal and proximal interphalangeal joints. Arthropathy may accompany the cutaneous eruption but frequently follows it. The arthritis is usually self-limiting, requiring only non-steroidal antiinflammatory drugs for symptomatic relief. In about 20% of patients, the arthritis may become chronic, and it has been suggested that infection with HPB19 may be a trigger for autoimmune arthritis and connective tissue disease. HPVB19 infection can induce autoantibody formation, including antinuclear antibody and numerous subsets, rheumatoid factor, and ANCA.

In predisposed individuals with underlying disorders of hemolysis, decreased erythrocyte production, or active bleeding, HPB19 infection can cause a transient aplastic crisis. This acute anemia may be self-limited and asymptomatic, but transfusion may be required if severe. In addition to anemia, there may be moderate neutropenia and thrombocytopenia. Severe, recalcitrant cases of aplastic anemia may require intravenous immunoglobulin (IVIG) or bone marrow transplantation. Chronic HPB19 infection in immunosuppressed patients can result in pure red blood cell aplasia, a form of chronic anemia that results from the inability to create neutralizing antibodies to the virus. Children who are already anemic due to other causes, such as malaria, malnutrition, or parasites, can become profoundly anemic with HPB19 infection.

Patients with AIDS and chronic anemia secondary to HPB19 infection, who are treated with highly active antiretroviral therapy (HAART), with recovery of CD4 counts, have had resolution of their anemia. AIDS patients started on HAART can experience an immune reconstitution syndrome with overwhelming systemic involvement of parvovirus, resulting in encephalitis, severe anemia, or other severe sequelae.

Fetal infection with parvovirus B19 may result in mild-to-severe anemia, thrombocytopenia, high-output congestive heart

failure, non-immune hydrops fetalis, and fetal death. Fetal stroke and other neurologic sequelae have also been reported. Fetal infection occurs usually during the first 20 weeks of pregnancy, although third trimester hydrops-related and spontaneous non-hydrops-related fetal demise has been reported. One-third or more of women of childbearing age do not have IgG antibodies to HPB19 and are susceptible to primary infection. Testing maternal serum for IgM and IgG titers and/or HPB19 DNA with polymerase chain reaction (PCR) analysis should be performed in pregnant women who develop symptoms of HPB19 infection or are in contact with children with a known parvovirus infection. If they have serologic evidence of primary infection, serial fetal ultrasonography should be performed to evaluate for signs of fetal anemia and hydrops fetalis.

Rarely, additional systemic involvement, including renal, neurologic, hepatic, cardiac, respiratory, ocular, and endocrine manifestations, has been reported during acute infection with HPB19. Immunosuppressed patients are at greatest risk for systemic involvement due to both primary infection with, and reactivation of, HPB19. Liver and spleen enlargement can be pronounced, mimicking leukemia. HPB19-associated hemophagocytic lymphohistiocytosis has been reported in patients with underlying malignancy on chemotherapy. Viral myocarditis can cause ventricular dysfunction and heart failure. Neurologic sequelae include neuritis and Guillain-Barré syndrome. HPB19 infection can mimic various connective tissue disorders, in particular systemic lupus erythematosus, dermatomyositis, and vasculitis. Infection with HPB19 has been linked to a multitude of chronic conditions, including hepatitis, nephritis, neurologic disease, and malignancy. However, a causal relationship has not been established. Reactivation of HPB19 has also been reported in adults with DRESS (drug reaction with eosinophilia and systemic symptoms) presenting with the classic reticular rash seen with parvovirus.

Specific Investigations

- Hematology (complete blood count)
- Organ-specific testing depending on symptoms
- Serologic testing
- HPB19 PCR (blood or lesional skin)

Although most parvovirus infections are diagnosed clinically, atypical presentations with systemic concerns or new-onset arthropathy of unknown cause warrant diagnostic testing. Serologic testing includes analysis for IgM and IgG antibodies using enzyme-linked immunoassay (ELISA), radioimmunoassay, or immunofluorescence. IgM to HPB19 indicates recent infection. HPB19-specific IgG antibodies indicate past exposure and may be positive in over half the adult population. In at-risk patients or those who have symptoms of anemia, a complete blood count will establish whether there is any significant level of anemia requiring transfusion.

It is possible to detect parvovirus DNA in both the blood and lesional skin. PCR techniques are extremely sensitive and may be useful in the following clinical scenarios: patients with an atypical presentation of HPB19 infection, where the clinical suspicion of infection is high and antibody studies are negative, and in immunocompromised patients who cannot mount an appropriate immunoglobulin response. In addition, a window period exists during the first 7 days after exposure when IgG and IgM are negative, and a second period exists where IgM has become undetectable. PCR may also be helpful during these periods.

Exanthematous eruptions in children. Young T, Oza V. *Pediatr Ann* 2020; 49: 116–23.

This is a review of exanthematous eruptions in children that discusses HPB19 as a cause of classic and atypical presentations of viral exanthemas.

Unusual skin manifestations associated with parvovirus B19 primary infection in children. Ferrari B, Diaz M, Lopez M, et al. *Pediatr Dermatol* 2018; 35: 341–4.

This is a report of four cases of children presenting with unusual exanthems associated with HPB19 infection, including a purpuric periflexural pattern, a purpuric vasculitic pattern, and a combination of the two.

Different patterns of skin manifestations associated with parvovirus B19 primary infection in adults. Mage V, Lipsker D, Barbarot S, et al. *J Am Acad Dermatol* 2014; 71: 62–9.

This is a retrospective study aiming to describe the cutaneous presentations associated with primary HPB19 infection in adults. The authors suggest that acral or periflexural distribution of the rash and the presence of purpuric or annular/reticulate lesions are highly suggestive of HPB19 infection.

Human parvovirus B19 infection in patients with or without underlying diseases. Sim JY, Chang LY, Chen JM, et al. *J Microbiol Immunol Infect* 2019; 52(4): 534–41.

This is a retrospective study of patients with PCR-confirmed parvovirus B19 infection comparing the clinical presentations of previously healthy patients and patients with preexisting diseases. Patients with a preexisting disease were less likely to manifest classic parvovirus symptoms and more likely to be of older age and experience fatigue and anemia.

Outcome of fetuses with congenital parvovirus B19 infection: systematic review and meta-analysis. Bascietto F, Liberati M, Murgano D, et al. *Ultrasound Obstet Gynecol* 2018; 52: 569–76.

This is a meta-analysis exploring the outcome of fetuses affected by congenital HPB19 infection that shows that hydrops is the main determinant of mortality and adverse perinatal outcomes. Perinatal outcome in non-hydrotic fetuses is generally favorable.

Parvovirus B19 infection in sickle cell disease: an analysis from the Centers for Disease Control haemoglobinopathy blood surveillance project. Majumdar S, Bean C, De Staercke C, et al. *Transfus Med* 2020; 1–5.

A qualitative analysis of HPB19 serology using ELISA and quantitative HPB19 DNA by RT-PCR was performed in patients with sickle cell disease (SCD). Of 322 patients, 35% were parvovirus IgG positive and 37% were IgM positive at enrollment. Patients who were positive for HPB19 DNA received a significantly higher red blood cell transfusion volume in the prior year compared with patients who were negative.

Detection of human parvovirus B19 DNA in 22% of 1815 cutaneous biopsies of a wide variety of dermatological conditions suggests viral persistence after primary infection and casts doubts on its pathogenic significance. Santonja C, Santos-Briz A, Palmedo G, et al. *Br J Dermatol* 2017; 177: 1060–5.

Authors studied 1815 skin biopsies from 1749 patients with a wide variety of dermatological disorders and detected HPB19 DNA in 22% of skin samples of 394 patients with over 100 different clinical diagnoses. Vasculitis, pityriasis lichenoides,

pityriasis rosea, dermatitis/eczema, lichen planus, psoriasis, purpura, and erythema migrans were the most frequent HPB19 positive entities.

Infectious processes and systemic lupus erythematosus. Ill-escas-Montes R, Corona-Castro CC, Melguizo-Rodríguez L, et al. *Immunology* 2019; 158(3): 153–60.

A review of the role that infectious agents, including HPB19, have in systemic lupus erythematosus, including immunologic changes responsible for infectious processes or molecular mimicry between host structures and those of infectious agents.

Hypocomplementemia is a diagnostic clue for parvovirus B19 infection in adults. Hashizume H, Kageyama R. *J Dermatol* 2017; 44(3): e27.

This is a report of 15 adult patients with sudden emergence of generalized rash and arthralgia clinically suggestive of HPB19 infection. Patients with low serum levels of either CH50 or C4 had a significant association with positive antiparvovirus B19 IgM.

The clinical use of parvovirus B19 assays: recent advances. Gallinella G. *Expert Rev Mol Diagn* 2018; 18: 821–32.

This is a review including the pathogenetic mechanisms of HPB19 infection, the consequent requirements for different diagnostic approaches, the main diagnostic techniques, and more recent technical advancements in diagnosis.

Oral fluid: non-invasive alternative for parvovirus B19 diagnosis? Bodewes R, Kerkhof J, Cremer J, et al. *J Clin Virol* 2019; 117: 5–10.

This study evaluated the use of B19V-qPCR on oral fluid samples as a non-invasive alternative for laboratory diagnosis of HPB19 infections in children below 12 years of age with exanthema. B19V DNA was detected in oral fluid of 17 of the 25 children who were IgM positive as well as two children who were IgM-equivocal or negative.

First-Line Therapies

- Supportive care E
- Antipyretics (e.g., acetaminophen [paracetamol], ibuprofen) E

Second-Line Therapies

- NSAIDs E
- Systemic corticosteroids E
- Blood transfusion C

Third-Line Therapies

- Immunoglobulin infusion C
- Bone marrow/stem cell transplantation D
- Intrauterine transfusion C
- HAART E
- Hydroxyurea, cidofovir, and brincidofovir D

Intravenous immunoglobulin therapy for pure red cell aplasia related to human parvovirus B19 infection: a

retrospective study of 10 patients and review of the literature. Crabol Y, Terrier B, Rozenber F, et al. *Clin Infect Dis* 2013; 56: 968–77.

This is a review of the efficacy of IVIG for therapy of pure red cell aplasia (PRCA) related to HPV-B19 infection. IVIG was found to be effective for short-term use in immunocompromised patients with HPV-B19 PRCA.

Intravenous immunoglobulin treatment of four patients with juvenile polyarticular arthritis associated with persistent parvovirus B19 infection and antiphospholipid antibodies. Lehmann HW, Plentz A, Von Landenberg P, et al. *Arthritis Res Ther* 2004; 6: R1–6.

This is a small series of four children with oligoarthritis and polyarthritis and chronic HPB19 infection treated with IVIG (in addition to other therapies) with variable improvement in symptoms and quality-of-life measurements. Dosing for the IVIG was 0.4 g/kg/day for 5 successive days. Two cycles were given 1 month apart.

Mononeuropathy multiplex associated with acute parvovirus B19 infection: characteristics, treatment and outcome. Lenglet T, Haroche J, Schnuriger A, et al. *J Neurol* 2011; 258: 1321–6.

The course of three patients with HPB19 virus-positive neuropathy is described. Treatment with IVIG resulted in good but incomplete improvement in symptoms.

Parvovirus associated fulminant hepatic failure and aplastic anemia treated successfully with liver and bone marrow transplantation. Bathla L, Grant W, Mercer D, et al. *Am J Transplant* 2014; 14: 2645–50.

This is a report of two case reports of children with hepatic failure secondary to HPB19 complicated with aplastic anemia who underwent liver transplant and bone marrow transplantation with excellent outcomes.

Stem cell transplantation in 6 children with parvovirus B19-induced severe aplastic anaemia or myelodysplastic syndrome. Urban C, Lackner H, Müller E, et al. *Klin Padiatr* 2011; 223: 332–4.

This is a small series of children infected with HPB19 with resultant refractory bone marrow failure treated with stem cell transplantation.

Resolution of chronic parvovirus B19 induced anemia, by use of highly active antiretroviral therapy in a patient with acquired immunodeficiency syndrome. Ware M. *Clin Infect Dis* 2001; 32: E122–3.

This is a case of an AIDS patient with transfusion-dependent anemia caused by HPB19 that resolved with HAART therapy.

Antiviral activity of brincidofovir on parvovirus B19. Bua G, Conti I, Manaresi E, et al. *Antiviral Res* 2019; 162: 22–9.

Authors report the results of experiments demonstrating that brincidofovir, in comparison to cidofovir, exerts an enhanced inhibitory effect on replication of HPB19 in vitro.

Advances in the development of antiviral strategies against parvovirus B19. Manaresi E, Gallinella G. *Viruses* 2019; 11: 659.

This review article highlights updates in the development of antiviral strategies against HPB19. Hydroxyurea, cidofovir, and brincidofovir have shown antiviral activity against HPB19.

Pediculosis

Aakaash Varma, Hee J. Kim, Jacob O. Levitt



Lice are wingless, dorsoventrally flattened, blood-sucking insects that are obligate ectoparasites of birds and mammals. Pediculosis denotes an infestation by *Pediculus capitis* (head louse), *Pediculus humanus* (body or clothing louse), or *Phthirus pubis* (pubic or crab louse). The bites of lice are painless and can rarely be detected. The clinical signs and symptoms are the result of the host's reaction to the saliva, which has vasodilatory and anticoagulation properties. Saliva is injected into the dermis by the louse at the time of feeding. Depending on immune sensitivity and previous exposure, red macules or papules develop hours to days after feeding. Pruritus is the most common symptom of any type of pediculosis. If left untreated, superinfection of excoriations may lead to impetiginous crusts and regional lymphadenopathy.

PEDICULOSIS CAPITIS

Management Strategy

In the United States, an estimated 6–12 million people are infested with head lice every year. Children 3–12 years old and their parents are most commonly affected. Identification of live lice is the gold standard of diagnosis; however, finding nits alone in a patient who has not been treated warrants treatment. One study showed that around 20% of patients found to have nits alone eventually develop live lice. Nits are easier to spot, especially at the nape of the neck and behind the ears. Hatched nits are white; unhatched nits are brown. Detection combing of wet hair with a fine-toothed nit comb allows efficient recovery of lice and nits for diagnosis.

Management must take into consideration key elements of the head louse life cycle. It takes 4 days to develop a nervous system in the egg, 12 days at most to hatch, and 7 days after hatching for the nymph to lay eggs. Contrary to the direction of most non-ovicidal pediculicides, one retreatment in 7 days will not kill all viable nits. As such, therapies that do not kill eggs require three weekly treatments. Pediculicides that are ovicidal require two treatments separated by 1 week. Agents that act on the louse nervous system will not affect ova that are less than 4 days old. Lice are sensitive to dehydration but can live off the host for up to 55 hours. Transmission is mainly by direct head-to-head contact. Indirect spread through fomites is also possible. Until definitive safety data are available, the occasional patient under 2 years old should be treated with *mechanical methods*.

Laundryable items (worn clothing and used bedding, towels, scarves, and hats) should be placed in a dryer at 60°C (i.e., on high) for at least 10 minutes. Brushes, combs, and hair ornaments can be placed in hot (60°C or more) water for 10 minutes. Non-laundryable items (i.e., certain stuffed animals) should be placed in a bag for 3 days (not 15 days, as eggs laid off a host are unlikely to hatch near a host to obtain their first blood meal). Clothes, furniture, and rugs should be vacuumed. Fumigation of the home is discouraged.

Contacts of index cases, including classmates and family members, should be screened. Empiric therapy for close household contacts, particularly if they share a bed, is justifiable. Those likely to have had head-to-head contact with the index case in the prior 4–6 weeks should be identified and screened. Children should not be excluded from school for head lice, as the infestation often has been ongoing for months before its detection. Hair grows 1 cm per month, and lice lay eggs close to the scalp where it is moist and warm. Nits detected 2 cm from the scalp represent a 2-month-old infestation. Requiring therapy within a week of the detected infestation is reasonable.

Considerations guiding therapy include safety and efficacy. The efficacy of chemical modalities depends on regional resistance patterns of lice. Because of widespread resistance to permethrin and lindane, *malathion* formulated in isopropyl alcohol with terpineol remains the most effective therapy due to its ovicidal and pediculicidal properties. *Topical ivermectin* lotion and *spinosad topical suspension* have proven to be effective alternatives. A less reliable topical option is *benzyl alcohol lotion*. Alternatives that do not act on the louse nervous system are *mechanical methods*, such as louse occlusion, cuticle disruption, and physical removal. A newer option is *abametaipir lotion*, which works by inhibiting metalloproteinases crucial for lice and egg development. Barring shaving the head, these modalities are often unreliable and result in recurrent infestation between treatments and continued infectivity.

Specific Investigations

- Examination for nits and lice via detection combing
- Dermoscopy

Plastic detection comb better than visual screening for diagnosis of head louse infestation. Balcioglu C, Burgess IF, Limoncu ME, et al. *Epidemiol Infect* 2008; 136: 1425–31.

Detection combing is 3.84 times more effective than visual inspection for finding live head lice.

Dermoscopy for diagnosis and treatment monitoring of pediculosis capitis. Di Stefani A, Hofmann-Wellenhof R, Zalaudek I. *J Am Acad Dermatol* 2006; 54: 909–11.

A handheld non-contact dermatoscope can be used to differentiate eggs containing nymphs, empty cases of hatched lice, and pseudo-nits. Treatment success can also be monitored using the dermatoscope.

First-Line Therapies

• Malathion 0.5% lotion	A
• Benzyl alcohol 5% lotion	A
• Ivermectin 0.5% lotion	A
• Spinosad 0.9% topical suspension	A
• Permethrin 1% cream rinse	A
• Abametaipir 0.74% lotion	A

Therapy for head lice based on life cycle, resistance, and safety considerations. Lebowitz M, Clark L, Levitt J. *Pediatrics* 2007; 119: 965–74.

This article highlights the importance of designing treatment schedules in accordance with the head lice life cycle. Malathion 0.5% in isopropyl alcohol 78% with terpineol 12% is a safe, resistance-breaking formulation approved by the Food and Drug Administration as a first-line treatment for head lice. Two treatments 1 week apart correlate with the head lice life cycle. There is no evidence to suggest that the second application, 1 week later, is unsafe. A single treatment cures 70–80% of cases.

Knockdown resistance allele frequencies in North American head louse (*Anoplura: Pediculidae*) populations. Yoon KS, Previte DJ, Hodgdon HE, et al. *J Med Entomol* 2014; 51: 450–7.

A high frequency of *kdr*-type T917I mutation in head lice is reported: 84.4% in the United States from 1999 to 2009 increased to 99.6% from 2007 to 2009. This is responsible for complete insensitivity of the louse voltage-gated sodium channel to permethrin.

Effectiveness of Ovide against malathion-resistant head lice. Downs AM, Narayan S, Stafford KA, et al. *Arch Dermatol* 2005; 141: 1318.

In this *in vitro* study, Ovide (containing malathion, terpineol, and isopropyl alcohol) killed 100% of British head lice resistant to malathion after a 60-minute exposure. Terpineol and malathion appear to be effective in overcoming resistance.

Efficacy of a reduced application time of Ovide lotion (0.5% malathion) compared with Nix crème rinse (1% permethrin) for the treatment of head lice. Meinking TL, Vicaria M, Eyerdam DH, et al. *Pediatr Dermatol* 2004; 21: 670–4.

Reduced application time (20 minutes) of Ovide cured 98% (40 of 41) of subjects on day 15 compared to Nix (10 minutes), which cured 55% (12 of 22); 19.5% of Ovide patients and 40.9% of Nix patients required a second treatment on day 8. Reinfestation rates were 0% for Ovide and 23% for Nix.

Permethrin 1% obtained approval with well-done studies decades ago; however, resistance has caused permethrin cure rates to decline dramatically.

The clinical trials supporting benzyl alcohol lotion 5% (Ulesfia): a safe and effective topical treatment for head lice (*pediculus humanus capitis*). Meinking TL, Villar ME, Vicaria M, et al. *Pediatr Dermatol* 2010; 27: 19–24.

Benzyl alcohol lotion 5% was studied in 695 subjects. Two multicenter, randomized, double-blind, placebo-controlled trials showed a cure rate of ≈67% in 126 subjects.

Benzyl alcohol stuns breathing spiracles open, allowing the vehicle to asphyxiate the lice.

Assessment of topical versus oral ivermectin as a treatment for head lice. Ahmad HM, Abdel-Aziz ES, Abdel-Aziz RT. *Dermatol Ther* 2014; 27: 307–10.

This study compared the efficacy of a single topical application of 1% ivermectin solution to a single dose of oral (200 mcg/kg per dose) ivermectin. After 1 week, patients who received topical ivermectin had a significantly higher cure rate of 88%. No recurrence of infestation was observed after a 4-week end point.

Topical 0.5% ivermectin lotion for treatment of head lice. Pariser DM, Meinking TL, Bell M, et al. *N Engl J Med* 2012; 367: 1687–93.

Two placebo-controlled trials assessing the efficacy of a single 10-minute application of ivermectin lotion without nit combing were conducted in 765 individuals aged 6 months and older. Approximately 79% of subjects remained louse free for 15 days after a single treatment.

Efficacy and safety of spinosad and permethrin creme rinses for pediculosis capitis (head lice). Stough D, Shellabarger S, Quiring J, et al. *Pediatrics* 2009; 124: 389–95.

Two investigator-blinded studies compared 0.9% spinosad without nit combing to 1% permethrin with combing in 1038 subjects aged ≥6 months. The efficacy of spinosad (≈86%) was statistically superior to permethrin (≈44%). Spinosad did not require a combing step, and most patients required one rather than two applications.

Spinosad was more effective than permethrin, which is currently recommended first-line treatment by the American Academy of Pediatrics.

Clinical studies evaluating abametapir lotion, 0.74%, for the treatment of head louse infestation. Bowles VM, VanLuvane LJ, Alsop H, et al. *Pediatr Dermatol* 2018; 35: 616–21.

The results of two randomized, double-blind, multicenter, vehicle-controlled studies demonstrated that, in the intent-to-treat population (216 patients), 81.5% of subjects treated with abametapir lotion were lice free 14 days after a single 10-minute treatment, versus 49.1% with vehicle.

Abametapir inhibits metalloproteinases critical for lice and egg development, a novel mechanism of action for the treatment of pediculosis. It is not yet approved for use in the United States.

Second-Line Therapies

Topical occlusion therapy (suffocants)

- Dimeticone 4–100% lotion **A**
- Isopropyl myristate 50% in 50% ST-cyclomethicone **A**
- Cetaphil liquid cleanser **B**
- 1,2-Octanediol 1% spray **A**
- Tocopheryl acetate 20% spray **A**

Chemical agents

- Topical crotamiton 10% **B**
- Carbaryl 0.5% lotion **E**
- Melaleuca oil and lavender oil **A**

Nit picking

- Bug busting **A**
- Professional nit-picking services **E**

Single application of 4% dimeticone liquid gel versus two applications of 1% permethrin crème rinse for treatment of head louse infestation: a randomized controlled trial. Burgess IF, Brunton ER, Burgess NA. *BMC Dermatol* 2013; 13: 5.

In this single-center, parallel-group, randomized, controlled, open-label trial, one application of 4% dimeticone liquid gel for 15 minutes had a significantly higher success rate at 77.1% than that of 1% permethrin.

Dimeticone (also known as dimethicone) penetrates the respiratory spiracles of lice and interrupts oxygen supply, leading to organism death.

Randomised, controlled, parallel group clinical trials to evaluate the efficacy of isopropyl myristate/cyclomethicone solution against head lice. Burgess IF, Lee PN, Brown CM. *Pharmaceut J* 2008; 280: 371–5.

In this randomized, controlled, assessor-blind, parallel-group trial involving 168 subjects with head louse infestation, patients treated with 10-minute single application of isopropyl myristate/cyclomethicone (IPM/C) solution had a significantly higher cure rate of 82% on day 14 compared with those treated with permethrin 1%. IPM/C was easier to apply and less odorous.

A simple treatment for head lice: dry-on, suffocation-based pediculicide. Pearlman DL. *Pediatrics* 2004; 114: e275–9.

Cetaphil cleanser is applied to the hair and dried with a hair dryer, followed by nit combing. This is repeated three times at intervals of a week apart. A total of 133 patients were studied; 96% efficacy is claimed.

1,2-Octanediol, a novel surfactant, for treating head louse infestation: identification of activity, formulation, and randomised, controlled trials. Burgess IF, Lee PN, Kay K, et al. *PLoS One* 2012; 7: e35419.

In this observer-blinded study of 520 subjects, the cure rate of an application of 1,2-octanediol 5% lotion was 70.9% for 2–2.5 hours and 87.9% for 8 hours/overnight, both more effective than 0.5% malathion liquid.

Octanediol eliminates lice by disrupting the insects' cuticular lipid and causing dehydration.

Tocopheryl acetate 20% spray for elimination of head louse infestation: a randomised controlled trial comparing with 1% permethrin creme rinse. Burgess IF, Burgess NA, Brunton ER. *BMC Pharmacol Toxicol* 2013; 14: 43.

Two treatments, 7 days apart, with tocopheryl acetate 20% spray (applied to dry hair for 20 minutes and then washed), had a cure rate of 73.9% (17/23) in comparison to 22.7% (5/22) with permethrin 1% crème rinse.

Tocopheryl acetate immobilizes lice and inhibits eggs from hatching via physical mechanism of action.

A single application of crothamiton lotion in the treatment of patients with pediculosis capitis. Karacic I, Yawalkar SJ. *Int J Dermatol* 1982; 21: 611–3.

One application of crothamiton 10% lotion cured 47 of 49 subjects, and the remaining two were cured with a second application in 1 week.

The trial was open label and never independently validated.

A randomised, assessor blind, parallel group comparative efficacy trial of three products for the treatment of head lice in children – melaleuca oil and lavender oil, pyrethrins and piperonyl butoxide, and a 'suffocation' product. Barker SC, Altman PM. *BMC Dermatol* 2010; 10: 6.

Cure rates were as follows: melaleuca (tea tree) oil and lavender oil (41/42; 98%); NeutraLice, a suffocation product (40/41; 98%); products containing pyrethrins and piperonyl butoxide (10/40; 25%).

Single blind, randomised, comparative study of the Bug Buster kit and over the counter pediculicide treatments against head lice in the United Kingdom. Hill N, Moor G, Cameron MM, et al. *Br Med J* 2005; 331: 384–7.

A cure rate of 57% (32/56) is reported for wet combing with conditioner in four sessions over 13 days.

Nit combing can be painful and time consuming but may be worthwhile for treatment of lice that are resistant to pharmacotherapy.

Third-Line Therapies

• Oral ivermectin	A
• Oral trimethoprim–sulfamethoxazole	B
• Desiccation	B
• Head shaving	E

Lindane toxicity: a comprehensive review of the medical literature. Nolan K, Kamrath J, Levitt J. *Pediatr Dermatol* 2012; 29: 141–6.

Lindane has been associated with significant adverse reactions, including death, seizures, shortness of breath, and hematologic effects. It is no longer recommended for use in children younger than 10 years old, those weighing less than 50 kg, breastfeeding women, older adults, or people with compromised dermal barriers.

Given the significant toxicity associated with lindane and the availability of other safer treatments, lindane should be avoided.

Oral ivermectin versus malathion lotion for difficult-to-treat head lice. Chosidow O, Giraudeau B, Cottrell J, et al. *N Engl J Med* 2010; 362: 896–905.

This multicenter, cluster-randomized, double-blind, controlled trial conducted in 812 patients compared oral ivermectin (at a dose of 400 mcg/kg body weight) with 0.5% malathion lotion, each given on days 1 and 8. Included were subjects who had live lice resistant to topical insecticide used 2–6 weeks prior to enrollment. In the intention-to-treat population, 95.2% of patients who received oral ivermectin were lice free on day 15, compared to 85.0% in those who used topical malathion. Oral ivermectin had superior efficacy without increase in side effects.

Safety studies of oral ivermectin in children are lacking.

Head lice infestation: single drug versus combination therapy with one percent permethrin and trimethoprim/sulfamethoxazole. Hipolito RB, Mallorca FG, Zuniga-Macaraig ZO, et al. *Pediatrics* 2001; 107: E30.

Permethrin (1%) and trimethoprim (10 mg/kg/day divided BID)–sulfamethoxazole (TMP–SMX) cured 38 of 40 (95%) subjects by week 2. TMP–SMX monotherapy was 83% effective, and permethrin monotherapy was 79.5% effective.

Efficacy of the LouseBuster, a new medical device for treating head lice (Anoplura: Pediculidae). Bush SE, Rock AN, Jones SL, et al. *J Med Entomol* 2011; 48: 67–72.

LouseBuster is a medical device designed to kill head lice in all life stages by delivering heated air (59 ± 1.5°C) at two to three times greater airflow than a regular blow dryer. After 30-min treatment, mortality of lice and eggs was ≈94% for both experienced and novice operators.

PEDICULOSIS CORPORIS

Management Strategy

Because body lice live in the seams of clothing, treatment revolves around laundering of clothes and bedding in high heat (>60°C) for at least 10 minutes. Infested mattresses should be abandoned for 3 weeks. Given that resistance patterns in head lice follow those of body lice, topical malathion, carbaryl, and permethrin are good first choices. Oral ivermectin is another alternative. All household contacts should be treated. Patients should

be monitored for symptoms of louseborne illnesses, specifically epidemic typhus (*Rickettsia prowazekii*), relapsing fever (*Borrelia recurrentis*), and trench fever (*Bartonella quintana*).

First-Line Therapies

• Laundering of clothes and bedding	E
• Personal hygiene	E
• Malathion 0.5% lotion	E
• Permethrin 5% cream	E
• Oral ivermectin	B

Human lice and their management. Burgess IF. Adv Parasitol 1995; 36: 271–342.

A comprehensive review of human lice is provided. For body lice, laundering of clothing is stressed, and the use of pediculicides on the patient is questioned. In mass eradication, fomites can be dusted with malathion or permethrin.

Given the safety of topical therapy, two treatments applied for 8–12 hours 1 week apart outweigh the risk of stray lice on the host reestablishing infestation.

Oral ivermectin in the treatment of body lice. Foucault C, Ranque S, Badiaga S, et al. J Infect Dis 2006; 193: 474–6.

Administration of three doses of oral ivermectin 12 mg with a 7-day interval decreased the prevalence of subjects infested with body lice from 84.9% to 18.5% over a 14-day period. However, this effect was not sustained on day 45 after treatment. More studies need to be conducted to evaluate the efficacy of oral ivermectin.

PEDICULOSIS PUBIS

Management Strategy

Crab lice commonly affect pubic (mons and perianal), thigh, chest, and axillary hair, eyelashes, and, rarely, scalp hair. Pediculicide should be applied to these areas to ensure eradication, and repeat application is recommended after 7 days. Eyelash infestation should be treated separately (see later). Household contacts and sexual partners of the prior month should be treated. Fomites should be laundered as for head lice. Screening for other sexually transmitted diseases is advised.

First-Line Therapies

• Malathion 0.5% lotion	E
• Permethrin 1% crème rinse	B
• Permethrin 5% cream	E
• Pyrethrin 0.33% with piperonyl butoxide shampoo	E
• Oral ivermectin 200 mcg/kg/day	E

Scabies and pediculosis pubis: an update of treatment regimens and general review. Leone PA. Clin Infect Dis 2007; 44 (Suppl 3): S153–9.

A comprehensive review of scabies and pediculosis pubis is provided. No significant treatment failure of pediculosis pubis has been reported since 1996. One study reported in vitro pubic lice resistance to pyrethrins; however, it was susceptible to permethrin 5% lotion. Lindane 1% shampoo is no longer recommended due to its toxicity.

PHTHIRIASIS PALPEBRARUM

Management Strategy

Phthiriasis palpebrarum is an infestation of the eyelashes by crab lice. In children, the infested mother is often the source of infestation. Patients should be treated with application of either permethrin 1% lotion for at least 10 minutes or an occlusive ointment such as petroleum jelly twice a day for 10 days. Alternatives include yellow mercuric oxide, physostigmine 1% eye ointment, and mechanical removal. Other second-line therapies are listed below. Treatment of household and sexual contacts and fomites is warranted.

First-Line Therapies

• Petroleum jelly	E
• Permethrin 1% lotion	E
• Yellow mercuric oxide 1% ointment	B
• Physostigmine 0.25% or 1% ointment	E
• Mechanical lice and nit removal	E

Yellow mercuric oxide: a treatment of choice for phthiriasis palpebrarum. Ashkenazi I, Desatnik HR, Abraham FA. Br J Ophthalmol 1991; 75: 356–8.

Yellow mercuric oxide 1% ointment was applied four times daily for 14 days in 35 patients with phthiriasis palpebrarum. Complete eradication of lice and eggs was reported.

Pediculosis ciliaris. Chin GN, Denslow GT. J Pediatr Ophthalmol Strabismus 1978; 15: 173–5.

Physostigmine 1% ointment applied to eyelid margins twice a day for 14 days is reported. Other suggestions for therapy include (1) thick application of petroleum jelly twice a day for 8 days; (2) mechanical removal of lice and nits with forceps and cotton-tipped swabs followed by application of yellow oxide of mercury 1–2% ointment twice a day for 1 week; or (3) cryotherapy.

Second-Line Therapies

• Oral ivermectin	E
• Cryotherapy	E
• Argon laser	E
• Malathion 1% aqueous shampoo	E
• Fluorescein solution	E

Oral ivermectin therapy for phthiriasis palpebrum. Burkhart CN, Burkhart CG. Arch Ophthalmol 2000; 118: 134–5.

Four patients were cured of phthiriasis palpebrarum after two doses of oral ivermectin 200 mcg/kg spaced 1 week apart.

Other studies have shown success with doses spaced 2 weeks apart.

Phthirus pubis infestation of the eyelids. Rundle PA, Hughes DS. Br J Ophthalmol 1993; 77: 815–6.

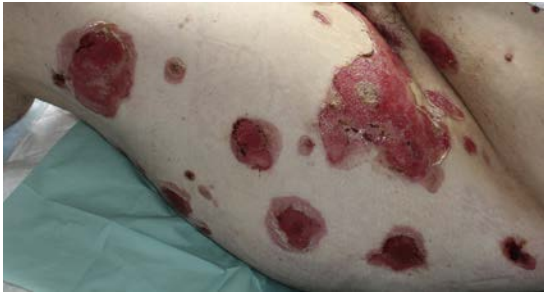
Malathion 1% aqueous shampoo applied to lid margins for 5 minutes on day 0 and day 2 resulted in complete resolution of lash infestation 2 weeks later.

A new treatment of phthiriasis palpebrarum. Mathew M, D'Souza P, Mehta DK. Ann Ophthalmol 1982; 14: 439–41.

A single application of 20% fluorescein was demonstrated to kill lice and nits upon contact.

Pemphigus

Alexandre Lemieux, Pascal Joly



Pemphigus is a severe autoimmune blistering disease that affects the skin and mucosa and includes three main variants: pemphigus vulgaris; pemphigus foliaceus; and paraneoplastic pemphigus. It is caused by the production of autoantibodies directed against epidermal adhesion proteins, mostly desmoglein 1 and desmoglein 3. On histology, it is characterized by the loss of cell-to-cell adhesion (acantholysis) that induces intraepidermal blisters. The clinical hallmark is a flaccid vesicle or bullae of the oral mucous membrane and/or the skin that leads to an erosion. When untreated, it can lead to extensive erosive areas and have a high rate of morbidity and mortality, which are now mostly associated with treatment side effects.

MANAGEMENT STRATEGY

Very few randomized controlled trials (RCT) are available for pemphigus given the rarity of the disease, and guidelines or recommendations are mostly based on experts' opinions and consensus. The initial investigation should always include a thorough evaluation of the patient's medications to exclude a drug-induced pemphigus. Pemphigus treatments must be adapted to the patient's comorbidities and initial disease extent.

Management can be divided in two important phases: (1) induction of remission and (2) maintenance of remission. The objective in the initial phase is to control disease activity, which is reached when no new lesions are forming and existing lesions are starting to heal. The consolidation phase then follows, during which the initial dose of treatment is maintained until no new blisters have formed for 2 weeks and approximately 80% of the established lesions have healed. Then, the maintenance phase starts during which treatments are progressively tapered to reach complete remission on minimal therapy, then off therapy, while minimizing the risk of relapse and side effects. Systemic corticosteroids (CS) remain the mainstay of treatment for pemphigus. They are most often combined with adjuvant conventional immunosuppressants or rituximab. CS generally act rapidly, within 3–4 weeks, to control the disease (usually more rapidly on skin lesions than on mucosal lesions). Conversely, immunosuppressive drugs need a 2–3-month delay to be effective during the maintenance phase. They are usually maintained for a duration of between 12 and 36 months according to patient's clinical response.

Oral corticosteroids are generally prescribed as prednisone/prednisolone 0.5–1 mg/kg/day for mild-to-moderate pemphigus and 1–1.5 mg/kg/day for severe pemphigus. When the disease control is achieved, several guidelines suggest decreasing prednisone dose by 25% every 2 weeks until 20 mg/day, then by 2.5 mg every week until 10 mg/day. No clear recommendations exist in the literature on the best way of tapering prednisone under 10 mg/day. Most clinicians recommend tapering prednisone dose from 1 mg every 3–4 weeks while others recommend a more rapid tapering using 5 mg steps, especially in patients who do not have serum antidesmoglein antibodies anymore. The exact attitude toward CS withdrawal in patients in complete remission on minimal therapy (defined as a dose of prednisone < 10 mg/day for at least 2 months) is still not defined. Persistent negative or low level of autoantibodies measured by enzyme-linked immunosorbent assay (ELISA) are good indicators that immunosuppression can be further tapered. Three options may be considered beyond 0.1 mg/kg/day:

- Slow tapering of 1 mg per 3–4 weeks until complete withdrawal
- Discontinuing CS, in particular in patients with no detectable circulating autoantibodies
- Maintaining a minimal dose of CS (usually between 3 and 6 mg/day), in particular in patients with persistent circulating antidesmoglein autoantibodies

Rituximab (RTX), an anti-CD20 monoclonal antibody, is the recommended first-line immunosuppressant, and is generally prescribed using the rheumatoid arthritis regimen with 1000 mg intravenous (IV) on days 0 and 14, with possible maintenance IV infusions of 500–1000 mg at 12 and 18 months. Lately, the usefulness of maintenance infusions at 6 months has been shown in patients who have not reached complete remission at that time point, or in those with an initially severe pemphigus. The lymphoma protocol using a 375 mg/m² weekly dose for 4 weeks has also been used in several cases, but not tested in any RCT. When RTX is used, the 0.5 mg/kg/day starting dose of prednisone can be tapered over 3 months for moderate pemphigus. Patients with severe pemphigus are treated with a starting prednisone dose of 1 mg/kg/day, which is tapered over 6 months. In a recent clinical trial (NCT02383589), RTX was shown to be superior to mycophenolate mofetil (MMF). The rate of sustained complete remission at 12 months was 40% in the RTX group, compared with 9% in the MMF group ($p < 0.0001$). The secondary end point, including the total cumulative dose of corticosteroids, the rate of relapse, and the improvement in the quality of life, were all in favor of RTX. Finally, patients initially treated with RTX and who have presented with relapses have been shown to be efficiently re-treated with repeated cycles of RTX using the same initial dosage.

In second-line treatment, or when RTX is contraindicated or unavailable, *mycophenolate mofetil* (MMF) or *azathioprine* (AZA) can be used as an adjuvant immunosuppressant with systemic CS. MMF is generally prescribed at 2–3 g/day, with an adjustment necessary in patients with renal failure. When this form is not tolerated, its active metabolite, *mycophenolic acid* 720–1080 mg twice daily may be used. MMF is sometimes preferred over AZA, because it has a better safety profile, especially a lower liver toxicity. When used, AZA is prescribed at 2–3 mg/kg/day (introduce at 50 mg/day) and may be lowered at 1 mg/kg/day in case of reduced thiopurine methyltransferase activity and renal failure. This immunosuppressant has a better steroid-sparing effect than MMF but would be slightly less effective for reaching disease control.

For initially severe or refractory cases, *high-dose intravenous immunoglobulins* (IVIG), *immunoadsorption*, or *pulsed IV corticosteroids* may be used. The latter is used as *methylprednisolone* 500–1000 mg/day for 3–5 consecutive days and should be given

over 2–3 hours under cardiac monitoring. *High-dose IVIG* are prescribed at 2 g/kg given over 3–5 days, and can be repeated monthly if needed. This treatment has the advantages of acting quickly, not being immunosuppressive, and could even be a first-line treatment in initially severe and extensive cases of pemphigus. This treatment is very expensive and may have severe side effects, such as aseptic meningitis. *Immunoadsorption* is an extracorporeal apheresis that selectively removes circulating IgG and may be used when available to rapidly reduce the level of circulating antibodies. It is generally performed over 3–4 days to prevent a rebound increase in the circulating antibodies level and can be repeated every month when needed. *Plasmapheresis*, on the other hand, is generally no longer recommended. This method also removes clotting factors and plasma proteins, and was shown to significantly increase the risk of serious adverse events.

When all the other options mentioned earlier are ineffective or contraindicated, *cyclophosphamide* or *methotrexate* (MTX) can be used as third-line agents. *Cyclophosphamide* can be prescribed as a daily oral dose of 1–2 mg/kg/day (usually 75–150 mg/day), adjusted in case of renal failure, or as a monthly IV pulse therapy at 500–1000 mg/m² IV every 4 weeks. Cyclophosphamide is generally proposed as a third-line option because of its side-effect profile, which includes infertility and risk of bladder carcinoma and hemorrhagic cystitis with long-term exposure. *Methotrexate* may be used at 7.5–20 mg/week orally or subcutaneously. There are in fact only very few studies to suggest that MTX has a CS sparing effect. *Ciclosporin* is no longer recommended in the treatment of pemphigus because a small RCT showed no superiority and more side effects in the group treated with this agent compared with CS alone. Few agents are also rarely used nowadays, but are worth mentioning in case no other options are available and include *chlorambucil*, *dapsone*, *sulfasalazine*, and *tetracycline* in milder cases.

Specific Investigations

- Drug history to rule out a drug-induced pemphigus
- Biopsy of lesional skin for routine histology
- Biopsy of perilesional skin for direct immunofluorescence (DIF) microscopy
- Serological tests: indirect immunofluorescence (IIF) microscopy and/or ELISA for antibodies against desmoglein 1 and 3
- Consider pre-immunosuppressive investigations, including complete blood count, renal and liver function tests, fasting glucose, hepatitis B/C and HIV serology, tuberculosis screening test, and pregnancy test, when appropriate
- Consider baseline osteoporosis screening in patients at risk
- Appropriate malignancy screening test when paraneoplastic pemphigus is suspected
- Consider *herpes simplex* polymerase chain reaction in refractory oral lesions

Drug-induced pemphigus. Ruocco V, Brenner SA, Bialy-Golan V. *Clin Dermatol* 1998; 16(3): 393–7.

An overview of the main drugs capable of inducing pemphigus, which mostly included thiol drugs (captopril, penicillamine), phenol drugs (rifampin, aspirin), and non-thiol/non-phenol drugs (calcium channel blockers, non-steroidal antiinflammatory drugs).

Diagnosis and management of pemphigus: recommendations of an international panel of experts. Murrell DF, Pena S, Joly P, et al. *J Am Acad Dermatol* 2020; 82(3): 575–85. e1.

The diagnosis of pemphigus is based on (1) the clinical presentation; (2) the histopathology; (3) the direct immunofluorescence microscopy; and (4) the serological detection of circulating autoantibodies, either by indirect immunofluorescence microscopy or an ELISA.

Laboratory diagnosis of pemphigus: direct immunofluorescence remains the gold standard. Giurdanella F, Diercks GFH, Jonkman ME, et al. *Br J Dermatol* 2016; 175(1): 185–6.

A retrospective study of 233 patients that evaluated the sensitivity of the IIF on monkey esophagus and ELISA for antibodies against Dsg1 and Dsg3. Using DIF as a gold standard, IIF had an estimated sensitivity of 86%, and ELISA, 89%. Only four patients out of 237 examined had a negative DIF and a positive serological test. With these data, DIF remains a gold standard in the diagnosis of pemphigus, and a complementary serological test may help in the diagnosis and the monitoring of disease.

Clinical markers of herpes simplex virus infection in patients with pemphigus vulgaris. Konda DL, Chandrashekar R, Dhodapkar R, et al. *J Am Acad Dermatol* 2019 Jun 10; S0190-9622(19)30905-3. doi: 10.1016/j.jaad.2019.06.002 [Epub ahead of print].

A total of 60 patients with pemphigus vulgaris and oral lesions were included, and 23 were diagnosed with superimposed herpes simplex virus (HSV) infection. It was noted that the presence of fissures, hemorrhagic crusts, erosions with angulated margins, and linear erosions were clinical signs associated with the presence of HSV, and screening could be considered in these cases.

First-Line Therapies

• Oral corticosteroids	A
• Rituximab	A

First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial. Joly P, Maho-Vaillant M, Prost-Squarioni C, et al. *Lancet* 2017; 389(10083): 2031–40.

A prospective, multicenter, and randomized clinical trial that included 90 patients newly diagnosed with pemphigus vulgaris or foliaceus. This study compared the use of RTX combined with a short course of systemic CS (rituximab 1000 mg on days 0 and 14, with maintenance infusions of 500 mg at months 12 and 18, with prednisone 0.5–1 mg/kg/day tapered over 3–6 months) with a standard systemic CS regimen (prednisone 1–1.5 mg/kg/day tapered over 12–18 months). The primary end point, defined as complete remission off therapy for 2 months at 2 years, was achieved in 89% of patients from the RTX group, compared with 34% in the CS group ($p < 0.0001$). In the RTX group, 24% of patients relapsed during the first year of treatment. Rituximab had an important corticosteroid-sparing effect, reducing to about a third of the dose compared with the standard regimen, and the rate of complications was about 50% lower.

This is the only RCT demonstrating the significant benefit of RTX in the treatment of pemphigus. Based on these findings, the US Food and Drug Administration and the European Agency of Medicine (EMA) approved its use as a first-line treatment for

moderate-to-severe pemphigus. The rheumatoid arthritis regimen is still the most commonly used and recommended by most national and international guidelines in comparison to the lymphoma protocol, but a direct comparison of these two dosing regimens has yet to be done. The rheumatoid arthritis regimen has the advantage of requiring fewer visits, being less expensive, and having very few side effects.

Efficacy of rituximab for pemphigus: a systematic review and meta-analysis of different regimens. Wang HH, Liu CH, Huang YC. *Acta Derm Venereol* 2015; 95(8): 928–32.

This meta-analysis included 30 studies for a total of 578 patients with pemphigus and treated with RTX, including mostly second- or third-line treatments. After one cycle of RTX, 76% of patients achieved complete remission with a 40% rate of relapse during follow-ups. The rheumatoid arthritis and lymphoma regimens showed similar efficacy.

Factors associated with short-term relapse in patients with pemphigus who receive rituximab as first-line therapy: a post hoc analysis of a randomized clinical trial. Mignard C, Maho-Vaillan M, Golinski ML, et al. *JAMA Dermatol* 2020; 156(5): 545–52.

This post hoc analysis of the RITUX3 trial included 47 patients with pemphigus vulgaris or foliaceus and treated with RTX as a first-line agent, including nine patients who relapsed in the first 12 months. A baseline Pemphigus Disease Area Index (PDAI) score >45 and a persistence of antidesmoglein 1 antibodies >20 IU/mL or antidesmoglein 3 antibodies >130 IU/mL at 3 months on ELISA could predict a relapse with a positive predictive value of 50% and a negative predictive value of 94%.

Therapy with rituximab for autoimmune pemphigus: results from a single-center observational study on 42 cases with long-term follow-up. Cianchini G, Lupi F, Corona R, et al. *J Am Acad Dermatol* 2012; 67(4): 617–22.

Forty-two patients with pemphigus were included and treated with RTX with rapidly tapered systemic CS. At 6 months, 86% of patients achieved complete remission on or off therapy. Interestingly, patients who were not in complete remission were re-treated with rituximab at 6 months and also reached remission later on with a higher rate than those who were previously in complete remission at that time. A total of 34 relapses was seen in 20 patients, and they were all efficiently re-treated with 500 mg of rituximab.

The optimal dosing and maintenance regimen for rituximab still needs to be studied, but these data show that patients who are not in complete remission at 6 months may benefit from an additional rituximab infusion. With the previously mentioned study, these patients can also be identified with the baseline PDAI and/or the persistence of their antidesmoglein antibodies with an ELISA, and could all benefit from this additional infusion. Relapses in patients treated with rituximab may also be efficiently treated with subsequent rituximab infusions.

First-line treatment of pemphigus vulgaris with a combination of rituximab and high-potency topical corticosteroids. Ingen-Housz-Oro S, Valeyrie-Allanore L, Cosnes A, et al. *JAMA Dermatol* 2015; 151(2): 200–3.

Five female patients with pemphigus vulgaris and absolute contraindications to systemic CS were successfully treated with RTX and topical CS, with a mean time to healing of 15 weeks. In these specific patients, RTX could possibly be used as systemic monotherapy.

Second-Line Therapies

• Mycophenolate mofetil or mycophenolic acid	B
• Azathioprine	B
• High-dose intravenous immunoglobulins	B
• Immunoabsorption	D
• Pulsed intravenous corticosteroids	D

The role of adjuvant therapy in pemphigus: a systematic review and meta-analysis. Atzmony L, Hodak E, Leshem YA, et al. *J Am Acad Dermatol* 2015; 73(2): 264–71.

This meta-analysis included 10 RCT with a total of 559 patients with pemphigus who were all treated with adjuvants including azathioprine, MMF, cyclophosphamide, ciclosporin, IVIG, plasma exchange, or infliximab. Collectively, they lowered the risk of relapse by 29%, but did not show any increase in the rate of complete remission compared with systemic corticosteroids alone. Azathioprine and cyclophosphamide had a better steroid-sparing effect than MMF, and IVIG was the only adjuvant that independently increased the rate of disease control.

AZA and MMF are the two most common immunosuppressive adjuvants used in second-line treatment, or when RTX is unavailable or contraindicated. AZA is prescribed at 2–3 mg/kg/day (usually introduced at 50 mg/day), and a lower dose of 1 mg/kg/day should be used in case of reduced thiopurine methyltransferase (TPMT) activity and/or renal failure. MMF is prescribed at 2–3 g/day with an adjustment in case of renal failure. Doses can be optimized by the measure of the area under the curve if there is limited response. In case of intolerance, its active metabolite, mycophenolic acid, may be used. Its dose is usually 720–1080 mg twice daily.

A comparison of azathioprine and mycophenolate mofetil as adjuvant drugs in patients with pemphigus: a retrospective cohort study. Sukanjanapong S, Thongtan D, Kanokrunge S, et al. *Dermatol Ther (Heidelb)* 2020; 10(1): 179–89.

A retrospective study that included 62 patients with pemphigus, including 37 treated with prednisolone and azathioprine, and 25 with prednisolone and MMF. Azathioprine was started at a mean initial dose of 0.83 mg/kg/day, which was then titrated up to a mean maximum dose of 1.41 mg/kg/day. Patients who were treated with MMF had a mean initial dose of 910 mg/day, which was then titrated up to a mean maximum dose of 1530 mg/day. The rate of complete remission on therapy was similar in both groups with, respectively, 73% and 72%, but the median time to reach it was significantly lower in the MMF group with 7.3 months in comparison to 12.5 months in the azathioprine group ($P=0.019$). In this study, MMF also had a slightly better steroid-sparing effect.

A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of pemphigus. Beissert S, Werfel T, Frieling U, et al. *Arch Dermatol* 2006; 142(11): 1447–54.

This prospective, multicenter, non-blinded, and randomized clinical trial included 33 patients with pemphigus vulgaris and seven with pemphigus foliaceus. They were assigned to receive either oral methylprednisolone and azathioprine or oral methylprednisolone and MMF. In 13 (72%) of 18 patients with pemphigus receiving oral methylprednisolone and azathioprine, complete remission was achieved after a mean 74 days compared with 20 (95%) of 21 patients receiving oral methylprednisolone

and MMF in whom complete remission occurred after a mean 91 days. In six (33%) of 18 patients treated with azathioprine, severe adverse effects were documented in contrast to four (19%) of 21 patients who received MMF.

Azathioprine and MMF can be considered as second-line agents with similar efficacy in the treatment of pemphigus in terms of reaching disease control, preventing relapse, and lowering the needed dose of corticosteroids in general, but MMF may be preferred because of its favorable side effect profile over azathioprine. The side effects of the latter include a risk of life-threatening myelosuppression, which can be lowered if the dose is adjusted to the TPMT activity.

A randomized double-blind trial of intravenous immunoglobulin for pemphigus. Amagai M, Ikeda S, Shimizu H, et al. *J Am Acad Dermatol* 2009; 60(4): 595–603.

A prospective, multicenter, randomized, and double-blind clinical trial that included 61 patients with pemphigus vulgaris or foliaceus who did not respond to more than 20 mg/day of prednisolone. They evaluated the effect of a single cycle of intravenous immunoglobulins by randomizing patients in three groups: 400, 200, or 0 mg/kg/day administered over 5 consecutive days. The time-to-escape from the protocol was a few weeks longer in the 400 mg/kg/day group, but not in the 200 mg/kg/day group compared with the 0 mg/kg/day ($p < 0.001$) group, and a dose-response was noted among the three groups ($p < 0.001$).

High-dose IVIG is a safe alternative in refractory cases of pemphigus, and may also be considered in initially severe and extensive cases. IVIG are generally combined with other, more conventional treatments, including corticosteroids and rituximab.

Protein A immunoadsorption: a novel and effective adjuvant treatment of severe pemphigus. Schmidt E, Klinker E, Opitz A, et al. *Br J Dermatol* 2003; 148(6): 1222–9.

Five patients included in this series were treated with staphylococcal protein A immunoadsorption combined with methylprednisolone 0.5 mg/kg/day and tapered. Three patients were refractory to previous usual treatments. A dramatic clinical improvement was seen in all patients in 2 weeks.

Combined treatment with immunoadsorption and rituximab leads to fast and prolonged clinical remission in difficult-to-treat pemphigus vulgaris. Behzad M, Möbs C, Kneisel A, et al. *Br J Dermatol* 2012; 166(4): 844–52.

This retrospective study included 10 patients with difficult-to-treat pemphigus vulgaris. They were all treated with a combination of systemic CS slowly tapered over 12 months, RTX prescribed using either the rheumatoid arthritis or lymphoma protocol, and immunoadsorption. Six months after the initial treatment, eight patients were in complete remission on therapy, and one patient had a partial response.

Immunoadsorption, when available, is mostly used in conjunction with RTX and/or other, more conventional treatments. In case of severe and extensive pemphigus, it may help to rapidly reduce the level of circulating autoantibodies, but more controlled and comparative studies are needed.

High-dose intravenous 'pulse' methylprednisone in the treatment of severe oropharyngeal pemphigus: a pilot study. Mignogna MD, Lo Muzio L, Ruoppo E, et al. *J Oral Pathol Med* 2002; 31(6): 339–44.

This series included 12 patients with severe oropharyngeal pemphigus vulgaris. To gain a rapid clinical remission, they were treated with pulsed IV methylprednisolone 30 mg/kg (maximum

1000 mg per dose) repeated for 3–5 consecutive days. All patients responded within 1 week following the initial treatment. Complete remission was noted in all patients after the second or third cycle of pulse and no severe adverse events happened.

There is still no evidence showing that the use of pulsed IV methylprednisolone could allow a better rate of complete remission in comparison with standard oral corticosteroids. However, this strategy may be useful to rapidly reach disease control in initially severe cases, or when the oral dose needed to control the disease is above 100 mg/day.

Randomized controlled trial of adjuvant oral dexamethasone pulse therapy in pemphigus vulgaris: PEMPULS trial. Mentink LE, Mackenzie MW, Toth GG, et al. *Arch Dermatol* 2006; 142(5): 570–6.

This prospective, randomized controlled trial included only 20 patients. They all were treated with oral prednisolone 80 mg/day tapered over 19 weeks and azathioprine 3 mg/kg/day and were randomized to receive either oral dexamethasone in 3000 mg pulses (DP group) or placebo (PP group). In the DP group, 73% of patients achieved remission, compared with 90% in the PP group. The addition of pulsed oral dexamethasone did not add any benefit. There was a major lack of statistical power in this study.

Third-Line Therapies

• Cyclophosphamide (oral or pulsed intravenous)	B
• Methotrexate	D
• Topical or intralesional corticosteroids	B
• Intralesional rituximab	B

Oral cyclophosphamide for treatment of pemphigus vulgaris and foliaceus. Cummins DL, Mimouni D, Anhalt GJ, et al. *J Am Acad Dermatol* 2003; 49(2): 276–80.

In this study, 23 patients with refractory pemphigus were treated with oral cyclophosphamide; a complete response was obtained in 19 with a median time of 8.5 months.

Cyclophosphamide remains a third-line agent because of the higher rate and severity of side effects, but can efficiently be used in pemphigus cases refractory to the usual adjuvant immunosuppressant. It can be used as a daily oral dose of 1–2 mg/kg/day (usually 75–150 mg/day), with an adjustment necessary in case of renal failure, older age, anemia, leucopenia, or lymphopenia, and will be tapered over 12–24 months.

Pulsed intravenous cyclophosphamide and methylprednisolone therapy in refractory pemphigus. Saha M, Powell AM, Bhogal B, et al. *Br J Dermatol* 2010; 162: 790–7.

The 21 patients included in this study were presenting with pemphigus refractory to prednisone combined with azathioprine or MMF. They were treated with a monthly pulsed intravenous (IV) methylprednisolone and cyclophosphamide regimen. Nine of them had at least a good response and four patients finally achieved complete remission, but with a higher rate of side effects.

This pulsed therapy may be prescribed as IV cyclophosphamide 500–1000 mg/m² every 4 weeks with systemic CS. The latter may be prescribed as a daily oral dose, or IV methylprednisolone 500–1000 mg/day (or equivalent dose of dexamethasone) for 3–5 consecutive days and over 2–3 hours under cardiac monitoring.

Methotrexate in the treatment of pemphigus vulgaris: experience in 23 patients. Tran KD, Wolverton JE, Soter NA. *Br J Dermatol* 2013; 169(4): 916–21.

This retrospective study included 23 patients treated with methotrexate, combined or not with systemic corticosteroids. Significant improvement was noted in 91% of patients without significant side effects.

MTX may be prescribed as a weekly dose of 7.5–20 mg orally or subcutaneously and tapered as the other adjuvants according to the clinical response. However, this study does not clearly demonstrate the efficacy of MTX as adjuvant therapy. The use of MTX as adjuvant therapy in pemphigus is no longer recommended in the recently revised European guidelines.

Methotrexate is an effective and safe adjuvant therapy for pemphigus vulgaris. Baum SS, Greenberger L, Samuelov M, et al. *Eur J Dermatol* 2012; 22(1): 83–7.

In this retrospective study, 30 patients included were treated with 15 mg of MTX per week. Among patients with a moderate-to-severe pemphigus, 84% improved, with side effects seen in 13% of patients.

Comparison between the efficacy of intralesional rituximab versus intralesional triamcinolone in the treatment refractory pemphigus vulgaris lesions: a randomized clinical trial.

Iraji F, Danesh F, Faghihi G, et al. *Int Immunopharmacol* 2019; 73: 94–7.

This clinical trial included 21 patients with pemphigus vulgaris in whom two refractory lesions were respectively assigned to intralesional triamcinolone or RTX. They received injections twice, 1 month apart. Both approaches were as effective in treating the lesions with no side effects.

Intralesional rituximab in the treatment of refractory oral pemphigus vulgaris. Vinay K, Kanwar AJ, Mittal A, et al. *JAMA Dermatol* 2015; 151(8): 878–82.

This series included three patients treated with two intralesional injections of RTX 5 mg/cm² 1 month apart, and all patients improved.

Ineffectiveness of cyclosporine as an adjuvant to corticosteroids in the treatment of pemphigus. Ioannides D, Chrysomallis F, Bystryn JC. *Arch Dermatol* 2000; 136(7): 868–72.

This study included 33 consecutive patients hospitalized for pemphigus (29 pemphigus vulgaris and four pemphigus foliaceus) that were treated either with prednisone alone or prednisolone or prednisolone plus cyclosporin 5 mg/kg once a day. The response was similar in both groups, but the rate of side effects was significantly higher in the cyclosporin group.

Perforating dermatoses

Avi Bitterman, Mark G. Lebwohl



The perforating dermatoses are a varied group of conditions characterized by the transepidermal elimination of dermal material. Four primary conditions are included in the discussion of the perforating disorders:

- Reactive perforating collagenosis (RPC), which is characterized by the transepidermal elimination of collagen
- Elastosis perforans serpiginosa (EPS), characterized by transepidermal extrusion of elastic material
- Perforating folliculitis, in which epidermal perforation involves hair follicles
- Kyrle disease, in which dermal connective tissue perforates through the epidermis

MANAGEMENT STRATEGY

Definitive diagnosis of the perforating disorders depends on the demonstration of transepidermal elimination on skin biopsy. Differentiation between the different forms of perforating disorders can be accomplished by Masson trichrome stains for collagen (RPC), Verhoeff–van Gieson stains for elastic tissue (EPS), and step-sectioning to look for hair follicles (perforating folliculitis). Differentiation between these various disorders may be important, as EPS is associated with other diseases such as pseudoxanthoma elasticum, Down syndrome, osteogenesis imperfecta, Ehlers–Danlos syndrome, Rothmund–Thomson syndrome, Marfan syndrome, and penicillamine treatment. RPC is commonly associated with diabetes and chronic kidney disease.

Acquired perforating dermatoses have been associated with several medications, including sorafenib, natalizumab, azathioprine, and telaprevir. In particular, acquired RPC has occurred in patients treated with indinavir, erlotinib, sorafenib, and sirolimus. Perforating folliculitis has been reported in patients treated with tumor necrosis factor- α blockers, nilotinib, lenalidomide, and sorafenib; a patient with cystic fibrosis; and a patient who had previously suffered from varicella in the same distribution as the perforating folliculitis lesions.

Management of the perforating diseases involves determination of underlying etiologies. Most often, conditions such as diabetes mellitus and renal failure will be known to the patient who presents with perforating skin lesions. When the underlying cause is not apparent, serum chemistry for renal and liver function tests and oral glucose tolerance test or hemoglobin A_{1C} may be helpful.

Once the diagnosis of underlying diseases is ascertained, treatment is directed at associated symptoms. Pruritus can be managed initially with *topical or intralesional corticosteroids, topical anesthetics, and menthol*, as well as *oral antihistamines*, but the latter agents are usually not sufficiently effective. Minimizing pruritus is important because many of the perforating disorders typically exhibit a Koebner phenomenon, meaning that lesions develop in traumatized or scratched skin. Topical antipruritic agents such as menthol, phenol, or camphor and topical anesthetics such as lidocaine and pramocaine are useful. *Topical doxepin hydrochloride* or oral antihistamines may also be of some benefit. Trimming the fingernails to minimize trauma to the skin and avoidance of scratching are key elements of treatment. *Topical tretinoin* and *topical tazarotene* have been shown to be effective for some patients. For those patients whose condition is exacerbated by sun exposure, sunscreens may be helpful. Conversely, in patients with renal disease ultraviolet B (UVB) is dramatically effective for pruritus and has been reported to benefit perforating skin lesions as well. If UVB and topical retinoids are ineffective, *oral retinoids, allopurinol, or antibiotics* can be tried. More recently, case reports have detailed improvement with *amitriptyline* (10–25 mg daily for several weeks), topical *tacrolimus*, and topical vitamin D analogs, including *tacalcitol* and *maxacalcitol*.

Specific Investigations

- Skin biopsy with Masson trichrome stains and Verhoeff–van Gieson stains
- Serum blood urea nitrogen, creatinine, amino alanine transferase, aspartate amino transferase, alkaline phosphatase, bilirubin, uric acid
- Serum glucose, oral glucose tolerance test, or hemoglobin A_{1C}
- Hepatitis C virus antibodies
- Thyroid function tests

Clinicopathological features of 25 patients with acquired perforating dermatosis. Akoglu G, Emre S, Sungu N, et al. Eur J Dermatol 2013; 23: 864–71.

Of the 25 patients with acquired perforating dermatosis, 17 (68%) had acquired RPC, 7 patients (28%) had perforating folliculitis, and 1 patient (4%) had Kyrle disease. The most commonly associated disease was diabetes mellitus (12 patients, 48%); 5 patients (20%) had chronic kidney disease, 2 patients had thyroid disease, and 1 patient had hepatitis C.

First-Line Therapies

• Tretinoin 0.1%	D
• Tazarotene gel 0.1%	E
• Broadband UVB	E
• Narrowband UVB	D

Familial reactive perforating collagenosis: a clinical, histopathological study of 10 cases. Ramesh V, Sood N, Kubba A, et al. J Eur Acad Dermatol Venereol 2007; 21: 766–70.

Ten patients with familial RPC responded to topical retinoic acid. The authors suggested that sunscreens may benefit patients whose lesions develop in the summer.

Familial RPC may be a distinct entity that occurs in infancy or early childhood. It is of interest that sunlight might play a role in the development of this condition, as phototherapy is used therapeutically in adults with perforating disorders.

Tazarotene is an effective therapy for elastosis perforans serpiginosa. Outland JD, Brown TS, Callen JP. Arch Dermatol 2002; 138: 169–71.

Two patients with EPS responded to daily treatment with 0.1% tazarotene gel. A 22-year-old woman had been treated unsuccessfully with liquid nitrogen cryotherapy, topical tretinoin, oral isotretinoin, and carbon dioxide (CO₂) laser surgery. A 56-year-old woman had failed to respond to cryotherapy, corticosteroids, tretinoin, and triamcinolone acetonide. Both patients were treated with tazarotene. The skin condition of the 22-year-old greatly improved, and that of the 56-year-old improved moderately.

Successful treatment of Kyrle disease with narrowband ultraviolet B. Matsuzaki Y, Yokoyama S, Rokunohe A, et al. J Dermatol 2017; 44: 721–2.

A 36-year-old woman with Kyrle disease was treated with narrowband UVB. After 24 exposures (cumulative dose: 25,700 mJ/cm²), pruritus resolved with improvement of lesions at 6 months.

In another case report, an 8-year-old boy with familial RPC received narrowband UVB three times a week. After 25 exposures (cumulative dose: 38,150 mJ/cm²) the lesions completely regressed with residual scars and pigmentation changes.

Broadband UVB is also a well-established modality for uremic pruritus. Because many patients with perforating diseases have associated renal failure, UVB phototherapy may dramatically benefit pruritus and reduce the number of skin lesions.

Second-Line Therapies

• Allopurinol	D
• Isotretinoin	E
• Psoralen and ultraviolet A (PUVA)	E
• Acitretin	E

Acquired reactive perforating collagenosis: four patients with a giant variant treated with allopurinol. Hoque SR, Ameen M, Holden CA. Br J Dermatol 2006; 154: 759–62.

Four patients failed topical and oral corticosteroids and antibiotics and were started on allopurinol 100 mg once daily despite normal serum uric acid levels. Three of the four experienced dramatic improvement at 2–4 months, with prevention of new lesions, a reduction in pruritus, and clearance of existing lesions. The fourth patient died before the follow-up examination.

In another case report, a patient treated with 100 mg allopurinol daily had full resolution of pruritus and lesions within 4 weeks, without recurrence at 14 months' follow-up. Numerous anecdotal reports have documented improvement of perforating disorders with allopurinol treatment, regardless of whether uric acid levels are elevated or normal.

D-penicillamine-induced pseudo-pseudoxanthoma elasticum and extensive elastosis perforans serpiginosa with excellent response to acitretin. Chisti MA, Binamer Y, Alfadley A, et al. Ann Saudi Med 2019; 39: 56–60.

A 37-year-old man with D-penicillamine-induced EPS was treated with oral acitretin 25 mg/day for 2 weeks followed by

30 mg/day, and experienced almost total clearance of lesions at 9 weeks. A maintenance dose of 25 mg every other day was required to prevent flaring.

Kyrle's disease effectively treated with oral isotretinoin. Maurelli M, Gisondi P, Girolomoni G. J Dermatol Treat 2018; 29: 630–2.

A 63-year-old patient with Kyrle disease refractory to treatment with systemic corticosteroids and narrowband UVB was treated with oral isotretinoin 20 mg/day for 6 months followed by 10 mg/day for 4 months once remission was complete. Lesions remained clear at 9 months' follow-up.

Reactive perforating collagenosis responsive to PUVA. Serano G, Aliaga A, Lorente M. Int J Dermatol 1988; 27: 118–9.

A 21-year-old woman with a 10-year history of RPC was treated with PUVA four times per week. Improvement was noted in 2 weeks. Lesions stopped developing after completion of PUVA therapy (326 J/cm² total), without any new lesions in over a year of follow-up.

Third-Line Therapies

• Doxycycline	E
• Oral metronidazole	E
• Oral clindamycin	E
• Oral hydroxychloroquine	E
• Imiquimod	E
• Surgical debridement	E
• Cryotherapy	E
• Cantharidin	E
• Ultrapulse laser	E
• CO ₂ laser	E
• Excimer laser	E
• Photodynamic therapy	E
• Transcutaneous electrical nerve stimulation (TENS)	E
• Amitriptyline	E
• Tacrolimus 0.1%	E
• Tacalcitol, maxacalcitol	E
• Benzoyl peroxide + topical steroid	E

Successful treatment of acquired reactive perforating collagenosis with doxycycline. Brinkmeier T, Schaller J, Herbst RA, et al. Acta Derm Venereol 2002; 82: 393–5.

An 87-year-old woman with acquired RPC responded to treatment with oral doxycycline 100 mg daily for 2 weeks. Most lesions healed within 10 days.

Regression of skin lesions of Kyrle's disease with metronidazole in a diabetic patient. Khalifa M, Slim I, Kaabia N, et al. J Infect 2007; 55: e139–40.

Metronidazole 500 mg twice daily for 1 month completely cleared lesions of Kyrle disease. Lesions did not recur during 12 months of follow-up.

Regression of skin lesions of Kyrle's disease with clindamycin: implications for an infectious component in the etiology of the disease. Kasiakou SK, Peppas G, Kapaskelis AM, et al. J Infect 2005; 50: 412–6.

A patient with old, uninfamed hyperkeratotic lesions of Kyrle disease and newer inflamed lesions was successfully treated with a combination of oral clindamycin and surgical removal of large lesions.

Sirolimus-induced inflammatory papules with acquired reactive perforating collagenosis. Lübke J, Sorg O, Malé PJ, et al. *Dermatology* 2008; 216: 239–42.

A patient with acquired RPC attributed to sirolimus after liver transplantation responded to oral hydroxychloroquine 200 mg daily with continuation of sirolimus. Skin remained clear for 6 months, despite continuation of hydroxychloroquine and sirolimus.

Imiquimod therapy for elastosis perforans serpiginosa. Kelly SC, Purcell SM. *Arch Dermatol* 2006; 142: 829–30.

A 14-year-old girl with EPS was treated with imiquimod cream applied nightly for 6 weeks and then three times weekly for 4 weeks. After 10 weeks her skin cleared completely.

A new treatment for acquired reactive perforating collagenosis. Oziemski MA, Billson VR, Crosthwaite GL, et al. *Australas J Dermatol* 1991; 32: 71–4.

A single patient with RPC was successfully treated with surgical debridement and split-skin grafting of the affected areas.

Because skin lesions are often numerous, surgical removal and skin grafting may be impractical.

Elastosis perforans serpiginosa: treatment with liquid nitrogen cryotherapy and review of the literature. Humphrey S, Hemmati I, Randhawa R, et al. *J Cutan Med Surg* 2010; 14: 38–42.

A 13-year-old male with EPS of the face was successfully treated with liquid nitrogen cryotherapy.

Treatment of acquired perforating dermatosis with cantharidin. Wong J, Phelps R, Levitt J. *Arch Dermatol* 2012; 148: 160–2.

Cantharidin was used to successfully treat the acquired perforating dermatosis in a 65-year-old woman with diabetes and chronic renal failure.

Idiopathic elastosis perforans serpiginosa with satisfactory response after 5-ALA photodynamic therapy. Alique-García S, Company-Quiroga J, Horcajada-Reales C, et al. *Photodiagnosis Photodyn Ther* 2018; 21: 55–7.

A 30-year-old was successfully treated with photodynamic therapy using red light (dose: 37 J/cm²) once a month for 4 months with almost complete resolution of lesions, and no new lesions at 1-year follow-up.

Localized idiopathic elastosis perforans serpiginosa effectively treated by the coherent ultrapulse 5000C esthetic laser. Abdullah A, Colloby PS, Foulds IS, et al. *Int J Dermatol* 2000; 39: 719–20.

Portions of lesions of EPS were treated by laser, with complete clearing of treated sites but no changes in untreated sites.

Response of elastosis perforans serpiginosa to pulsed CO₂, Er:YAG, and dye lasers. Saxena M, Tope WD. *Dermatol Surg* 2003; 29: 677–8.

A 17-year-old male presenting with EPS on the neck was treated with CO₂ laser on the right neck and erbium:yttrium aluminum garnet (Er:YAG) laser on the left neck. Only mild improvement of EPS was achieved, and subtle atrophic scarring occurred on the area treated with the CO₂ laser. The patient then received pulsed dye laser therapy on both sides of the neck, resulting in minimal improvement.

Treatment of elastosis perforans serpiginosa with the pin-hole method using a carbon dioxide laser. Yang JH, Han SS, Won CH, et al. *Dermatol Surg* 2011; 37: 524–6.

Conflicting reports concerning the usefulness of the CO₂ laser for EPS suggest that this modality may be useful as a last resort in some, but not all, patients with EPS.

Treatment of acquired reactive perforating collagenosis with a 308-nm excimer laser. Matsui A, Nakano H, Aizu T, et al. *Clin Exp Dermatol* 2016; 41: 820–1.

A 35-year-old man with acquired RPC who did not respond to topical corticosteroids was treated with a 308 nm xenon-chloride laser. Lesions were treated weekly for 10 treatments (cumulative dose: 3900 mJ/cm²). Skin lesions resolved and did not recur at 5 months' follow-up.

Treatment of pruritus of reactive perforating collagenosis using transcutaneous electrical nerve stimulation. Chan LY, Tang WY, Lo KK. *Eur J Dermatol* 2000; 10: 59–61.

A 47-year-old woman and an 85-year-old woman, each of whom had failed to respond to treatment with topical steroids and antihistamines, received TENS therapy for 1 hour daily over the course of 3 weeks. Skin lesions cleared within 3 months of treatment in both patients.

Effective treatment of uremic pruritus and acquired perforating dermatosis with amitriptyline. Yong A, Chong WS, Tey HL. *Australas J Dermatol* 2014; 55: 54–7.

Two patients with a history of chronic kidney disease were diagnosed with acquired perforating dermatosis. The first patient, whose biopsy was consistent with Kyrle disease, received amitriptyline 25 mg daily. Within 1 week, his itch score markedly decreased, and the nodules had flattened. The itch and lesions reappeared after discontinuing amitriptyline but responded to retreatment. The second patient received amitriptyline 10 mg daily, and within 2 weeks, the itching resolved and the excoriated papules healed. His dose was later increased to 25 mg daily when the itch reappeared.

Efficacy of topical tacrolimus for treating Kyrle's disease. Kinoshita M, Ogawa Y, Kawamura T, et al. *J Dermatol* 2017; 44: e81–2.

A 49-year-old male with diabetes and renal failure was diagnosed with Kyrle disease. The patient did not respond to topical corticosteroids but was successfully treated with topical tacrolimus 0.1%.

Tacalcitol in the treatment of acquired perforating collagenosis. Escribano-Stable JC, Domenech C, Matarredona J, et al. *Case Rep Dermatol* 2014; 6: 69–73.

A 65-year-old patient who had failed topical corticosteroids and antihistamines achieved complete remission after 2 months of topical tacalcitol once daily. The lesions returned 4 weeks after finishing treatment but responded to retreatment within 3 weeks.

In a different case report, pruritus and papules resolved after the use of 0.0025% maxacalcitol ointment twice daily (total of 60 g) for 2 months.

Successful treatment of acquired reactive perforating collagenosis with topical benzoyl peroxide: a possible therapeutic action underlying structural and metabolic turnover. Miyanaga M, Oyama N, Sakai Y, et al. *J Dermatol* 2020; 47: e12–4.

Benzoyl peroxide 2.5% combined with an unspecified topical corticosteroid were applied once daily for 7 months to the scalp, neck, and back with improvement of pruritus and of skin lesions.

Perioral dermatitis

Allison Zarbo, Tor Shwayder



Perioral dermatitis is a benign, acneiform, facial eruption of children and young female adults. It commonly affects the perioral area with small, inflammatory papules with or without an eczematous dermatitis with a classic zone of sparing the vermilion border and a burning sensation. It may also affect the perinasal and periorbital areas and as such may be referred to as periorificial dermatitis. Although the etiology is unknown, contributing factors include topical, inhaled, and/or systemic corticosteroids. Other suspected triggers include infectious agents (*Demodex*, *Candida albicans*, fusiform bacteria), fluoride and antitartar toothpaste, cosmetics/moisturizers, sunscreens, dental fillings, orthognathic surgery, chewing gum, hormones (premenstrual flares, oral contraceptives, pregnancy), and atopic dermatitis. Granulomatous periorificial dermatitis is a variant more common in prepubescent children characterized by red-brown inflammatory papules without papulopustules or papulovesicles in the typical distribution that may affect extrafacial areas.

MANAGEMENT STRATEGY

The first step in management of perioral dermatitis is *elimination of triggers such as topical, inhaled, or oral corticosteroids* in addition to any other irritant triggers such as cosmetics or creams. Patients should be counseled on an expected flare after elimination of corticosteroids; thus, a slow taper of reduction in frequency of the corticosteroids or tapering from high to medium to low corticosteroids with the goal of complete elimination. Gentle cleansers and minimal use of topical, bland products should be recommended.

We recommend pursuing topical treatments prior to systemics, but this may be predicated upon severity of disease, age, and quality of life. *Tetracyclines* should not be used in children younger than 8 years of age due to discoloration of teeth and bone. Severe and refractory disease, especially the granulomatous variant, may be treated with *low-dose isotretinoin*.

Specific Investigations

- No investigation is routinely required

First-Line Therapies

• Topical pimecrolimus	A
• Oral tetracyclines	A
• Withdrawal of topical corticosteroids	B
• Topical ivermectin	B
• Topical erythromycin	B
• Topical metronidazole	B
• Topical praziquantel	B

Periorificial dermatitis in children and adolescents. Nguyen V, Eichenfield LF. *J Am Acad Dermatol* 2006; 55: 781–5.

A retrospective chart review with telephone follow-up revealed that of 79 children and adolescents, 72% had a history of topical, inhaled, or systemic steroid exposure. Treatment with topical metronidazole showed improvement on follow-up examination.

There was a high incidence of exposure to topical, inhaled, or systemic corticosteroids prior to onset of periorificial dermatitis in this cohort.

A randomized, double-blind, vehicle-controlled study of 1% pimecrolimus cream in adult patients with perioral dermatitis. Schwarz T, Kreislermaier I, Bieber T, et al. *J Am Acad Dermatol* 2008; 59: 34–40.

A multicenter, randomized, double-blind, parallel group study of 124 adults using pimecrolimus 1% cream twice daily versus vehicle twice daily for 4 weeks with follow-up at 4 and 8 weeks. Rapid improvement was seen with pimecrolimus within the first 2 weeks, with most benefit in patients with previous use of topical corticosteroids. No significant differences were appreciated at 4 weeks.

New indications for topical ivermectin 1% cream: a case series study. Baranńska-Rybak W, Kowalska-Olędzka E. *Adv Dermatol Allergol* 2019; 36: 58–62.

A prospective study of 20 cases of inflammatory facial dermatoses, including eight cases of perioral dermatitis (PD), were treated with topical ivermectin 1% oil-in-water base cream once daily for 1–3 months based on clinical response. The PD patients achieved complete or almost complete clearance in 8 weeks.

Topical metronidazole in the treatment of perioral dermatitis. Veien NK, Munkvad JM, Nielsen AO, et al. *J Am Acad Dermatol* 1991; 24: 258–69.

A prospective, double-blind, multicenter trial of 108 patients were randomized to metronidazole 1% cream compared with oral tetracycline 250 mg twice daily for 8 weeks. Tetracycline was significantly more efficacious than topical metronidazole, but both groups showed improvement.

A topical erythromycin preparation and oral tetracycline for the treatment of perioral dermatitis: a placebo-controlled trial. Weber K, Thurmayr R, Meisinger A. *J Dermatol Treat* 1993; 4: 57–9.

A randomized, prospective study evaluated 33 patients who received topical 1% erythromycin and 35 who received oral tetracycline (tapered from 500 mg twice daily for 10 days to 250 mg

twice daily for 10 days), and 31 who received an oral placebo. Both oral tetracycline and topical erythromycin were superior to placebo at day 20 with similar performance between the two groups.

Topical praziquantel as a new treatment for perioral dermatitis: results of a randomized vehicle-controlled pilot study. Bribeche MR, Fedotov VP, Jillella A, et al. Clin Exp Dermatol 2014; 39(4): 448–53.

A single-blind, vehicle-controlled study with 46 adult patients randomized to praziquantel 3% ointment versus placebo twice daily for 4 weeks demonstrated improvement in the praziquantel group.

Second-Line Therapies

• Topical tetracycline	C
• Topical azelaic acid	C
• Topical clindamycin	C
• Oral ivermectin	C
• Photodynamic therapy	C
• Oral azithromycin	D
• Topical sulfacetamide-sulfur	D

Topical tetracycline in the treatment of perioral dermatitis. Wilson RG. Arch Dermatol 1979; 115: 637.

Thirty patients were treated with topical tetracycline twice daily. After 5–28 days, 80% were completely clear.

Ivermectin therapy for papulopustular rosacea and periorificial dermatitis. Noguera-Morel L, Gerlero P, Torrelo A, et al. J Am Acad Dermatol 2017; 76: 567–9.

Seven patients with PD were treated with either a single dose of 200–250 mcg per kilogram oral ivermectin ($n=3$) or a compound of 1% ivermectin in an oil-in-water base cream applied once a day for 3 months ($n=6$). Overall response to both agents was excellent. Adverse event with topical ivermectin was noted to be transient, mild desquamation in less than half of the patients.

Steroid-induced periorificial dermatitis in children – clinical features and response to azelaic acid. Jansen T, Melnik BC, Schadendorf D. Pediatr Dermatol; 2010; 27: 137–42.

Ten children with periorificial dermatitis were treated with 20% azelaic acid cream twice daily with complete resolution in 4–8 weeks. Three patients had a transient exacerbation between days 2 and 6 of treatment. No recurrences were seen at 2 and 8 months.

Photodynamic therapy for perioral dermatitis. Richey DE, Hopson B. J Drugs Dermatol 2006; 5: 12–6.

A split-face study of 21 patients with topical clindamycin versus four times weekly aminolevulinic acid photodynamic therapy (PDT). Fourteen patients completed the study due to skin irritation in the PDT group. Treatment with PDT revealed a 92.1% clearance compared with 80.9% clearance with topical clindamycin ($P=0.0227$); however, three patients developed treatment-related postinflammatory hyperpigmentation related to PDT.

Pediatric periorificial dermatitis: clinical course and treatment outcomes in 222 patients. Goel NS, Burkhart CN, Morrell DS. Pediatr Dermatol 2015; 32: 333–6.

Retrospective chart review of 222 pediatric patients revealed treatments consisted of oral azithromycin, topical metronidazole, and sodium sulfacetamide lotion. Approximately 94% of the patients had resolution at follow-up visits.

Third-Line Therapies

• Topical adapalene	E
• Topical tacrolimus	E
• Oral metronidazole	E
• Oral erythromycin	E
• Oral isotretinoin	E

Perioral dermatitis successfully treated with topical adapalene. Jansen T. J Eur Acad Dermatol Venereol 2002; 16: 175–7.

Case report of a 32-year-old female with recalcitrant PD treated with adapalene 0.1% gel nightly for 4 weeks with complete resolution. No recurrence at 8 months.

[Perioral dermatitis following treatment with tacrolimus.] Gerber PA, Neumann NJ, Ruzicka T, et al. Hautarzt 2005; 56: 967–8. Article in German.

Case report of a 49-year-old female with recalcitrant PD successfully treated with tacrolimus 0.1% ointment after 4 weeks.

Childhood granulomatous periorificial dermatitis with a good response to oral metronidazole. Rodriguez-Caruncho C, Bielsa I, Fernandez-Figueras MT, et al. Pediatr Dermatol 2013; 30: e98–9.

A 9-year-old girl was treated with oral metronidazole 250 mg twice daily for 1 month with complete resolution. No recurrence at 1 year.

Case of childhood granulomatous periorificial dermatitis in a Korean boy treated by oral erythromycin. Choi YL, Lee KJ, Cho HJ, et al. J Dermatol 2006; 33: 806–8.

Case report of a child with PD treated with erythromycin 500 mg daily for 1 year with resolution.

Identical twins with perioral dermatitis. Weston WL, Morelli JG. Pediatr Dermatol 1998; 15: 144.

Case report of twin children treated 1 month of oral erythromycin with resolution.

Recalcitrant granulomatous periorificial dermatitis with good response to low-dose oral isotretinoin. Rodriguez-Garijo N, Querol-Cisneros E, Tomas-Velazquez A, et al. Pediatr Dermatol 2019; 36: 908–1.

Case report of an 18-year-old female with recalcitrant disease treated with oral isotretinoin alternating daily doses of 10–20 mg with significant improvement after 3 months and complete resolution at 6 months.

Isotretinoin may be considered with recalcitrant cases, specifically for the granulomatous variant.

Peutz–Jeghers syndrome

Chinmoy Bhate, Robert A. Schwartz



Created by Dr. Edward Cowen from <https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/melanocytic-macules-associated-with-peutz-jeghers-syndrome>.

Peutz–Jeghers syndrome (PJS) is a rare autosomal dominant disorder characterized by gastrointestinal polyps, hamartomas, mucocutaneous pigmentation, recurrent abdominal pain from intussusceptions, and an increased risk of intestinal and other malignancies. Clinically and histologically, the pigmented macules of PJS are simple lentiginos. They are typically found on the lips and oral mucosa but may involve epithelium around the eyes, nostrils, and anus; they may also be seen on the dorsum or volar aspect of the hands and feet. These brown to black macules are generally round or oval and 1–5 mm in diameter. They may be irregular in shape and may occasionally manifest with a blue–gray hue.

Most patients have a germline mutation of the serine/threonine kinase 11 (STK11/LKB1) tumor suppressor gene, located at chromosome 19p13.3. A second PJS disease locus exists at 19q13.4. Genetic testing may be useful in equivocal cases as well as in counseling at-risk families.

MANAGEMENT STRATEGY

Management is predicated upon the potential for visceral complications and familial inheritance. PJS must also be distinguished from other hereditary gastrointestinal cancer syndromes. This includes a review of family histories as well as an evaluation for associated findings, such as gastrointestinal polyps, which occur in nearly all PJS patients, gastrointestinal obstruction, recurrent intussusceptions, gastrointestinal bleeding, and a variety of other internal malignancies. Although symptoms may arise in early childhood, the disease is most often discovered between the ages of 10 and 30 years. Any child seen with recurrent, unexplained abdominal pain should raise concern for intussusception, a medical emergency often associated with PJS. Gastrointestinal polyps are most often found in the small bowel but may also be seen in the stomach, large bowel, and rectum; these polyps are at risk for

malignant degeneration. Esophagogastroduodenoscopy, capsule endoscopy, balloon enteroscopy, and colonoscopy are important in the evaluation and treatment of gastrointestinal polyposis.

Cancers of the esophagus, stomach, intestines, pancreas, lung, uterus, and testes (Sertoli cell) all have an elevated relative risk in patients with PJS. Women with this disorder also carry an increased risk of bilateral breast cancer. Ovarian neoplasms, especially granulosa cell tumors, may be seen. Both in men and women, sex cord tumors with annular tubules, and sex cord stromal tumors with sexual precocity, may develop.

Genetic testing in suspected cases may identify familial or de novo mutations. Genetic counseling of PJS patients and their relatives is recommended. Patients and families should be reassured that the mucocutaneous macules are benign and may improve or disappear in adulthood. Several aesthetic interventions for these pigmented macules have been described, with varying responses; removal may potentially mask the underlying disorder in patients with undiagnosed PJS.

The Q-switched Nd:YAG laser and ruby laser (Q-switched and short pulsed) have been used in the treatment of labial macules without sequelae or recurrences. Anesthesia is not usually required and minimal wound care is necessary. CO₂, alexandrite, and argon lasers, as well as intense pulsed light, have also been effective in the treatment of labial macules. Cryosurgery, surgical excision, electrodesiccation, and dermabrasion may lead to scarring and dyspigmentation, often without complete removal of the pigmented macules. Similarly, trichloroacetic acid may not produce total resolution.

Specific Investigations

- Gastrointestinal evaluation
- Screening for other internal malignant neoplasms
- Genetic testing (in some cases)
- Histology of polyps and mucocutaneous macules (if diagnosis is in question)
- Psychosocial evaluation

Optimization of the diagnosis of inherited colorectal cancer using NGS and capture of exonic and intronic sequences of panel genes. Baert-Desurmont S, Coutant S, Charbonnier F, et al. *Eur J Hum Genet* 2018; 26: 1597–602.

The authors describe a strategy for using next generation sequencing for efficient detection of mutations occurring in several inherited colorectal cancer syndromes, including PJS.

Genetic predisposition to breast and ovarian cancers: how many and which genes to test? Angeli D, Salvi S, Tedaldi G. *Int J Mol Sci* 2020; 21(3): 1128. <https://doi.org/10.3390/ijms21031128>.

This article reviews the implications of newer molecular techniques and large gene panels in detecting genes predisposing to cancer syndromes. The authors discuss considerations for prevention and personalized treatment for patients and families, including those with STK11/LKB1 mutations.

The STK11 gene mutation in PJS is autosomal dominant and has high penetrance for the risk of breast and ovarian cancers. National Comprehensive Cancer Network (NCCN) guidelines suggest clinical breast examinations every 6 months, plus mammography and breast MRI annually for affected women, beginning at the age of 25. NCCN guidelines also suggest annual pelvic exam plus Pap smear beginning at age 18–20.

Cancer risk in patients with Peutz–Jeghers syndrome: a retrospective cohort study of 336 cases. Chen HY, Jin XW, Li BR, et al. *Tumour Biol* 2017; 39(6): 1010428317705131. <https://doi.org/10.1177/1010428317705131>.

In this retrospective cohort study of patients with PJS in China, the cumulative cancer risk at the age of 60 years was 55%.

The authors provide insights into the surveillance of cancer in patients and families with PJS. The article also highlights surveillance of not only colorectal cancers but also cancers of the genital tract.

ACG Clinical Guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Syngal S, Brand RE, Church JM, et al. *Am J Gastroenterol* 2015; 110: 223–63.

A comprehensive document from the American College of Gastroenterology providing guidelines for evaluation, surveillance, and management of patients with a number of hereditary syndromes, including PJS. This review also provides recommendations for surveillance of associated internal malignancies.

Small bowel endoscopy and Peutz–Jeghers syndrome. Korse SE, Dewint P, Kuipers EJ, et al. *Best Practice & Research Clinical Gastroenterology* 2012; 26: 263–78.

This is a systematic review of endoscopic techniques used to examine the small bowel in patients with PJS.

Small bowel surveillance is recommended in patients with PJS every 2–3 years from the age of 8–10 years. Visualization of the small bowel is technically challenging.

Peutz–Jeghers syndrome: a systematic review and recommendations for management. Beggs AD, Latchford AR, Vasen HE, et al. *Gut* 2010; 59: 975–86.

A review of current genotype-phenotype studies and an outline of consensus recommendations for screening and follow-up from a group of European experts who previously produced guidelines for the management of Lynch syndrome and familial adenomatous polyposis.

Surveillance in PJS aims to a) reduce polyp burden and the incidence of intussusceptions in young patients, and b) reduce the burden of cancer. Capsule endoscopy allows for thorough, less invasive surveillance of the small bowel for polyposis. Evaluation of the small bowel with upper gastrointestinal (GI) endoscopy, colonoscopy, and double-balloon enteroscopy has been useful in preventing the need for subsequent surgical polypectomy; because double-balloon enteroscopy is often traumatic, it may be reserved as a treatment modality.

Primary experience of small bowel polypectomy with balloon-assisted enteroscopy in young pediatric Peutz–Jeghers syndrome patients. Li BR, Sun T, Li J, et al. *Eur J Pediatr* 2020; 179: 611–7.

The authors performed a prospective study and concluded that balloon-assisted enteroscopy of the small bowel is safe and effective in pediatric patients.

Quality of life and psychological distress in patients with Peutz–Jeghers syndrome. van Lier MG, Mathus-Vliegen EM, van Leerdam ME, Kuipers EJ, Looman CW, Wagner A, et al. *Clin Genet* 2010; 78: 219–26.

A cross-sectional study to assess the quality of life and psychological distress in PJS patients compared with the general population.

In comparison to the general population, PJS patients reported a lower general health perception, more limitations due to emotional problems, and lower mental well-being.

Peutz–Jeghers syndrome. Heymann WR. *J Am Acad Dermatol* 2007; 57: 513–4.

A synopsis of the syndrome correlating molecular advances with the cutaneous, malignant, and endocrinologic features of the disorder.

Further observations on LKB1/STK11 status and cancer risk in Peutz–Jeghers syndrome. Lim W, Hearle N, Shah B, et al. *Br J Cancer* 2003; 89: 308–13.

A genotype-phenotype analysis demonstrating significant genetic heterogeneity in PJS.

The authors demonstrated an elevated relative risk of cancer development in patients with PJS. They also demonstrated that PJS may occur either as a result of several types of mutations within the above gene or potentially even in the absence of a mutation.

Harold Jeghers (1904–1990). Schwartz RA. In: Löser, G. Plewig, Burgdorf WHC, eds. *Pantheon of Dermatology: Outstanding Historical Figures*. Berlin, Springer Verlag, 2013, 553–6.

A biography of Harold Jeghers is presented with a review of this syndrome, which carries his name.

First-Line Therapies

• Q-switched Nd:YAG laser	C
• Ruby and alexandrite lasers	D

A case of recurrent pigmented macules in Laugier–Hunziker syndrome treated using a Q-switched Nd:YAG laser. Choi ME, Jung CJ, Lee WJ, et al. *J Cosmet Laser Ther* 2019; 21: 395–7.

The authors describe long-term follow-up for a patient with Laugier–Hunziker syndrome (LHS) previously treated with QS-Nd:YAG laser for labial melanotic macules. Some previously treated labial macules recurred after 7 years; these and other previously untreated macules on the gums were successfully treated again with QS-Nd:YAG laser.

Laugier–Hunziker syndrome, a disorder of mucocutaneous pigmentation similar to PJS, has no associated gastrointestinal abnormalities. Treatment of pigmented lesions in this syndrome may provide insight into the treatment of those seen in PJS.

Q-switched Nd:YAG laser treatment for labial lentigines associated with Peutz–Jeghers syndrome. Ge Y, Jia G, Lin T. *J Dtsch Dermatol Ges* 2015; 13: 551–5.

Eleven patients with PJS received two to six treatments with Q-switched Nd:YAG laser (532 nm) with a spot size of 3 mm, fluence of 1.8–2.2 J/cm², and pulse duration ranging from 5–20 ns. Eight of 11 patients had greater than 75% clearance with minimal recurrence or complication after a mean follow-up of 41 months.

Q-switched alexandrite laser treatment of oral labial lentigines in Chinese subjects with Peutz–Jeghers syndrome. Xi Z, Hui Q, Zhong L. *Dermatol Surg* 2009; 35: 1084–8.

Fourteen cases of oral labial lentigines in patients with PJS were managed using a single treatment with Q-switched alexandrite laser with a 3-mm handpiece and a fluence of 4.0–9.0 J/cm². All exhibited successful elimination without scarring or recurrence at median 2-year follow-up.

Q-switched lasers, in particular the alexandrite laser, are preferred in the treatment of benign melanocytic lesions, including oral labial lentigines in PJS patients; acute side effects included edema, erythema, and occasional bleeding.

Q-switched ruby laser treatment of labial lentigos. Ashinoff R, Geronemus RG. *J Am Acad Dermatol* 1992; 27: 809–11.

The Q-switched ruby laser, with a wavelength of 694 nm and pulse duration of 40 ns, causes selective damage to pigmented cells. Three patients with labial lentigines treated with the Q-switched ruby laser noted dramatic clearing after one or two treatments with a fluence of 10 cm².

Ruby laser therapy for labial lentigines in Peutz–Jeghers syndrome. Kato S, Takeyama J, Tanita Y, et al. *Eur J Pediatr* 1998; 157: 622–4.

Two children with PJS and labial lentigines were treated successfully without sequelae or recurrence.

Q-switched ruby laser treatment of tattoos and benign pigmented lesions: a critical review. Raulin C, Schonemark MP, Greve B, et al. *Ann Plast Surg* 1998; 41: 555–65.

This review discusses indications for the use of the Q-switched ruby laser. These include tattoos, café au lait macules, and lentigines, especially those on the lips and eyelids.

Second-Line Therapies

• Other lasers	E
• Intense pulsed light	E
• Cryotherapy	E

Treatment of Peutz–Jeghers lentigines with the carbon dioxide laser. Benedict LM, Cohen B. *J Dermatol Surg Oncol* 1991; 17: 954–5.

One patient with PJS had successful treatment of perioral lentigines with a CO₂ laser.

Q-switched Alexandrite laser in the treatment of pigmented macules in Laugier–Hunziker syndrome. Papadavid E, Walker NP. *J Eur Acad Dermatol Venereol* 2001; 15: 468–9.

Two patients with labial pigmented macules were treated with the Q-switched alexandrite laser. Recurrences were easily treated again.

Treatment of pigmentation of the lips and oral mucosa in Peutz–Jeghers syndrome using ruby and argon lasers. Ohshiro T, Maruyama Y, Nakajima H, et al. *Br J Plast Surg* 1980; 33: 346–9.

Three PJS patients had successful treatment of pigmented oral macules with ruby and argon lasers.

Treatment of facial lentigines in Peutz–Jeghers syndrome with intense pulsed light source. Remington BK, Remington TK. *Dermatol Surg* 2002; 28: 1079–81.

A 10-year-old child had complete clearance of cosmetically concerning lentigines over the course of 12 treatment sessions to different facial regions. Most resolved with a single treatment.

This report demonstrated the first use of intense pulsed light in PJS and provided a viable alternative to laser treatment.

Simple cryosurgical treatment of the oral melanotic macule. Yeh CJ. *Clin Oral Maxillofac Surg* 2000; 90: 12–3.

Simple cryotherapy for labial melanotic macules is discussed; a specific protocol is provided.

Cryosurgery requires no sophisticated equipment and is inexpensive. Recurrence is common, and inadequate destruction may occur.

Chemopreventive efficacy of rapamycin on Peutz–Jeghers syndrome in a mouse model. Wei C, Amos CI, Zhang N, et al. *Cancer Lett* 2009; 18: 149–54.

Rapamycin treatment of mice with LKB1 mutations led to a reduction in both polyp burden and polyp size, suggesting that rapamycin may be an option for chemoprevention in humans with PJS.

Suppression of Peutz–Jeghers polyposis by targeting mammalian target of rapamycin signaling. Wei C, Amos CI, Zhang N, et al. *Clin Cancer Res* 2008; 14: 1167–71.

Mice with germline LKB1 mutations and polyposis were treated with rapamycin at the dose of 2 mg/kg/day for 2 months. Rapamycin decreased the tumor burden of large polyps (> 8 mm).

Rapamycin effectively suppresses Peutz–Jeghers polyposis in a mouse model, suggesting that it and other inhibitors of the mammalian target of rapamycin (mTOR) may represent targeted therapy for this disorder.

Pinta and yaws

Omar Lupi, Daniela Martinez, Helena Camasmie



Pinta and yaws belong to the group of neglected endemic and non-venereal treponematoses. These distinct and chronic diseases predominantly affect economically disadvantaged, isolated, rural areas of tropical and subtropical countries.

Yaws is currently thought to be endemic in 14 countries, mostly in West Africa, Southeast Asia, and the Pacific, while pinta is restricted to Latin America, in particular Mexico and Colombia. Pinta is caused by *Treponema carateum* and yaws by *T. pallidum* ssp. *pertenue*. Both are Gram-negative spirochetes, morphologically and antigenically identical to each other and to the etiologic agent of syphilis; therefore, specification has to be based on clinical and epidemiological aspects. Recent genome sequencing showed that intrastrain heterogeneity within individual treponemal strains exists, differentiating *T. pallidum* ssp. *pallidum* from *T. pallidum* ssp. *pertenue*, as well as differences in genomes from treponemes that belong to the same subspecies, but are originated from various geographic locations. This phenomenon likely represents both the selection of adaptive changes during host infection as well as an ongoing diversifying evolutionary process. The only known reservoir is humans.

Both treponematoses are transmitted by direct skin contact. Spirochetes cannot enter intact skin; it must be facilitated by breaks in the skin from small cuts, scratches, or other skin damage. Most patients acquire the infection during childhood. Both diseases comprise multiple stages.

Pinta is considered the most benign among them, with skin-limited manifestations. It is classified into two different clinical stages. The primary stage is divided into two phases: an early phase (initial period) and a secondary phase (period of cutaneous dissemination). The primary lesions appear 7–10 days after inoculation, characterized by erythematous papules on the face and upper and lower extremities. These lesions tend to grow in extension, producing erythematous or hyperpigmented asymptomatic plaques. Within 6 months to 2–3 years of the first lesions' appearance, erythematohypochromic patches take place, initiating the period of cutaneous dissemination. They are polymorphic and referred to as *pintides*, affecting larger areas of the body with normal skin in the center.

The hallmark of the late stage, 2–5 years after the first lesion, is the appearance of achromic patches, especially over body prominences.

Plantar hyperkeratosis is frequent. There is no evidence of involvement of other organs, even after many years of evolution.

The initial lesion of yaws is called '*mother yaw*', arising at the site of entry of the organism most commonly on the lower limbs, 21 days after inoculation. *Mother yaw* is an erythematous infiltrated papule or a group of papules on an erythematous base. Those lesions may form a vegetative, raspberry-like round to oval ulcer. They are painless and considered highly infectious. *Mother yaws* frequently heals spontaneously, leaving an atrophic and hypopigmented scar. Systemic symptoms such as fever and joint pain are sometimes present, as well as regional lymphadenopathy.

Disseminated cutaneous lesions appear in untreated cases after the healing of the initial lesion, characterizing the secondary stage: a bilateral and symmetrical eruption that may be present in two main clinical features: a large one that resembles the mother yaws and is called '*daughter yaws*' and a micropapular type, called '*miniature yaws*'. The mostly affected locations are the face and intertriginous moist surfaces. Usually the soles present hyperkeratotic plaques with fissures and pain, forcing the patients to walk with a peculiar gait known as '*crab yaws*'. Cutaneous lesions usually heal, leaving a hypochromic area. Painful osteoperiostitis and polydactylitis may occur, as well as systemic symptoms (fever, headache, generalized adenopathy, and nocturnal bone pain).

Late tertiary yaws appears in 10% of cases after several years, involving subcutaneous tissues, mucous membranes, bones, and joints. The presence of neurological, cardiovascular, and ophthalmological lesions is very controversial. The lesions of late yaws are characterized by nodular and tubercular pianides, gummatous lesions, palmar and plantar keratoderma, osteoarticular lesions, palate and nasal septum destruction (*gangosa*), exostoses of the nasal bridge (*goundou*), and juxtaarticular nodes.

Serological tests, such as rapid plasma reagin, venereal disease research laboratory (VDRL), FTA-ABS, and treponema pallidum particle agglutination and hemagglutination (TPHA) assays remain the cornerstone of the diagnosis, although they cannot distinguish syphilis from any of the non-venereal treponematoses. Dark-field microscopic examination and radiological and histopathological studies have also been used. Pathogenic treponemes cannot be cultured in vitro. Rapid point-of-care (PoC) treponemal tests have become available in the form of immunochromatographic strips; however, it is not able to differentiate between active and treated infection. Available *T. pallidum* polymerase chain reaction (PCR) assays can be applied to the diagnosis of endemic treponematoses as a direct method with high sensitivity.

There is no proof of a spontaneous cure for the disease and because cell-mediated immunity is not completely effective, the infection persists indefinitely. Patients may harbor subclinical disease and be contagious for a long time.

Intramuscular *benzathine penicillin* remains the mainstay of treatment for the endemic treponemal diseases for over 50 years. A single dose is effective, which ranges from 1.2 million units for patients over 10 years old, with half the dose necessary for patients aged under 10 and contacts.

World Health Organization (WHO) programs in the 1950s–60s successfully reduced the number of cases of yaws by administering single-dose penicillin, but failure to adequately identify and treat contacts and latent cases led to non-eradication of the disease.

A study was conducted in infected children with a 30 mg/kg single oral dose of *azithromycin* and it was proven to be non-inferior to penicillin, with the benefit of avoiding the need for injection equipment and medically trained personnel. Changing to the simpler azithromycin treatment regimen could enable yaws elimination through mass drug administration programs, renewing WHO's efforts to eradicate the disease by 2020 – the Morges

Strategy. Follow-up at 6 months includes clinical and serological surveys to detect and treat remaining cases and their contacts. Awareness to the possibility of azithromycin resistance is important, as it has occurred in syphilis.

At present date, WHO has not yet developed a specific strategy for the control or eradication of pinta.

Specific Investigations

- Serologic tests
- Dark-field microscopy
- Direct fluorescent antibody test
- Histopathology
- PCR

Yaws. Marks M, Mitjá O, Solomon AW, et al. Br Med Bull 2015; 113: 91–100.

Dark-field microscopy allows direct visualization of spirochetes.

Diagnostics for Yaws eradication: insights from direct next-generation sequencing of cutaneous strains of *Treponema pallidum*. Marks M, Fookes M, et al. Clin Infect Dis. 2018 5; 66: 818–24.

Genome analyses also shed light on treponemal evolution and on chromosomal targets for molecular diagnostics of treponemal infections. PCR is a reliable tool for yaws diagnosis.

A retrospective study on genetic heterogeneity within *Treponema* strains: subpopulations are genetically distinct in a limited number of positions. Čejková D, Strouhal M, Norris SJ. PLoS Negl Trop 2015; 9: e0004110.

Heterogeneous sites likely represent both the selection of adaptive changes during infection of the host as well as an ongoing diversifying evolutionary process.

Advances in the diagnosis of endemic treponematoses: yaws, bejel, and pinta. Mitjá O, Šmajš D, Bassat Q. PLoS Negl Trop Dis 2013; 7: e2283.

Serological tests are still considered standard laboratory methods for the diagnosis of endemic treponematoses and new rapid PoC treponemal tests have become available. In the past 10 years, there has been an increasing effort to apply PCR to treponematoses, and whole genome fingerprinting techniques have identified genetic signatures that can differentiate the existing treponemal strains.

Histopathology is important for the diagnosis. It is possible to demonstrate the presence of the treponeme in the epidermis through special stains like Warthin–Starry in all lesions, with the exception of achromic lesions.

First-Line Therapies

- Penicillin G benzathine **B**
- Azithromycin (yaws) **B**

Pinta: Latin America's forgotten disease? Stamm LV. Am J Trop Med Hyg 2015; 93(5): 901–3.

All stages of pinta are treatable with a single intramuscular injection of penicillin.

Serologic cross-reactivity of syphilis, yaws, and pinta. de Caprariis PJ, Della-Latta P. Am Fam Physician 2013; 15; 87: 80.

Penicillin G benzathine is the recommended treatment for all three treponemal diseases; a single dose is adequate for yaws, pinta, and primary syphilis, but inadequate for late latent and tertiary syphilis.

Endemic treponemal diseases. Marks M, Solomon AW, Mabey DC. Trans R Soc Trop Med Hyg 2014; 108: 601–7.

For endemic treponemal diseases a dose of 1.2 million units is recommended for patients aged 10 or over, while a dose of 0.6 million units is recommended for patients aged under 10 and for contacts

Single-dose azithromycin versus benzathine benzylpenicillin for treatment of yaws in children in Papua New Guinea: an open-label, non-inferiority, randomised trial. Mitjá O, Hays R, Ipai A, et al. Lancet 2012; 379: 342–7.

A single dose of oral azithromycin (30 mg/kg with a maximum of 2 g) is as effective as intramuscular benzathine penicillin for treatment of yaws in children in Papua New Guinea.

Yaws: renewed hope for eradication. Stamm LV. JAMA Dermatol 2014; 150(9): 933–4.

Although azithromycin is safer than penicillin and should make mass treatment significantly easier, its use will require monitoring for emergence of resistance due to 23S ribosomal RNA point mutations, as observed with the syphilis agent.

The endemic treponematoses. Giacani L, Lukehart SA. Clin Microbiol Rev 2014; 27: 89–115.

In 2012, WHO officially set a goal for yaws eradication by 2020. This challenging but potentially feasible endeavor is favored by the adoption of oral azithromycin for mass treatment and the currently focused distribution of yaws and endemic treponematoses and has revived global interest in these fascinating diseases and their causative agents.

Second-Line Therapies

- Tetracycline **E**
- Doxycycline **E**
- Erythromycin **E**

Yaws in the Western Pacific Region: a review of the literature. Capuano C, Ozaki M. J Trop Med 2011(3): 642832.

Tetracycline, erythromycin, or doxycycline can be used for patients with penicillin hypersensitivity.

New treatment schemes for yaws: the path toward eradication. Mitjá O, Hays R, Rinaldi AC, et al. Clin Infect Dis 2012; 55(3): 406–12.

Oral tetracycline, doxycycline, or erythromycin for 15 days are also likely to be effective. These recommendations, however, are based solely upon known clinical efficacy in small series of patients and not upon the results of any clinical trials.

Yaws. Marks M, Lebari D, Solomon AW, et al. Int J STD AIDS 2015; 26: 696–703.

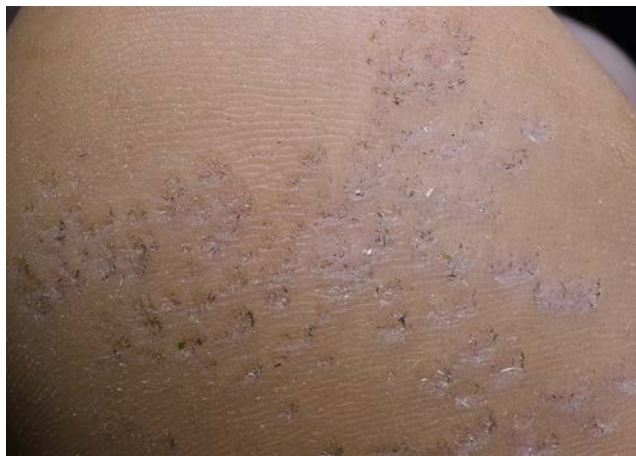
Penicillin remains the drug of choice, but the tetracycline class of antibiotics and erythromycin also appear to be effective.

Tropical dermatology: bacterial tropical diseases. Lupi O, Madkan V, Tying SK. J Am Acad Dermatol 2006; 54: 559–78.

This is a large update on bacterial tropical diseases including pinta and yaws. Alternative therapies such as tetracycline or erythromycin are discussed.

Pitted and ringed keratolysis (keratolysis plantare sulcatum)

Eunice Tan, John Berth-Jones



Pitted keratolysis (PK) manifests as shallow, punched-out, circular erosions, primarily on weight-bearing, sweaty areas of the feet, and less commonly on the non-weight-bearing areas of the feet, and on the palms. This superficial infection of the stratum corneum is caused by *Corynebacterium*, *Dermatophilus*, *Actinomyces*, or *Kytococcus* (formerly named *Micrococcus*). These organisms possess keratin-degrading enzymes and produce sulfur-compounds, resulting in a foul odor. Hyperhidrosis and maceration often occur concurrently.

MANAGEMENT STRATEGY

Most patients experience little or mild irritation. Maceration, foul odor, and soreness are the main reasons for consultation. Hyperhidrosis, sweat retention, prolonged occlusion, immersion, and increases in the skin pH appear to be important causes of PK. Industrial workers wearing rubber shoes or soldiers whose feet are continually occluded or wet are at high risk of developing this infection. Initial management strategies should therefore include instruction on foot hygiene and avoidance of occlusive footwear.

Treatment involves use of topical or systemic antimicrobial agents and/or reduction of the hyperhidrosis.

The availability of some topical antibiotic products has been restricted to variable degrees in different countries in order to reduce the occurrence of antimicrobial resistance, so not all formulations discussed here are universally available.

The topical antibiotic most commonly used by the authors is fusidic acid, which can be prescribed as 2% fusidic acid cream or ointment three to four times daily. Topical 1% clindamycin, benzoyl peroxide, 1% clindamycin with 5% benzoyl peroxide gel, 2%–4% erythromycin, mupirocin, and gentamicin sulfate

have been reported to be effective. Although 1% clindamycin hydrochloride can be made up with 660 mg dissolved in 55 mL of 70% isopropyl alcohol and 5% propylene glycol, we suggest that Dalacin T topical solution or Duac gel may be used instead. This can be applied two or three times daily. Erythromycin 2% cream or ointment has been reported to be effective if used twice daily. Japanese dermatologists have had some success in treating PK with gentamicin sulfate cream. Mupirocin 2% ointment may be administered two to three times daily; PK has also responded to topical antifungals such as clotrimazole and miconazole; 1% clotrimazole cream or 2% miconazole cream or ointment may be applied twice daily. Topical antiseptics, such as 4% chlorhexidine scrub, can be effective.

Systemic antibiotics can be reserved for severe and resistant cases. A 7-day course of oral erythromycin at 250 mg four times a day is usually well tolerated. The use of penicillin or sulfonamides does not seem to be effective. Antibiotic resistance has been reported with *Micrococcus sedentarius* to penicillin, methicillin, ampicillin, oxacillin, and erythromycin.

Topical 20% aluminum chloride hexahydrate, available as Dri-clor or Anhydrol Forte, may reduce hyperhidrosis and odor, but the pits remain. The solution is applied at night, allowed to dry, and washed off the following day. Initially it should be used daily until the condition is brought under control, when it can be used less frequently. The use of 20% aluminum chloride hexahydrate for palmoplantar hyperhidrosis has not been as successful as its use for axillary hyperhidrosis.

Topical 4% formaldehyde solution applied with gauze soaks as the patient sits or stands with their feet on the gauze in a bowl for 10–15 min once or twice daily reduces the hyperhidrosis. Alternatively, immersion of the soles in 5% formaldehyde may be utilized. Formalin ointment 40% has been used with some success but is not commercially available in the UK.

Iontophoresis is frequently used in palmar and plantar hyperhidrosis and can be used in the treatment of PK. Botulinum toxin has also been used. Oral anticholinergics are perhaps excessive.

Specific Investigations

No investigation is routinely required

- Wood light examination may reveal a coral red fluorescence, but this is not consistently helpful
- Dermoscopy may reveal small black pits in a parallel pattern on the ridges of the stratum corneum
- Starch iodine test may identify areas of hyperhidrosis
- Shave biopsies processed with methenamine silver stain, Gram stain, or periodic acid–Schiff stains are more helpful than punch biopsies
- Swabs may be obtained for cultures of the organisms

Pitted keratolysis. The role of *Micrococcus sedentarius*. Nordstrom KM, McGinley KJ, Cappiello L, et al. Arch Dermatol 1987; 123: 1320–5.

Micrococcus sedentarius isolated from PK lesions on the feet of eight patients was tested for antibiotic sensitivities and found to be resistant to penicillin, ampicillin, methicillin, and oxacillin. PK lesions were reproduced in one volunteer inoculated with *M. sedentarius* after 6 weeks of occlusion.

Isolation and characterization of micrococci from human skin, including two new species: *Micrococcus lylae* and *Micrococcus kristinae*. Kloos WE, Torrabene TG, Schleifer KH. Int J Syst Bacteriol 1974; 24: 79–101.

M. sedentarius was observed to be resistant to penicillin, methicillin, and erythromycin, which is characteristic of the genus *Micrococcus*.

First-Line Therapies

- Topical fusidic acid E
- Topical aluminum chloride hexahydrate E

Pitted keratolysis in an adolescent, diagnosed using conventional and molecular microbiology and successfully treated with fusidic acid. Papaparaskevas J, Stathi A, Alexandrou-Athanasoulis H, et al. Eur J Dermatol 2014; 24: 499–500.

A case report of a patient with PK successfully treated with fusidic acid.

Isolation of *Kytococcus sedentarius* from a case of pitted keratolysis. Ertam I, Aytimur D, Yüksel SE. Ege Tip Dergisi 2005; 44: 117–8.

A case report of a patient with plantar PK, in which *Kytococcus* was isolated, with complete response to 3 weeks of oral erythromycin and topical fusidic acid.

Second-Line Therapies

- Topical mupirocin D
- Topical clindamycin C
- Topical erythromycin B
- Topical benzoyl peroxide B
- Chlorhexidine scrub B
- Topical clotrimazole E
- Topical miconazole E
- Topical formaldehyde E
- Oral erythromycin E

Mupirocin ointment for symptomatic pitted keratolysis. Vazquez-Lopez F, Perez-Oliva N. Infection 1996; 24: 55.

Four patients with PK failing to respond to conventional treatments were treated with mupirocin ointment, with rapid clearance.

Pitted keratolysis: successful management with mupirocin 2% ointment monotherapy. Greywal T, Cohen PR. Dermatol Online J 2015; 21(8).

A patient responded to mupirocin 2% ointment twice daily for 3 weeks.

***Kytococcus sedentarius* nail infection.** Towerser L, Azulay RD, Filho PJS, et al. J Am Acad Dermatol Supplement 2008; 58: AB88.

A case report of a patient with *Kytococcus* PK and associated nail dystrophy responding to systemic amoxicillin and potassium clavulanate, topical mupirocin cream for feet lesions, and gentamicin sulfate solution for nail lesions.

Pitted keratolysis: a new form of treatment. Burkhart CG. Arch Dermatol 1980; 116: 1104.

Three patients were treated with topical 1% clindamycin hydrochloride solution (660 mg dissolved in 55 mL of 70% isopropyl alcohol and 5% propylene glycol), applied to the plantar surface three times daily. Within 4 weeks there was complete resolution of the clinical lesions.

Road rash with a rotten odor. Schissel DJ, Aydelotte J, Keller R. Military Med 1999; 164: 65–7.

A soldier was treated with topical clotrimazole cream twice a day, topical clindamycin solution twice a day, and topical ammonium chloride each evening. At his 2-week follow-up appointment, he reported resolution of the odor, tenderness, and interdigital pruritus, and at 8 weeks he had complete resolution.

The use of a clindamycin 1%-benzoyl peroxide 5% topical gel in the treatment of pitted keratolysis: a novel therapy. Vlahovic TC, Dunne SP, Kemp K. Adv Skin Wound Care 2009; 22: 564–6.

The combination topical gel of clindamycin 1% with benzoyl peroxide 5% was reported to be effective in four patients, but efficacy required the concurrent use of aluminum chloride hexahydrate solution.

Pitted keratolysis: an infective cause of foot odour. Fernández-Crehuet P, Ricardo Ruiz-Villaverde R. CMAJ 2015; 187: 519.

A patient was treated with clindamycin 1% topical solution twice a day and aluminum chlorohydrate 25% alcoholic solution as an antiperspirant. Two weeks later, the condition had improved substantively.

Comparative study of benzoyl peroxide versus clindamycin phosphate in treatment of pitted keratolysis. Kim BJ, Park KU, Kim JY, et al. Korean J Med Mycol 2005; 10: 144–50.

In this report of 44 patients, 17 received benzoyl peroxide alone, 15 received clindamycin alone, and 12 received combination benzoyl peroxide and clindamycin therapy. There was no difference in treatment efficacy between monotherapy or combination therapy. Although not significant, the clindamycin group had a slightly higher recurrence rate. Four cases recurred within 3 months and all were related to hyperhidrosis.

Pitted keratolysis, erythromycin, and hyperhidrosis. Pranteda G, Carlesimo M, Pranteda G, et al. Dermatol Ther 2014; 27: 101–4.

Erythromycin 3% gel was applied twice daily in an uncontrolled study on 97 patients. Clinical manifestations regressed within 10 days.

Cost-effectiveness analysis and safety of erythromycin 4% gel and 4% chlorhexidine scrub for pitted keratolysis treatment. Leeyaphan C, Bunyaratavej S, Tachakhoonavudh S, et al. J Dermatol Treat 2019; 30: 627–9.

In this study, 125 naval cadets diagnosed with PK were treated with either 4% erythromycin gel or 4% chlorhexidine scrub for 4 weeks. Of the 64 treated with erythromycin, 80% had complete resolution, and foot odor was significantly improved at 2 months. Chlorhexidine had similar outcomes and so was more cost-effective.

Pitted keratolysis: a clinicopathologic review. Stanton RL, Schwartz RA, Aly R. J Am Podiatry Assoc 1982; 72: 436–9.

Topical 2% erythromycin applied twice daily resulted in resolution of PK in both feet within 4 weeks of treatment in one case.

Painful, plaque-like, pitted keratolysis occurring in childhood. Shah AS, Kamino H, Prose NS. Pediatr Dermatol 1992; 9: 251–4.

Two percent erythromycin solution twice a day was curative in two children within 3 weeks of commencing treatment.

Plantar pitted keratolysis: a study from non-risk groups. Kaptanoglu AF, Yüksel O, Ozyurt S. Dermatol Reports 2012; 4(1): e4.

Forty-one patients were treated with 4% erythromycin gel. Nine (21.9%) who had malodor and slight pits received monotherapy; 32 (78.1%) with more severe clinical appearance (malodor, hyperkeratosis, deep pitted lesions, and maceration) also received oral roxithromycin (derivative of erythromycin) 300 mg/day. Nineteen patients (46.4%) who had malodor, hyperkeratosis, and deeper pitted lesions were also treated with 10% salicylic acid. In patients with severe maceration, 0.01% KMnO₄ (potassium permanganate) solution was also used for its astringent and drying properties. Patients were reviewed weekly and topical treatments were continued until symptoms had completely disappeared, between 1 and 8 weeks (mean 19 days). During the 1-year follow-up, recurrence was observed in 7 (17%) patients. Time to recurrence was 4–12 months. The common feature of these patients was the highly hyperkeratotic tissue of the sole.

Randomized, controlled trial testing the effectiveness and safety of 2.5% and 5% benzoyl peroxide for the treatment of hyperhidrosis. Leeyaphan C, Limphoka P, Kiratiwongwan R, et al. *J Dermatol Treat* <https://doi.org/10.1080/09546634.2019.1708244> (accessed Jan 2020).

Randomized control trial in which 42 naval cadets with PK were treated with 2.5% benzoyl peroxide (BP) and 47 cadets with PK were treated with 5% BP once daily for 2 weeks. In both groups visual analog scale showed significant improvement. The pitted lesions improved in 2.5% and 5% BP groups (69% versus 63.8%, respectively; $p=0.457$). Side effects did not differ between the two groups.

Pitted keratolysis. Leung AKC, Barankin B. *J Pediatric* 2015; 167: 1165.

Topical BP daily for 21 days resulted in resolution of the lesions and odor in an adolescent patient.

Formaldehyde treatment for pitted keratolysis. Primary Care Dermatological Society website: <http://www.pcds.org.uk/patient-information-leaflets> (accessed Feb 2020).

Patient information leaflet: 4% formaldehyde soaks for 10 minutes daily for 4–6 weeks for the treatment of PK.

Coexistent erythrasma, trichomycosis axillaris, and pitted keratolysis: an overlooked corynebacterial triad? Shelley WB, Shelley ED. *J Am Acad Dermatol* 1982; 7: 752–7.

A case report of two patients with this triad, one of whom was treated with oral erythromycin 250 mg four times daily and a solution of 20% aluminum chloride applied nightly to the soles. Three weeks later the plantar hyperhidrosis and odor were significantly reduced, but the pits remained. The other patient declined treatment for PK.

Third-Line Therapies

• Topical gentamicin	E
• Botulinum toxin injections	E

Keratolysis plantare sulcatum. Higashi N. *Jpn J Clin Dermatol* 1972; 26: 321–5.

Two patients were treated with topical gentamicin sulfate cream and were reported to have good results.

Plantar hyperhidrosis and pitted keratolysis treated with botulinum toxin injection. Tamura BM, Cucé LC, Souza RL, et al. *Dermatol Surg* 2004; 30: 1510–4.

Two patients resistant to topical and systemic treatments responded completely to one course of low-dose botulinum toxin injections to the plantar aspects of the feet.

Pityriasis lichenoides chronica

Matthew J. Scorer, Graham A. Johnston



Pityriasis lichenoides chronica (PLC) typically consists of small, erythematous papules, which may be purpuric. These develop a characteristic, shiny, mica-like scale attached to the center. They occur predominantly over the trunk and proximal limbs. As the name implies, PLC may persist for many years, though spontaneous resolution does occur. Patients should be warned that relapse is common and that recurrent courses of therapy may be required.

Anecdotally, PLC was said to run a more benign, self-limiting course in children, but more recently it has been shown that in children it is more likely to run an unremitting course, with greater lesional distribution, more dyspigmentation, and a poorer response to treatment. Some authors argue that there is an overlap with cutaneous lymphoma.

Pityriasis lichenoides chronica: stratification by molecular and phenotypic profile. Crowson AN, Morrison C, Li J. Hum Pathol 2007; 38: 479–90.

A prospective study of 46 patients concluded that PLC is an indolent, cutaneous T-cell dyscrasia with a limited propensity for progression to mycosis fungoides.

MANAGEMENT STRATEGY

There are few therapeutic trials for this condition, and case series are only small. In many therapeutic trials PLC has been grouped together with pityriasis lichenoides et varioliformis acuta (PLEVA), and management strategies are therefore often similar or interchangeable.

Topical corticosteroids are generally reported as effective anecdotally in textbooks rather than in studies. They are often used with *antihistamines* to reduce pruritus, but they are not reported to affect the course of the disease.

The majority of reports describe benefits with *ultraviolet (UV) therapy*, and therefore either UV alone or *psoralen plus UVA (PUVA)* therapy is recommended for all patients. The response appears to be unpredictable, however, and the total dose required is extremely variable.

Antibiotics appear to be more helpful in children, sometimes used in combination therapy.

For severe or refractory cases, *methotrexate*, *acitretin* combined with PUVA, and *etanercept* have all been described as effective in small numbers of patients.

For most treatment modalities, patients who have been described as improved have usually had fewer new lesions developing, a shortened disease course, and a greater time to relapse than untreated patients.

Specific Investigation

- Consider skin biopsy

Although a skin biopsy is usually unnecessary in clinically obvious cases, it may be useful before commencing systemic therapy with more potential adverse effects.

An infective etiology is often suggested, but no pathogen has yet been implicated, though associations with toxoplasmosis, human herpesvirus-8 (HHV-8), and parvovirus B19 have been described. These reports tend to come from endemic areas, and so investigation for a triggering infection is unnecessary in cases without evidence of specific infection.

The relationship between toxoplasmosis and pityriasis lichenoides chronica. Nassef NE, Hamman MA. J Egypt Soc Parasitol 1997; 27: 93–9.

Twenty-two patients with PLC and 20 healthy controls were examined clinically and serologically for toxoplasmosis. Three (15%) of the controls had toxoplasmosis, compared with 8 (36%) of the patients with PLC. Five of the latter had subsidence of skin lesions after pyrimethamine and sulfapyrimidine treatment.

Pityriasis lichenoides et varioliformis acuta and pityriasis lichenoides chronica: comparison of lesional T-cell subsets and investigation of viral associations. Kim JE, Yun WJ, Mun SK, et al. J Cutan Pathol 2011; 38: 649–56.

Fifty-one patients with pityriasis lichenoides (not subdivided into PLEVA and PLC) were analyzed. HHV-8 was found in 11 (21%) of affected patients but in none of the 25 controls.

Pityriasis lichenoides: a cytotoxic T-cell-mediated skin disorder. Evidence of human parvovirus B19 DNA in nine cases. Tomasini D, Tomasini CF, Cerri A, et al. J Cutan Pathol 2004; 31: 531–8.

Thirty tissue samples from cases of pityriasis lichenoides (both PLEVA and PLC) underwent molecular investigation for parvovirus B19 DNA, which was present in nine cases (30%).

First-Line Therapies

• Narrowband ultraviolet B (NB-UVB)	B
• Combined UVA and UVB	D
• PUVA	D

Is narrowband ultraviolet B monotherapy effective in the treatment of pityriasis lichenoides? Park JM, Jwa SW, Song M, et al. Int J Dermatol 2013; 52: 1013–8.

This retrospective study of 70 patients did not separate PLEVA from PLC but reported a 91.9% complete response rate with narrowband ultraviolet B (NB-UVB). This was not significantly different from the response rate to systemic immunosuppressive therapy or a combination of systemic therapy and NB-UVB.

The effectiveness of narrow band UVB (NB-UVB) in the treatment of pityriasis lichenoides chronica (PLC) in Vietnam. Huu DL, Minh TN, Van TN, et al. Open Access Maced J Med Sci 2019; 7: 221–3.

In this prospective study, PLC completely responded to NB-UVB in 24 out of 29 patients (82.8%), after a mean number of 13.8 treatments.

Phototherapy for pityriasis lichenoides: our experience. Macías VC, Marques-Pinto G, Cardoso J. Cutan Ocul Toxicol 2013; 32: 124–7.

This retrospective study reports the use of PUVA or UVA combined with UVB in 13 patients (11 with PLC, 2 with PLEVA). Complete response to PUVA was achieved in five patients, with partial response in two. In the UVA/UVB group, two patients had complete response, and two had partial response. One patient in each treatment group did not have a therapeutic response.

Comparison of the therapeutic effects of narrowband UVB vs. PUVA in patients with pityriasis lichenoides. Farnaghi F, Seirafi H, Ehsani AH, et al. J Eur Acad Dermatol Venereol 2011; 25: 913–6.

This was a study of 15 patients (it was not stated how many were PLC or PLEVA) who were randomized to receive UVB (complete response 7 of 8, partial 1 of 8) or PUVA (complete 5 of 7, partial 2 of 7). The authors state that the difference in response is insignificant and that both options are acceptable.

Comparative studies of treatments for pityriasis lichenoides. Gritiyarangsang P, Pruenglampoo S, Ruangratanarote P. J Dermatol 1987; 14: 258–61.

In this open study, 30 patients with pityriasis lichenoides were recruited, although the authors did not specify how many had PLEVA and how many PLC. The first group of eight were given topical corticosteroid, and half had a partial or complete response. The second group were also given oral tetracycline, and the majority had a partial response. The third group of eight chronic refractory cases were given oral methoxypsoralen 0.6 mg/kg with UVA three times per week for an average of 2 months; five were cleared and two had a partial response.

Second-Line Therapies

• Erythromycin	B
• Azithromycin	E
• Tetracyclines	D

Pityriasis lichenoides in childhood: a retrospective review of 124 patients. Ersoy-Evans S, Greco MF, Mancini AJ, et al. J Am Acad Dermatol 2007; 56: 205–10.

This was a retrospective study of 124 children, of whom 46 had PLC. The median age of onset was 60 months and median duration was 20 months (range 3–132 months). Two-thirds of children had at least a partial response to erythromycin.

Childhood pityriasis lichenoides and oral erythromycin. Hapa A, Ersoy-Evans S, Karaduman A. Pediatr Dermatol 2012; 29: 719–24.

The records of 24 children (age range 2–14), 15 with PLC, six with PLEVA, and three overlap, started on erythromycin (30–50 mg/kg/day for 1–4 months) were reviewed. Sixty-four percent showed a good response at 1 month, rising to 83% at 3 months. Of 16 patients with follow-up, three relapsed (time not given).

Pityriasis lichenoides chronica: rapid response after a single cycle of azithromycin therapy. Feola H, Mancinelli MC, Perez-Klala MV, et al. Dermatol Ther 2020; 33(3): e13303.

A 28-year-old woman with PLC was treated successfully with a solitary course of azithromycin 500 mg/day on day 1 and 250 mg/day from day 2 to day 5.

Tetracycline for the treatment of pityriasis lichenoides. Piamphongsant T. Br J Dermatol 1974; 91: 319.

Thirteen patients with undifferentiated pityriasis lichenoides were treated with tetracycline 2g daily. Twelve responded within 4 weeks, with five complete remissions. The non-responsive patient had Mucha-Habermann disease.

Pityriasis lichenoides chronica responds to minocycline in three patients. Alajlan A. Int J Dermatol 2016; 55: 1027–9.

Two patients unresponsive to methotrexate and NB-UVB, respectively, responded to minocycline 100 mg twice daily for 2 months. A further treatment-naïve patient responded to minocycline 100 mg twice daily for 1 month, followed by doxycycline 100 mg twice daily for 1 month.

Third-Line Therapies

• Methotrexate	E
• Acitretin plus PUVA	E
• UVA1	E
• Topical tacrolimus	E
• Etanercept	E

Methotrexate treatment of pityriasis lichenoides and lymphomatoid papulosis. Lynch PJ, Saied NK. Cutis 1979; 23: 635–6.

Three patients received methotrexate 25 mg/week intramuscularly or orally. All responded within weeks, but two relapsed on cessation of therapy.

Pityriasis lichenoides chronica induced by adalimumab therapy for Crohn's disease: report of 2 cases successfully treated with methotrexate. Said BB, Kanitakis J, Graber I, et al. Inflamm Bowel Dis 2010; 16: 912–3.

Pityriasis lichenoides chronica induced by infliximab, with response to methotrexate. López-Ferrer A, Puig L, Moreno G, et al. Eur J Dermatol 2010; 20: 511–2.

Adalimumab-induced pityriasis lichenoides chronica that responded well to methotrexate in a patient with psoriasis. Martínez-Peinado C, Galán-Gutiérrez M, Ruiz-Villaverde R, et al. Actas Dermosifiliogr 2016; 107: 167–9.

There are four reported cases of PLC, all thought to have been caused by anti-TNF- α therapies, that responded well to methotrexate.

Photochemotherapy for pityriasis lichenoides: 3 cases. Panse I, Bourrat E, Rybojad M, et al. Ann Dermatol Venereol 2004; 131: 201–3.

One patient with pityriasis lichenoides and two patients with PLEVA unresponsive to other therapies, including topical corticosteroids, antibiotics, and UVB, responded within weeks to acitretin plus PUVA.

Medium-dose ultraviolet A1 therapy for pityriasis lichenoides varioliformis acuta and pityriasis lichenoides chronica. Pinton PC, Capezzera R, Zane C, et al. J Am Acad Dermatol 2002; 47: 410–4.

Eight patients (5 with PLC and 3 with PLEVA) were treated. Three patients with PLC showed complete clinical and histologic recovery. Two showed partial improvement.

Successful treatment of pityriasis lichenoides with topical tacrolimus. Simon D, Boudny C, Nievergelt H, et al. Br J Dermatol 2004; 150: 1033–5.

Two children with long-lasting refractory PLC were cleared of skin lesions after 14 and 18 weeks of treatment, respectively.

Etanercept in therapy multiresistant overlapping pityriasis lichenoides. Nikkels AF, Gillard P, Pierard GE. J Drugs Dermatol 2008; 7: 990–2.

A 65-year-old woman had a 5-year history of pityriasis lichenoides that was not helped by UVB, PUVA, methotrexate, dapsone, and ciclosporin. She was commenced on etanercept with marked improvement in pruritus and inflammation after 2 months and no new lesions after 4 months when treatment was stopped. However, she relapsed after 1 month.

Conflictingly, there are reports of etanercept, infliximab, and adalimumab causing pityriasis lichenoides.

Pityriasis lichenoides et varioliformis acuta

Sara Twaij, Graham A. Johnston



Pityriasis lichenoides et varioliformis acuta (PLEVA) is an eruption of small, erythematous papules that can become vesicular and hemorrhagic. Some ulcerate and necrose, leaving pitted scars. The name refers to the morphology, not the duration, of the condition because a significant proportion of cases regress, with or without treatment, only to recur. Patients should be warned that relapse is common and that recurrent courses of therapy may be required. Febrile ulceronecrotic Mucha–Habermann disease (FUMHD) is a rare and severe form of PLEVA characterized by an abrupt onset of an ulceronecrotic eruption associated with a high fever and systemic symptoms.

An infective etiology for PLEVA is suggested by reports of clustering of cases, resolution after tonsillectomy, and occurrence in five members of a family. Varicella zoster virus (VZV) has been isolated from lesional skin, and DNA from VZV has been demonstrated using polymerase chain reaction in skin samples of patients with PLEVA. Case reports have associated PLEVA with parvovirus, adenovirus in the urine, staphylococci from throat cultures, Epstein–Barr virus, toxoplasmosis, human immunodeficiency virus (HIV), and human herpesvirus 7 (HHV-7); therefore, investigation for an infective trigger may be useful.

Drug causes are unusual, although one case has been reported of an association with Nivolumab, an immunomodulatory agent targeting PD1-A, and another case associated with injected vaccines against measles–rubella (MR), *Haemophilus influenza* type b (Hib), and pneumococcus.

There have been case reports of patients with a history of PLEVA developing mycosis fungoides (MF) and, therefore, some authorities recommend long-term follow-up of these patients.

MANAGEMENT STRATEGY

There are only a handful of controlled trials for this condition, and large series are rare. Unfortunately, in many therapeutic trials PLEVA is often reported with and alongside pityriasis lichenoides chronica (PLC), and management strategies are therefore often similar or interchangeable.

Although a ‘wait and see’ approach is justifiable in infants, children should be given a 6-week course of *high-dose erythromycin*. Tetracycline should not be given because of its effects on dentition.

Topical corticosteroids are only reported anecdotally in textbooks rather than in studies. They are used with *oral antihistamines* to reduce pruritus but have no reported effect on disease course.

Second-line therapy in children, and possibly first-line in adults, is *ultraviolet B (UVB)* or *psoralen plus ultraviolet A (PUVA)* (PUVA). The only comparative study has shown PUVA to be more effective.

In more extensive or symptomatic disease *low-dose methotrexate* is useful, and *systemic corticosteroids* or *ciclosporin* have also been used. Patients who develop gastrointestinal side effects with methotrexate can be transferred to subcutaneous methotrexate.

In Mucha–Habermann disease, given its severe nature, *combination therapy* is often prescribed. Intravenous immunoglobulin (IVIG) has been utilized recently.

Specific Investigation

- Consider skin biopsy

A diagnostic skin biopsy is unnecessary in clinically obvious cases but may be useful to exclude lymphomatoid papulosis or before commencing aggressive systemic therapy. Classically a lichenoid infiltrate is seen in the superficial dermis with parakeratosis in the stratum corneum and keratinocyte necrosis in the epidermis. There may be red cell extravasation, including trapped red cells in the epidermis, and a lymphocytic infiltration around the dermal vascular plexus and the dermoepidermal junction.

Pityriasis lichenoides in childhood. Alcalá R, Vicente A, Gonzalez-Ensenat MA, et al. In: Proceedings of the 17th Annual Meeting of the European Society for Pediatric Dermatology, ESPD 2017. Blackwell Publishing Inc.; 2017; 34 (Suppl 2): S32.

This is a retrospective longitudinal study in Spain of 57 patients aged <18 years old with pityriasis lichenoides from 2006 to 2016 confirmed histologically. Of these, 39% had PLEVA and 61% PLC. Oral erythromycin was most commonly prescribed for PLEVA. Three cases manifested mycosis fungoides and they concluded that patients with active disease should be followed up long term as pityriasis lichenoides can progress to CTCL.

Relationship between pityriasis lichenoides and mycosis fungoides: a clinicopathological, immunohistochemical, and molecular study. Zaaroura H, Sahar D, Bick T, et al. *Am J Dermatopathol* 2018; 40(6): 409–15.

In this study of 58 patients with pityriasis lichenoides, three patients developed MF following 3–11 years of persistent disease. They concluded that pointers to progression to MF include

persistent disease, progression into patches and plaques, reduction of apoptotic keratinocytes and CD7+ and CD8+ lymphocytes, significant lymphocytic nuclear atypia, and gene rearrangement of clonal T-lymphocyte receptors.

Pityriasis lichenoides et varioliformis acuta after vaccination. Moriawaki M, Tanaka A, Tanaka M, et al. J Cutan Immunol Allergy 2018; 1: 37–8.

This is a case report of a 13-month-old female who developed PLEVA 7 days after receiving her first vaccine injection against measles–rubella (MR) and fourth vaccine injection against *Haemophilus influenzae* b (Hib) and pneumococcus. She was treated with topical difluprednate 0.05% ointment and her skin improved gradually over 12 weeks without recurrence.

Varicella zoster virus as a possible trigger for the development of pityriasis lichenoides et varioliformis acuta: retrospective analysis of our institutional cases. Horie C, Mizukawa Y, Yamazaki Y, et al. Clin Exp Dermatol 2018; 43(6): 703–7.

This study analyzed the endothelial cells and eccrine epithelium of PLEVA patients to see if VZV glycoprotein (g)E is detected. This was identified in 5/6 cases of PLEVA, suggesting that VZV could be a possible cause of PLEVA.

Pityriasis lichenoides et varioliformis acuta as presenting feature of acute human immunodeficiency virus infection. Relvas M, Santiago L, Cardoso JC, et al. BMJ Case Rep 2019; 26; 12(8).

This is a case report of a 38-year-old female who presented with PLEVA and was also found to have an acute HIV infection. One week after, she was treated with topical corticosteroid and antiretroviral therapy, resulting in improvement of her skin. The authors recommend testing for HIV in cases of PLEVA as acute HIV infection may be a cause of PLEVA.

Febrile ulceronecrotic Mucha–Habermann disease: proposed diagnostic criteria and therapeutic evaluation. Nofal A, Assaf M, Alakad R, et al. Int J Dermatol 2016; 55: 729–38.

The authors propose diagnostic features of FUMHD including fever, acute onset of generalized ulceronecrotic papules and plaques, rapid and progressive course, and histopathology consistent with PLEVA.

First-Line Therapies

- Methotrexate **D**
- Oral erythromycin **C**

A systematic review of treatments for pityriasis lichenoides. Bellinato F, Maurelli M, Gisoni P, et al. J Eur Acad Dermatol Venereol 2019; 33(11): 2039–49.

In this systematic review of 37 manuscripts between 1970 and 2019 on treatments for pityriasis lichenoides in adults and children, three were PLEVA, 10 PLC, and 24 pityriasis lichenoides (both PLEVA and PLC). The recommendations from this systematic review, based on the PLEVA only articles for adults, are: methotrexate (7.5–20 mg/week) or oral erythromycin (500 mg two or three times daily) ± topical corticosteroids; and for children oral erythromycin (30–50 mg/kg/day) ± topical corticosteroids. For the pityriasis lichenoides (PLEVA and PLC) articles, phototherapy was also recommended.

Febrile ulceronecrotic Mucha–Habermann disease responding to methotrexate. Sadlier M, Neville S, Fitzgerald S, et al.

In: Proceedings of the Pediatric Dermatology Conference: 13th World Congress of Pediatric Dermatology; 2017 July, Chicago. Blackwell Publishing Inc.; 2017; 34(Suppl 1): S196.

A 12-year-old male was diagnosed with PLEVA, which then developed into FUMHD. He was treated with oral methotrexate 15 mg/week, which had to be stopped after 6 weeks due to nausea, resulting in recurrence of PLEVA within 2 weeks. He was subsequently started on subcutaneous methotrexate, which resulted in clearance of cutaneous lesions.

Pityriasis lichenoides in childhood: a retrospective review of 124 patients. Ersoy-Evans S, Greco ME, Mancini AJ, et al. J Am Acad Dermatol 2007; 56: 205–10.

This was a retrospective study of 124 children, 71 of whom had PLEVA. The disease was recurrent in 77%. Erythromycin was given to 79.7% of the affected children, and 66.6% of these showed at least a partial response.

Second-Line Therapies

- Narrowband UVB **C**
- Acitretin and PUVA **E**

Pityriasis lichenoides: long-term follow-up study. Zang JB, Coates SJ, Huang J, et al. Pediatr Dermatol 2018; 35(2): 213–9.

In a study of 75 patients with PL from 1997 to 2013, 50 (67%) patients had PLC, 22 (29%) had PLEVA, and three (4%) had mixed PLC and PLEVA. Long-term follow-up was carried out via telephone interview for 46 of the patients. At long-term follow-up, three of 16 PLEVA patients (19%) had active disease and 13 (81%) had complete disease resolution. A 50% improvement of cutaneous lesions was classed as response to treatment. They concluded that phototherapy (NB-UVB) was the most effective treatment for PLEVA (75% response rate), followed by heliotherapy (43%), oral antibiotics (36%), and topical steroids (25%).

Narrowband UVB (311 nm, TL01) phototherapy for pityriasis lichenoides. Aydogan K, Saricaoglu H, Turan H. Photodermatol Photoimmunol Photomed 2008; 24: 128–33.

TL01 treatment led to a complete response in 15 out of 23 PLEVA patients with a mean cumulative dose of 23 J/cm² after a mean of 43.4 exposures. There was a partial response in eight patients (34.8%) with a cumulative dose of 15.6 J/cm² after a mean of 32.3 exposures.

Photochemotherapy for pityriasis lichenoides. Panse I, Bourrat E, Rybojad M, et al. Ann Dermatol Venereol 2004; 131: 201–3.

Two patients, aged 6 and 18 years, presented with a 1-month and 3-month history of PLEVA, respectively. They had received topical corticosteroids, oral antibiotics, UVB therapy, and dapsone with no effect. A combination of acitretin and PUVA (Re-PUVA) was described as dramatically effective within a few weeks.

Third-Line Therapies

- Methotrexate **E**
- Ciclosporin **E**
- Systemic corticosteroids **E**
- Intravenous immunoglobulin **E**
- Azithromycin and topical tacrolimus **E**
- Doxycycline **E**

Febrile ulceronecrotic Mucha–Habermann disease: two cases with excellent response to methotrexate. Griffith-Bauer K, Leitenberger SL, Krol A. *Pediatr Dermatol* 2015; 32: 307–8.

Two biopsy-proven cases of this condition in 6- and 7-year-old boys. One was treated with clindamycin and corticosteroids with minimal benefit. The other was treated with corticosteroids and cefazolin without benefit. Both were then commenced on 7.5 mg/week of methotrexate, leading to clinical improvement within 4 weeks.

Resistant pityriasis lichenoides et varioliformis acuta in a 3-year-old boy: successful treatment with methotrexate. Lazaridou E, Fotiadou C, Tsorova C, et al. *Int J Dermatol* 2010; 49: 215–7.

A 3-year-old boy was diagnosed with biopsy-proven PLEVA. The only therapeutic approach that eventually managed to cease the disease evolution was the combination of prednisolone (1 mg/kg for 8 weeks) and methotrexate (5 mg/week for 8 weeks).

Successful therapy of cyclosporin A in pityriasis lichenoides et varioliformis acuta preceded by hand, foot and mouth disease. Lis-Swięty A, Michalska-Bańkowska A, Zielonka-Kucharszewska A, et al. *Antivir Ther* 2015; 21(3): 273–5.

Enteroviral infection complicated by biopsy-proven PLEVA in a 30-year-old woman. Treatment with 3 mg/kg/day cyclosporin A resulted in rapid clinical improvement and discontinuation after 4 weeks.

Successful long-term use of cyclosporin A in HIV-induced pityriasis lichenoides chronica. Griffiths JK. *J AIDS* 1998; 18: 396.

A 42-year-old woman with AIDS developed biopsy-proven PLC, which then developed into life-threatening, febrile, ulceronecrotic PLEVA. Treatment with cyclosporin 200 mg daily produced a rapid response, though prolonged maintenance treatment was required. Interestingly, the severity of symptoms appeared to parallel the viral load.

Pityriasis lichenoides et varioliformis acuta: case report and review of the literature. Pereira N, Brinca A, Manuel Brites M, et al. *Case Rep Dermatol* 2012; 4: 61–5.

A 63-year-old man with biopsy-proven PLEVA was treated with erythromycin (1 g/day) and methylprednisolone (32 mg/

day), reduced gradually over 5 months, with a slow but complete response.

Febrile ulceronecrotic Mucha–Habermann disease: treatment with infliximab and intravenous immunoglobulins and review of the literature. Meziane L, Caudron A, Dhaille F, et al. *Dermatology* 2012; 225: 344–8.

A 65-year-old woman with a resistant form of Mucha–Habermann disease was treated with the TNF- α inhibitor infliximab (5 mg/kg 6-weekly). However, despite treatment every 6 weeks for 12 months, the patient began to develop new lesions, and treatment became complicated by severe sepsis. The introduction of IVIG (2 mg/kg monthly) induced improvement after 'several' months.

High dose immunoglobulins and extracorporeal photochemotherapy in the treatment of febrile ulceronecrotic Mucha–Habermann disease. Marengo F, Fava MT, Quaglini P, et al. *Dermatol Ther* 2010; 23: 419–22.

A 23-year-old man responded to IVIG (400 mg/kg/day for 5 days monthly) plus methotrexate 10 mg/m² weekly with remission after five courses. He was then started on extracorporeal chemotherapy as maintenance treatment.

Successful association in the treatment of pityriasis lichenoides et varioliformis acuta. Di Constanzo L, Balato N, La Bella S, et al. *J Eur Acad Dermatol Venereol* 2009; 23: 971–2.

A 9-year-old girl who failed on oral erythromycin showed 'significant improvement' on oral azithromycin 500 mg/day for 3 consecutive days on alternate weeks and daily topical tacrolimus 0.1% ointment. Total duration of treatment was not stated, but there was no recurrence at 4 months.

Frequent relapses in a child with nephrotic syndrome due to PLEVA. Deepthi B, Goyal S, Dhull RS, et al. *Trop Doct* 2018; 48(4): 348–9.

This is a case report of a 7-year-old male with frequently relapsing nephrotic syndrome (FRNS) and PLEVA. Each PLEVA relapse preceded FRNS. He was treated with a 7-day course of doxycycline 100 mg twice daily which resulted in the PLEVA and FRNS resolving and the patient remaining asymptomatic at follow-up. Patients with acute severe aggressive disease may need early and aggressive combination therapy.

Pityriasis rosea

Tara Jennings, Warren R. Heymann



Pityriasis rosea (PR) is a common, acute, self-limiting, papulosquamous disorder affecting the trunk and extremities. PR is most commonly seen in the 10- to 35-year age group and has a recorded incidence between 0.5% and 2%. Epidemiologic and microbiologic studies strongly suggest a viral etiology. While controversial, multiple studies suggest a causative relationship with human herpesvirus 6 (HHV-6) and HHV-7. Studies have investigated an etiologic role for HHV-8, and there are two case reports of a PR-like eruption occurring in patients with H1N1 influenza A virus. PR-like eruptions can occur after many drugs, including captopril, ketotifen, and, more recently, adalimumab, imatinib mesylate, and etanercept; however, there is no evidence that classical PR is drug-induced. PR has a characteristic appearance beginning with a single, round, salmon-colored (in light skinned individuals) or violet/red-brown (in darker skinned individuals) 'herald patch' with fine scale located on the trunk. Within 7–14 days, similar smaller lesions appear on the trunk or extremities. PR is associated with little or no constitutional symptoms but may be pruritic. Secondary syphilis and drug eruptions are diagnostic pitfalls and should be ruled out based on serologic studies and a detailed drug history, respectively.

MANAGEMENT STRATEGY

PR typically resolves spontaneously between 2 and 12 weeks, and, if asymptomatic, reassurance is all that is required. Although typically self-limiting, therapeutic guidelines suggest that patients with an extensive exanthem, or severe symptoms such as pruritus,

may benefit from treatment with macrolides, phototherapy, and/or antivirals.

For patients requiring treatment, *emollients and oral antihistamines* have demonstrated efficacy in symptom reduction. Additionally, *topical corticosteroids* may be helpful, although evidence for this is anecdotal.

Ultraviolet light is a second-line therapy. Studies have shown that ultraviolet (UV) B can reduce itch and disease severity. Low-dose UVA1 phototherapy has shown significant diminution in the extent of the disease but little impact on pruritus.

For patients with severe eruptions, oral prednisolone can be utilized; however, this should be prescribed with caution, as patients treated with oral steroids are more likely to develop relapse of disease. In addition, data suggests that oral steroids can exacerbate the condition in certain cases.

A trial of *oral erythromycin* led to complete clearance after 2 weeks in the majority of patients, the best results having occurred when treatment is initiated within the first 2 weeks of the appearance of the eruption. There has been one case report of vesicular PR responding to 10 days of oral erythromycin at a dose of 250 mg four times a day, but further trials using oral erythromycin, azithromycin, and clarithromycin have all failed to show any benefit.

Oral *acyclovir* has been used at both high and low doses for PR with positive results yielding a reduction in severity of symptoms and a shortening of disease course. One study compared high-dose acyclovir with erythromycin and found acyclovir to be more effective. There has also been one case report of PR clearing after oral acyclovir and another demonstrating clearance with dapsone.

Studies have not been conducted for treatment of PR in pregnancy. Despite this, authors propose that patients should be treated with low-dose oral acyclovir for 1 week as there is a proven correlation between PR patients in their first 15 weeks of gestation and miscarriage.

Specific Investigations

- Consider mycologic examination
- Consider syphilis serology

First-Line Therapies

• Topical corticosteroids	E
• Emollients	A
• Oral antihistamines	A

Pityriasis rosea update: 1986. Parsons JM. J Am Acad Dermatol 1986; 15: 159–67.

The author relates his own experience of using topical corticosteroids, emollients, and oral antihistamines in the treatment of PR. He claims all three treatments to have been of some benefit.

Second-Line Therapies

• Narrowband UVB (NB-UVB)	B
• UVA1	C

Narrowband UVB phototherapy in pityriasis rosea. Jairath V, Mohan M, Jindal N, et al. Indian Dermatol Online J 2015; 6(5): 326–9.

One hundred patients were randomly divided into two groups. Group A received treatment with a fixed dose of NB-UVB 250 mJ/cm² three times a week, non-consecutively, for 4 weeks. Group B received placebo treatment. The intensity of pruritus, course and duration of disease, and PR severity score (PRSS) were compared between the two groups. Fixed-dose NB-UVB phototherapy resulted in marked improvement in the severity and symptoms of the disease as quantitatively assessed by PRSS.

Low-dose ultraviolet A1 phototherapy for treating pityriasis rosea. Lim SH, Kim SM, Oh BH, et al. *Ann Dermatol* 2009; 21: 230–6.

Fifteen patients were treated with UVA1 starting at doses of 10–20 J/cm² using 20% increments up to 30 J/cm² given two to three times a week until complete clearance was achieved. Twelve out of the 15 patients showed complete clearance, and the other three showed significant improvement with less than 25% of lesions persisting. The mean number of treatments was 6.5.

Third-Line Therapies

• Oral prednisolone	A
• Oral erythromycin	B
• Oral aciclovir	A
• Dapsone	E

Double-blind randomized placebo-controlled trial to evaluate the efficacy and safety of short-course low-dose oral prednisolone in pityriasis rosea. Sonthalia S, Kumar A, Zawar V, et al. *J Dermatolog Treat* 2018; 29(6): 617–22.

In this placebo-controlled, randomized, double-blind study design the treatment group (35 patients) received tapering doses of oral prednisolone over 2 weeks and the control group (35 patients) received a placebo. The treatment group received prednisolone 20 mg/day (taken as a single dose after breakfast) for 5 days, 15 mg/day for next 5 days, and 10 mg/day for 5 days with a total treatment duration of 15 days. Results of the treatment group demonstrated improvement in the pruritus score as well as the objective rash score. No adverse effects were reported in either group. The relapse rate at 12 weeks was higher in the prednisolone treated group, and therefore authors report that a low-dose prednisolone taper should not be the first line of therapy for PR, unless highly symptomatic or with an extensive disease burden.

Interventions for pityriasis rosea. Contreras-Ruiz J, Peternel S, Jiménez Gutiérrez C, et al. *Cochrane Database of Systematic Reviews* 2019; Issue 10: Art. No. CD005068.

This analysis used 14 randomized control studies of interventions in PR. When compared with placebo or no treatment, three studies indicated that oral aciclovir (most commonly used at 400 mg three times per day for 1 week) led to rash improvement, but the effect on itch was inconclusive. There was moderate evidence that erythromycin reduces itch in comparison to placebo. There was no difference between clarithromycin and placebo. The quality of the evidence for the main comparisons was low to moderate; further research and randomized controlled trial studies are needed.

Comparative study of effectiveness of oral acyclovir with oral erythromycin in the treatment of pityriasis rosea. Amaty A, Rajouria EA, Karn DK. *Kathmandu Univ Med J (KUMJ)* 2012; 10(37): 57–61.

In this study, 42 patients were randomized into two groups. One group was given high-dose oral aciclovir (800 mg 5 times daily for 1 week) and one group was given oral erythromycin (800 mg 4 times daily for 1 week). The aciclovir group demonstrated complete response within 1 month after therapy as opposed to 2 months after therapy in the erythromycin group.

Effectiveness of acyclovir in the treatment of pityriasis rosea. A systematic review and meta-analysis. Rodriguez-Zuniga M, Torres N, Garcia-Perdomo H. *An Bras Dermatol* 2018; 93(5): 686–95.

A systematic review and meta-analysis of experimental studies reviewing seven papers with 324 participants, of which 159 received aciclovir and 165 were controls. Results of the meta-analysis demonstrated that aciclovir was superior to placebo for complete regression of lesions at week 1. However, aciclovir combined with symptomatic treatment (topical steroids and antihistamines) was not superior to symptomatic treatment alone. Furthermore, aciclovir was shown to be superior to placebo and symptomatic treatment for the control of symptoms and pruritus. The authors concluded that symptomatic treatment should be used as baseline PR treatment, and the addition of aciclovir is justified for the control of symptoms and pruritus.

The efficacy of oral acyclovir during early course of pityriasis rosea: a systematic review and meta-analysis. Chang HC, Sung CW, Lin MH. *J Dermatolog Treat* 2019; 30(3): 288–93.

In this systematic review and meta-analysis, five clinical trials including four randomized controlled trials were identified that compared the effects of oral aciclovir ($n=133$) and non-aciclovir ($n=140$) in patients with PR. Results of the analysis demonstrated that oral aciclovir significantly reduced erythema and limited lesion formation compared with non-aciclovir treatment on the 14th day.

Erythromycin in pityriasis rosea: a double-blind, placebo-controlled clinical trial. Sharma PK, Yadav TP, Gautam RK, et al. *J Am Acad Dermatol* 2000; 42: 241–4.

Ninety patients, including children, were randomly assigned to a treatment or a control group. Those in the treatment group received 2 weeks of oral erythromycin 250 mg four times a day for adults or 25–40 mg/kg in four divided doses for children. Of patients in the treatment group, 73% had a complete response compared with none of the controls.

Dapsone treatment in a case of vesicular pityriasis rosea. Anderson CR. *Lancet* 1971; 2: 493.

A case report of a 55-year-old man with histologically proven PR resistant to oral prednisolone responded to dapsone 100 mg twice daily for 1 month.

Pityriasis rosea: risk and treatment during pregnancy. Alajmi A, Jfri A, Pehr K. *J Cutan Med Surg* 2020; 24: 207–8.

In a letter to the editor, the authors reviewed previous studies demonstrating the increased risk of miscarriage in pregnant patients with PR. The authors suggest that given its safety in pregnancy, a course of aciclovir 400 mg three times per day for 1 week can be given to pregnant patients, especially during the first 15 weeks of pregnancy, with high HHV-6 load, exanthem, widespread eruption, or severe pruritus.

Pityriasis rubra pilaris

Steven Krueger, Alireza Firooz, Mehdi Rashighi



Pityriasis rubra pilaris (PRP) is a rare, papulosquamous disorder with a variable presentation and course. It is characterized by follicular hyperkeratotic papules and coalescing salmon-colored plaques with 'islands of sparing' that can progress to erythroderma. PRP can be divided into six subtypes based on age of onset, morphologic phenotype, and the presence of HIV infection:

- Type I: classical adult
- Type II: atypical adult
- Type III: classical juvenile
- Type IV: circumscribed juvenile
- Type V: atypical juvenile
- Type VI: HIV-associated

Type I (classical adult) PRP is the most common form of the disease (>50% of all cases) and presents with rapid-onset erythroderma, diffuse scale, and keratoderma. Patients with types I and III PRP usually experience spontaneous remission within 1–3 years, while the other types demonstrate a variable or chronic course.

While PRP is typically an idiopathic disorder, it has also been reported in association with various drugs, infections, malignancies, autoimmune diseases, skin trauma, and ultraviolet (UV) exposure. In addition, there are reports of familial cases most commonly associated with mutations in *CARD14*.

Given the rarity of the condition, there are no randomized controlled trials assessing treatment efficacy in PRP. Furthermore, it is often unclear whether clinical improvement represents real treatment efficacy or spontaneous remission of the disease. Treatment recommendations are based on case reports and small case series. Recently, multiple robust systematic reviews have been published evaluating the various systemic therapies used to treat this disease.

MANAGEMENT STRATEGY

Topical therapies mainly serve as adjuncts to systemic treatment for PRP. *Emollient* use should be encouraged in combination with

keratolytics. Topical steroids may reduce pruritus but are often ineffective. Additional topical treatments to be considered include retinoids, vitamin D analogs, and calcineurin inhibitors.

There are a few case reports of the effective use of both narrow-band UVB and psoralen and ultraviolet A (PUVA) for PRP. However, given there are also reported cases of UV-induced worsening or onset of PRP, phototherapy should be used cautiously and only when other treatments are contraindicated. Pretreatment phototesting is recommended.

Oral retinoids are considered the first-line treatment for most forms of PRP. In a recent systematic review, significantly higher rates of excellent response were observed with isotretinoin and alitretinoin compared with acitretin. The considerably shorter half-life of the former two drugs (5 weeks) compared to acitretin (3 years) should also be considered when selecting a systemic retinoid.

It is recommended to initiate treatment with isotretinoin at 0.5–2 mg/kg daily for rapid improvement, and then add a second agent if intolerable side effects ensue or if the response is inadequate.

Methotrexate has been reported in several case series as being effective in type I PRP. The long-term efficacy of methotrexate is well established. The reported effective doses range from 10 to 25 mg weekly, but in some patients, higher doses may be necessary. Despite concerns for hepatotoxicity, the concomitant use of methotrexate and retinoids has been reported as a safe combination.

Due to their clinical similarity and evidence of shared immune pathogenesis, targeted treatments for psoriasis have been tested in patients with PRP. Multiple systematic reviews and case reports have demonstrated the successful use of biologics and small molecule inhibitors in treating PRP, including tumor necrosis factor- α (TNF- α) inhibitors, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, and apremilast.

Type VI PRP may respond to antiretroviral therapy. The response appears to correlate with a reduction in viral load.

There is anecdotal evidence (mostly isolated case reports) detailing the successful use of the following in PRP: intravenous immunoglobulin, extracorporeal photochemotherapy, azathioprine, mycophenolate, fumarates, penicillins, and pulsed dye laser.

Specific Investigations

- Histology
- Comprehensive metabolic panel and complete blood count
- HIV testing
- Flow cytometry

Histology of the affected skin can be useful in aiding the diagnosis. Routine blood tests are recommended as markers of general health and as screening for the use of systemic agents.

An HIV test should be done in all patients. Furthermore, if any suspicion exists, it may be necessary to obtain peripheral blood flow cytometry to rule out cutaneous T-cell lymphoma.

SYSTEMATIC REVIEWS

Systemic therapies of pityriasis rubra pilaris: a systematic review. Kromer C, Sabat R, Celis D, et al. *J Dtsch Dermatol Ges* 2019; 17: 243–59.

In this systematic review of 182 studies reporting on 475 patients, an excellent response was achieved in 42% of patients

treated with retinoids, 33% treated with methotrexate, and 51% treated with biologics. Considering multiple factors, including effectiveness, safety, and costs, the investigators suggest starting with isotretinoin as first line, methotrexate as second line, and biologics as third line.

Treatment of pityriasis rubra pilaris type I: a systematic review. Engelmann C, Elsner P, Miguel D. *Eur J Dermatol* 2019; 29: 524–37.

In this systematic review of 105 studies documenting therapies for type I PRP, the authors suggest first-line treatment with a systemic retinoid; second-line treatment with a combination of retinoid and methotrexate, azathioprine, or ciclosporin; and third-line treatment with biologics, in addition to continuous topical treatment and phototherapy when appropriate.

First-Line Therapy

- Retinoids

B

Pityriasis rubra pilaris response to 13-cis-retinoic acid (isotretinoin). Goldsmith LA, Weinrich AE, Shupack J. *J Am Acad Dermatol* 1982; 6: 710–5.

In this prospective, single-arm, non-blinded study, 28 of 45 patients (62%) treated with isotretinoin had marked improvement within 4 weeks, and all 34 patients who returned for follow-up showed marked improvement after 16 weeks of treatment.

The publications above support the use of isotretinoin in doses of 0.5–2 mg/kg daily. Additional options for systemic retinoid therapy include alitretinoin, etretinate, and acitretin.

Second-Line Therapy

- Methotrexate

C

Methotrexate treatment for pityriasis rubra pilaris: a case series and literature review. Koch L, Schöffl C, Aberer W, et al. *Acta Derm Venereol* 2018; 98: 501–5.

In this review of 116 patients treated with methotrexate, the overall response rate was 65.5%, with complete clearing in 23.3% and excellent improvement in 17.2%. The doses most commonly administered were between 15 and 25 mg weekly, and doses higher than 25 mg weekly did not show any trend toward a better outcome.

Third-Line Therapies

- TNF- α inhibitors
- Ustekinumab
- IL-17 inhibitors
- IL-23 inhibitors
- Apremilast
- Ciclosporin

C

C

D

E

E

D

Use of biologics in pityriasis rubra pilaris refractory to first-line systemic therapy: a systematic review. Naidoo A, Sibbald C, Fleming PJ, et al. *J Cutan Med Surg* 2020; 24: 73–8.

TNF- α inhibitors: infliximab was the most commonly reported biologic used in treatment-refractory PRP after either failing or having contraindications to first-line therapies (retinoids or methotrexate). Out of 35 patients who received one of the TNF- α

inhibitors (infliximab, etanercept, or adalimumab), the average rate of complete response was approximately 80%.

Ustekinumab: out of 15 patients who received ustekinumab, 92.3% had a complete response.

Biologics for pityriasis rubra pilaris treatment: a review of the literature. Napolitano M, Abeni D, Didona B. *J Am Acad Dermatol* 2018; 79: 353–9.

TNF- α inhibitors: etanercept was found to have the highest rate of marked to complete response (72.8%), followed by infliximab (68%) and adalimumab (50%).

Ustekinumab: out of 18 patients who received ustekinumab, 78% achieved a marked to complete response.

Systemic therapies of pityriasis rubra pilaris: a systematic review. Kromer C, Sabat R, Celis D, et al. *J Dtsch Dermatol Ges* 2019; 17: 243–59.

TNF- α inhibitors: infliximab was found to have the highest rate of excellent response (57.1%), followed by etanercept (53.3%) and adalimumab (46.4%).

Ustekinumab: out of 16 patients who received ustekinumab, 62.5% achieved an excellent response.

The same doses of TNF- α inhibitors used for psoriasis have been effective for PRP: subcutaneous etanercept at doses of 25 mg twice weekly or 50 mg one to two times weekly; subcutaneous adalimumab at doses of 80 mg followed by 40 mg every other week; and infusions of infliximab at doses of 5 mg/kg at weeks 0, 2, and 6, and every 6–8 weeks thereafter.

Ustekinumab (IL-12/23 inhibitor) has been used successfully for PRP in several case reports using standard psoriasis dosing (45 mg under 100 kg and 90 mg over 100 kg) at weeks 0 and 4, and every 12 weeks thereafter.

Cosentyx (secukinumab) for the treatment of adult onset pityriasis rubra pilaris. ClinicalTrials.gov identifier: NCT03342573

This single-arm, open-label study is currently enrolling patients.

Successful treatment of refractory pityriasis rubra pilaris with secukinumab. Schuster D, Pfister-Wartha A, Bruckner-Tuderman L, et al. *JAMA Dermatol* 2016; 152: 1278–80.

A patient with PRP refractory to acitretin responded to secukinumab at standard psoriasis dosing: 300 mg subcutaneously weekly for 5 weeks followed by 300 mg monthly. Response was noted in 3 weeks and complete clearing by 8 weeks.

Evaluation of ixekizumab treatment for patients with pityriasis rubra pilaris: a single-arm trial. Haynes D, Strunck JL, Topham CA, et al. *JAMA Dermatol* 2020 Jun 1 [Epub ahead of print].

In this single-arm trial of adult patients with PRP treated with ixekizumab using psoriasis dosing, seven of 12 subjects achieved a 50% or greater reduction in the Psoriasis Area and Severity Index after 24 weeks of treatment. There was a measurable improvement in quality of life, pain, and itch scores as well.

Successful treatment of TNF α inhibitor-resistant pityriasis rubra pilaris with ixekizumab and acitretin. Chastagner M, Hoelt P, Kanitakis J, et al. *Eur J Dermatol* 2019; 29: 218–20.

A 48-year-old woman with type I PRP had a marked response to ixekizumab (80 mg subcutaneously every 2 weeks) in conjunction with acitretin after failing treatment with methotrexate, infliximab, and adalimumab.

Successful treatment of type I pityriasis rubra pilaris with ixekizumab. Heibel MD, Heibel HD. JAAD Case Rep 2018; 4: 774–6.

Familial pityriasis rubra pilaris successfully treated with brodalumab. De Felice C, Graceffa D, Morrone A, et al. Int J Dermatol 2020 Mar 23 [Epub ahead of print].

After failing multiple systemic treatments, a 52-year-old female with familial type V PRP achieved a complete response to brodalumab at standard psoriasis dosing (210 mg subcutaneously every 2 weeks after three loading doses at weeks 0, 1, and 2).

Treatment of pityriasis rubra pilaris with guselkumab. Pilz AC, Seiringer P, Biedermann T, et al. JAMA Dermatol 2019 Oct 2 [Epub ahead of print].

Two patients with severe PRP experienced marked responses to guselkumab 100 mg administered subcutaneously at weeks 0 and 4 and then every 8 weeks thereafter.

A case of severe pityriasis rubra pilaris with a dramatic response to apremilast. Pellonnet L, Beltzung F, Franck F, et al. Eur J Dermatol 2018; 28: 128–9.

Treatment of refractory pityriasis rubra pilaris with novel phosphodiesterase 4 (PDE4) inhibitor apremilast. Krase

IZ, Cavanaugh K, Curiel-Lewandrowski C. JAMA Dermatol 2016; 152: 348–50.

A 70-year-old male developed leukemia shortly after starting infliximab for PRP. His treatment was changed to apremilast starting at 10 mg daily increased over 5 days to 30 mg twice daily (psoriasis dosing) with good response.

Treatment of pityriasis rubra pilaris type I: a systematic review. Engelmann C, Elsner P, Miguel D. Eur J Dermatol 2019; 29: 524–37.

Ciclosporin: the majority of 30 patients treated with ciclosporin showed a worsening of skin lesions or no significant improvement. Multiple cases showed an initial response to treatment, but either relapsed after dose reduction or discontinuation of ciclosporin treatment or discontinued the treatment due to severe side effects.

Systemic therapies of pityriasis rubra pilaris: a systematic review. Kromer C, Sabat R, Celis D, et al. J Dtsch Dermatol Ges 2019; 17: 243–59.

Ciclosporin: only 11.8% of 25 patients treated with ciclosporin (alone or in combination with other agents) achieved an excellent response. While ciclosporin has a rapid onset of action, its lower efficacy and unfavorable safety profile limit its use in PRP.

Polycystic ovary syndrome

Kanade Shinkai, Boya Abudu



Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects approximately 10% of reproductive-age women. The 2003 Rotterdam criteria are widely used to diagnose PCOS when two of the following three criteria are met: 1) oligomenorrhea or anovulation; 2) clinical or biochemical hyperandrogenism; and 3) polycystic ovaries on transvaginal ultrasound. PCOS is the most common cause of clinical hyperandrogenism in premenopausal women; the most reliable cutaneous sign of hyperandrogenism is hirsutism. Common skin features of PCOS include acne (present in 61% of patients who meet Rotterdam criteria for PCOS), hirsutism (53%), acanthosis nigricans (AN) (37%), and androgenic alopecia (AGA) (22%). Nearly a quarter of women with PCOS first present to a dermatologist with a skin or hair complaint.

Screening for PCOS should be considered in premenopausal females with hirsutism or menstrual abnormalities in combination with cutaneous signs of PCOS. Adolescents experiencing menstrual abnormalities and/or moderate-to-severe hirsutism should be screened if menstrual irregularities extend beyond 2 years after menarche. It is recommended that adolescents meet all three Rotterdam criteria before a diagnosis of PCOS is made or that a provisional diagnosis is made if pelvic ultrasound is deferred.

A diagnosis of PCOS also requires exclusion of alternative diagnoses. In addition to transvaginal ultrasound, initial tests should include free testosterone and 17-hydroxyprogesterone (17-OHP) levels (to exclude non-classical congenital adrenal hyperplasia). Amenorrhea workup includes thyroid stimulating hormone

(TSH), β -hCG, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Additional tests are prolactin, total testosterone, sex hormone-binding globulin, dehydroepiandrosterone sulfate (DHEAS), androstenedione, and cortisol; however, these are not recommended as part of the initial evaluation of patients and should be performed only if there is clinical evidence to suggest an alternative diagnosis (e.g., virilization) or the suspicion for PCOS is very strong and initial screening is negative. PCOS is associated with insulin resistance and diabetes mellitus; an oral glucose tolerance test and measurement of hemoglobin A1c is recommended after a diagnosis of PCOS is established.

MANAGEMENT STRATEGY

Treatment of cutaneous signs of PCOS is often warranted because the quality of life impact can be significant depending on the type, location, and severity of cutaneous manifestations present. Treatment with any antiandrogenic agent requires 3–6 months to see clinical benefit and always requires long-term treatment. It is unknown whether treating acne, hirsutism, AGA, or AN is similar or different in PCOS patients compared with healthy female patients. Selection of treatment depends on other systemic comorbidities of PCOS and whether the patient is actively attempting to conceive. *Lifestyle modifications (e.g., diet and physical activity)* may improve the cardiometabolic profile driving hormonal dysregulation but evidence is lacking on whether it improves cutaneous findings in PCOS.

Acne is a common yet non-specific skin finding in PCOS. The Food and Drug Administration-approved combination oral contraceptives (COCs) for acne in the general female population are *Yaz (ethinyl estradiol [EE] + drospirenone)*, *Ortho Tri-Cyclen (EE + norgestimate)*, and *Estrostep (EE + norethisterone)*, which demonstrate similar efficacy. A COC with the highest available non-phasic estrogen content and greater antiandrogenic properties of the progestin component (i.e., drospirenone) is theoretically ideal for PCOS management. COCs in combination with *spironolactone* ≥ 100 mg/dL are effective in PCOS. *Isotretinoin* is useful in PCOS patients who do not respond to alternative therapies. There is scant data on the efficacy of topical or non-hormonal oral therapy (e.g., antibiotics) for acne in the PCOS population.

Hirsutism is the most specific cutaneous sign of PCOS; more than half of patients are affected and its prevalence varies by Fitzpatrick skin type. Seventy percent of hirsute patients are ultimately diagnosed with PCOS. Affected areas include the upper cutaneous lip, chin, trunk, shoulders, and thighs and can be measured using the modified Ferriman–Gallwey (mFG) scale. COC monotherapy is indicated in patients with mild hirsutism. *Spironolactone* (≤ 200 mg daily) is efficacious in PCOS patients refractory to COC monotherapy or with moderate-to-severe hirsutism. Whether the combination of spironolactone and COC has additional benefit over spironolactone monotherapy is unknown. *Cyproterone acetate* (available in most developed countries except the United States and Japan) has shown benefit in PCOS patients with hirsutism. There is emerging data to support *bicalutamide* (≤ 50 mg daily) with COCs in PCOS. Data on other antiandrogens is limited to the general female population: use of flutamide is no longer recommended due to hepatotoxicity and *finasteride* may be less effective. *Laser and intense pulsed light* therapies are useful in PCOS but less effective in patients with higher Fitzpatrick skin types or lighter hair colors (e.g., white, red, or blonde hair). *Eflornithine hydrochloride* (13.9% cream) and *electrolysis* have not been studied in the PCOS population. *Metformin*, *statins*, and *thiazolidinediones* have a limited role in cutaneous therapy of PCOS.

AN is a sensitive and specific skin sign seen in 37% of patients with PCOS and affects the nape, axilla (most commonly affected site), inframammary region, central chest, inguinal folds, and face (e.g., periorificial). It is unclear whether lifestyle modifications and metformin improve AN in PCOS. Successful use of topical agents such as *keratolytics* (e.g., *ammonium lactate* 12%, *tretinoin*, *topical urea*) are limited to poor quality evidence (i.e., case reports) in the general female population.

The association between AGA and PCOS is unclear since this pattern of hair loss often occurs with normal or absent circulating androgens. *Minoxidil* has the strongest evidence for efficacy in the general female population, with 5% topical formulations once daily having similar efficacy to 2% twice daily. COCs and spironolactone have not been shown to improve AGA in the PCOS population.

Specific Investigations

- Detailed medical history
- Free testosterone, 17-hydroxyprogesterone, transvaginal ultrasound
- Consider amenorrhea workup: β -hCG, TSH, FSH, LH

Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. Legro RS, Arslanian SA, Ehrmann DA, et al. Endocrine Society. J Clin Endocrinol Metab 2013; 98: 4565–92.

Evidence-based guidelines on PCOS by the Endocrine Society based on systematic reviews of the literature.

First-Line Therapies

• Combination oral contraceptives	B
• Lifestyle modifications	B
• Spironolactone	B
• Intense pulsed light/laser hair removal	A
• Minoxidil	E

Combined oral contraceptives in the treatment of polycystic ovary syndrome. Vrbikova J, Cibula D. Hum Reprod Update 2005; 11: 277–91.

Review of the impact of COCs on the metabolic profile of PCOS.

Lifestyle changes in women with polycystic ovary syndrome. Lim SS, Hutchison SK, Van Ryswyk E, et al. Cochrane Database Syst Rev 2019; 3: CD007506.

Meta-analysis of 15 studies ($n=498$) found dietary changes, physical activity, and behavioral modifications improved body mass index but had an unclear role in glucose tolerance or hyperandrogenism.

Role of the combination spironolactone-norgestimate-estrogen in hirsute women with polycystic ovary syndrome. Hagag P, Steinschneider M, Weiss M. J Reprod Med 2014; 59: 455–63.

Prospective study ($n=167$) comparing spironolactone + norgestimate + EE, cyproterone acetate + EE, and EE + norgestimate showed a reduction in mFG score in the spironolactone-containing group compared with other groups.

High-dose spironolactone for acne in patients with polycystic ovarian syndrome: a single institution retrospective study. Basu P, Elman SA, Abudu B, et al. J Am Acad Dermatol 2019; S0190-9622: 32497-1.

Retrospective study ($n=61$) demonstrated tolerability of spironolactone at doses ≥ 100 mg/day. Patient-reported acne improvement was greater at higher doses of spironolactone (mean = 166 mg) compared to lower doses (mean = 130 mg).

A randomized controlled trial of laser treatment among hirsute women with polycystic ovary syndrome. Clayton WJ, Lipton M, Elford J, et al. Br J Dermatol 2005; 152: 986–92.

Eighty-eight patients receiving laser hair removal over a 6-month period showed improvement in hirsutism on a 10-point scale from 7.3 to 3.6 in the high-fluence group compared with 7.1–6.1 in the low-fluence group. Patient time spent on hair removal declined from 112 min/week to 21 min/week in the high-fluence group versus 92 min/week to 56 min/week in the low-fluence group.

Female pattern hair loss and androgen excess: a report from the multidisciplinary androgen excess and PCOS committee. Carmina E, Azziz R, Bergfeld W, et al. J Clin Endocrinol Metab 2019; 104: 2875–91.

Meta-analysis on the epidemiology, pathophysiology, diagnosis, and treatment of AGA. Topical minoxidil 5% is the first-line treatment. 5α -reductase inhibitors (e.g., finasteride 2.5 or 5 mg/dL) or antiandrogens (e.g., spironolactone 100–200 mg/dL) may enhance the effects of minoxidil. Evidence for dutasteride and cyproterone acetate is limited while risk of hepatotoxicity from flutamide is concerning. Evidence for platelet-rich plasma, low-level laser light therapy, and hair transplantation is limited.

Second-Line Therapies

• Cyproterone acetate	A
• Bicalutamide	A
• Oral isotretinoin	B

Comparative study of the therapeutic effects of oral contraceptive pills containing desogestrel, cyproterone acetate, and drospirenone in patients with polycystic ovary syndrome. Bhattacharya SM, Jha A. Fertil Steril 2012; 98: 1053–9.

Double-blind RCT ($n=171$) found cyproterone acetate reduced mFG scores in comparison to desogestrel and drospirenone-containing COCs while minimizing adverse effects.

Combined oral contraception and bicalutamide in polycystic ovary syndrome and severe hirsutism: a double-blind randomized controlled trial. Moretti C, Guccione L, Di Giacinto P, et al. J Clin Endocrinol Metab 2018; 103: 824–38.

Seventy patients receiving COC + bicalutamide 50 mg daily or COC + placebo showed significant reductions in mFG score in both groups.

The effects of oral isotretinoin in women with acne and polycystic ovary syndrome. Acmaz G, Cinar L, Acmaz B, et al. Biomed Res Int 2019; 2019: 2513067.

Prospective study ($n=40$) of patients with severe cystic acne and contraindications to COCs were treated with isotretinoin starting at 20 mg/day and going to 40 mg/day and had a decrease in mean acne score at 6 months.

Third-Line Therapies

• Flutamide	A
• Finasteride	A
• Thiazolidinediones (pioglitazone and rosiglitazone)	B
• Metformin	B

Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. Moghetti P, Tosi F, Tosti A, et al. J Clin Endocrinol Metab 2000; 85: 89–94.

Statistically significant reduction in mFG score in 40 patients treated with daily oral spironolactone 100 mg, flutamide 250 mg or finasteride 5 mg with no difference between antiandrogens.

This study did not stratify PCOS (n=21) vs. non-PCOS (n=19) patients, making the generalizability of the results in the PCOS population unclear.

Metformin vs thiazolidinediones for treatment of clinical, hormonal and metabolic characteristics of polycystic ovary syndrome: a meta-analysis. Li XJ, Yu YX, Liu CQ, et al. Clin Endocrinol 2011; 74: 332–9.

Comparison of 10 RCTs showed unclear clinical or metabolic benefit of metformin or thiazolidinediones in PCOS.

Polymorphic light eruption

Tsui Chin Ling



Polymorphic light eruption (PLE) is a highly prevalent photosensitivity disorder, estimated to affect 11–21% people in temperate countries. Typically, PLE appears as a recurrent pruritic eruption comprising papules, vesicles and/or plaques, which occurs on photoexposed skin sites following sun exposure, and which heals without scarring. Other forms include purpura, erythema multiforme, pinpoint papular (in African Americans), and 'juvenile spring eruption' described in young boys. Commoner in females, the etiology is uncertain, although there is evidence of an immune basis. Most patients only experience symptoms on sunny vacations, while the most severely affected may also be symptomatic in winter months. The diagnosis of PLE is usually made clinically; history and patient examination or photographs are necessary to exclude other photodermatoses. In atypical cases, positive photoprovocation test to UVA and UVB-emitting lamps, and histology of photoproved eruption, confirm the diagnosis.

MANAGEMENT STRATEGY

For most patients with PLE, the rash is mild, self-limiting, and quickly settles within a few days of sun avoidance. Treatments may be prophylactic or suppressive, and depend on disease severity, availability of equipment, and patient choice. In the majority of patients, prophylactic management is by *sun avoidance/reduced midday sun exposure, protective clothing, UV-protective umbrellas and swimsuits, and broad-spectrum sunscreens (i.e., UVA and UVB protective)*. Gradual *self-hardening* by regular exposure to natural sunlight in early spring may also be helpful. For the more severe patient, the disease may be triggered within 15–30 minutes of sun exposure and may require additional therapy.

For any exacerbations, the use of a *potent/very potent topical corticosteroid*, used liberally to the affected skin for a few days, is usually sufficient to bring the condition under control. There is also some evidence that pretreatment with topical corticosteroid before natural sun exposure that is expected to induce a flare can

be a helpful preventative measure. Oral antihistamines are helpful to alleviate pruritus but do not induce resolution and are not mainstays of treatment.

The mainstay of prophylactic management is phototherapy – *narrowband UVB (312 nm), systemic photochemotherapy with PUVA (psoralen-UVA), or broadband UVB*. This induces artificial skin hardening and can be administered in early spring, or just prior to a special sunny vacation abroad. Phototherapy administered for PLE is generally given as a relatively short course, over 4–6 weeks, using low initial UV doses compared with schedules used for psoriasis; the aim is to induce natural skin hardening rather than treat the disease. NB-UVB is the phototherapy of first choice due to its safety profile and convenience over systemic PUVA. NB-UVB has also superseded BB-UVB. There is a high risk of rash provocation (estimated up to 50%), which can be reduced by the use of potent/very potent topical corticosteroids immediately after each exposure. Any provocation of PLE can be managed by adjusting UV doses and use of corticosteroids. Specific advice should be given for continued regular cautious exposure to natural sunlight after completion of the course to maintain the level of hardening.

In PLE cases resistant to photoprotective measures and phototherapy, other antiinflammatory agents and immunomodulators include *azathioprine, ciclosporin, hydroxychloroquine, beta-carotene, nicotinamide, omega-3 polyunsaturated fatty acids, topical flavonoids, polypodium leucotomos, and others*.

Specific Investigations (Optional)

- Skin biopsy of naturally occurring or artificially provoked skin eruption
- Photoinvestigation (provocation testing and photopatch testing)
- Connective tissue disease screen (including antinuclear antibodies)

Antinuclear antibodies in patients with polymorphic light eruption: a long-term follow-up study. Tzaneva S, Volc-Platzer B, Kittler H, et al. *Br J Dermatol* 2008; 158(5): 1050–4.

Of the 472 patients with PLE who received PUVA, 12% had antinuclear antibodies (i.e., ANA titre >1:80), and 0.6% had anti-Ro/SS-A antibodies. Of all ANA-positive patients, 71% were followed up for a mean of 8 years; two-thirds had a persistently elevated ANA with median titre of 1:160, whereas in one-third the ANA titre had normalized. None progressed to lupus erythematosus (LE).

Routine ANA testing is unnecessary unless clinically indicated.

First-Line Therapies

• Restriction of sun exposure	E
• Protective clothing	E
• Education on application of broad-spectrum sunscreens	C
• Topical corticosteroids	A

Textiles and sun protection. Robson J, Diffey BL. *Photodermatol Photoimmunol Photomed* 1990; 7(1): 32–4.

The tightness of the weave of clothing fabrics determines the amount of photoprotection; thus, while a typical crêpe blouse gives a sun protection factor (SPF) of only 5, a jersey T-shirt has an SPF of 32 and a silk blouse 280. From a practical viewpoint, holding the fabric up against bright lighting will give the patient

some indication of the tightness of the weave and hence its suitability for protection. The transmission of UV radiation for all fabrics is increased when a fabric is wet.

Sunscreen application technique in photosensitive patients: a quantitative assessment of the effect of education. Azurdia RM, Pagliaro JA, Rhodes LE. Photodermatol Photoimmunol Photomed 2000; 16(2): 53–6.

The efficacy of the newer generation broad-spectrum sunscreens is well established. However, previous studies have demonstrated that photosensitive patients only apply approximately a quarter of the thickness of cream used under manufacturer's test conditions, i.e., 2 mg/cm². In this study, patient education resulted in sustained improvement in patient sunscreen application technique, with median sunscreen thickness on the face improving from a baseline of 0.33 mg/cm² to 1.51 mg/cm² at 6 months.

Is topical steroid effective in polymorphic light eruption? Man I, Dawe RS, Ibbotson SH, et al. Br J Dermatol 2000; 142 (Suppl 57): 112–4.

Potent/very potent topical corticosteroids may be adequate for exacerbations of PLE. This small double-blind study shows that routine application of topical steroid immediately after UVB phototherapy prevented provocation in 5/7 patients.

Topical steroids applied immediately after phototherapy may reduce the incidence and severity of provoked rash during treatment and enable patients to complete the course.

Second-Line Therapies

- Phototherapy A
- Photochemotherapy A

A comparison of narrow band phototherapy (TL-01) and photochemotherapy (PUVA) in the management of polymorphic light eruption. Bilisland D, George SA, Gibbs NK, et al. Br J Dermatol 1993; 129: 708–12.

A group of 13 patients were randomized to receive NB-UVB (and placebo tablets) and another of 12 to receive PUVA three times a week for 5 weeks in spring. About 85% of patients in each treatment group were adequately protected from developing PLE during summer, and there was no significant difference in the efficacy of NB-UVB and PUVA.

Artificial hardening for polymorphic light eruption: practical points from ten years' experience. Man I, Dawe RS, Ferguson J. Photodermatol Photoimmunol Photomed 1999; 15(3-4): 96–99.

This retrospective review of 170 PLE patients reports the efficacy of different phototherapy modalities – NB-UVB (128), PUVA (8), and BB-UVB (5); 29 patients who failed to respond satisfactorily to NB-UVB were given PUVA the following year. For NB-UVB, initial irradiation dose is 70% of MED with 20% increments three times weekly for 5 weeks (total 15 treatments). Good or moderate improvement was reported in 88% who received PUVA and 89% who received NB-UVB. Mild PLE is provoked in half the treatment courses, and patients were advised that the first course of phototherapy is often exploratory. Specific advice is given for continued sunlight exposure posttreatment to maintain hardening.

British Association of Dermatologists and British Photodermatology Group guidelines for the safe and effective use of psoralen-ultraviolet A therapy 2015. Ling TC, Clayton TH, Crawley J, et al. Br J Dermatol 2016; 174(1): 24–55.

The British Photodermatology Group recommends the use of PUVA in PLE if NB-UVB has failed or has previously triggered the eruption, or if there are other practical issues. PUVA should be considered even if NB-UVB had not previously been effective and should be considered before other systemic treatments.

Third-Line Therapies

- Prednisolone A
- Hydroxychloroquine/chloroquine C
- Topical flavonoid antioxidant A
- Polypodium leucotomos B
- Azathioprine E
- Ciclosporin E
- Beta-carotene-ineffective A
- Nicotinamide-ineffective B
- Omega-3 fatty acids (provocation study) C
- Topical liposomal DNA-repair enzymes (provocation study) C
- 1,25-dihydroxyvitamin D₃ analog (provocation study) C

Efficacy of short-course oral prednisolone in polymorphic light eruption: a randomized controlled trial. Patel DC, Bel-laney GJ, Seed PT, et al. Br J Dermatol 2000; 143(4): 828–31.

A total of 21 PLE patients were randomized to receive both prednisolone (25 mg) and placebo tablets prior to a sunny vacation. Eight who took prednisolone first or transferred to it from placebo found that the itch and rash settled more quickly compared with the two patients who took placebo first and remained on it. The authors suggested the use of 25 mg prednisolone daily for 4–5 days at the onset of an attack.

The potential long-term side effects of repeated courses of prednisolone must be considered, particularly since some patients may take several sunny vacations per year. Cautious use of prednisolone for those who do not respond to potent/very potent topical steroids can be considered.

Hydroxychloroquine in polymorphic light eruption: a controlled trial with drug and visual sensitivity monitoring. Murphy GM, Hawk JLM, Magnus IA. Br J Dermatol 1987; 116: 379–86.

This trial compared nine patients on active treatment with 10 on placebo. Hydroxychloroquine given in a dose of 400 mg daily for 1 month, and 200 mg daily for 2 months, has a modest benefit in reducing the rash and skin irritation, but PLE was not abolished in the majority of patients. No visual toxicity was observed.

Polymorphous light eruption (PLE) and a new potent antioxidant and UVA-protective formulation as prophylaxis. Hadshiew IM, Treder-Conrad C, Bülow RV, et al. Photodermatol Photoimmunol Photomed 2004; 20: 200–4.

A flavonoid antioxidant (α -glucosylrutin, vitamin E plus a broad-spectrum sunscreen, Eucerin Sun Allergy Protection Cream Gel 15, Beiersdorf AG, Hamburg, Germany) was more effective in preventing PLE than sunscreen alone or placebo. Of the 29 participants, 93% rated 'very effective' for this formulation compared with 24% on placebo and 48% on sunscreen and vitamin E only.

Oral polypodium leucotomos extract photoprotective activity in 57 patients with idiopathic photodermatoses. Caccialanza M, Recalcati S, Piccinno R. G Ital Dermatol Venereol 2011; 146(2): 85–7.

This prospective, uncontrolled trial in 53 patients with polymorphic light eruption (and four with solar urticaria) taking 480 mg/day of *polypodium leucotomos* extract (a fern native to Central America) reduced skin reaction and subjective symptoms in 74%. The drug was started 15 days before solar exposure and continued throughout the period of exposure and excluded the use of sunscreens.

Successful treatment of severe polymorphous light eruption with azathioprine. Norris PG, Hawk JL. Arch Dermatol 1989; 125(10): 1377–9.

Two patients with exquisite photosensitivity were treated with azathioprine at a dose of 50–150 mg daily (0.8–2.5 mg/kg) for 3 months, with marked improvement of symptoms and minimal erythematous responses to UVB and UVA.

Prophylactic short-term use of cyclosporin in refractory polymorphic light eruption. Lasa O, Trebol I, Gardeazabal J, et al. J Eur Acad Dermatol Venereol 2004; 18(6): 747–8.

Three patients received cyclosporin at a dose of 3–4 mg/kg/day over 2 or 4 weeks; treatment was started 1 week before traveling to sunny climates. The clinical response was excellent, and no adverse effects were observed.

Controlled therapeutic trials in polymorphic light eruption. Corbett ME, Hawk JL, Herxheimer A, et al. Br J Dermatol 1982; 107(5): 571–81.

Beta-carotene given in a dose of 150–200 mg daily for 12–15 weeks in this randomized, placebo-controlled trial showed a high overall dropout rate of approximately 40%, and no consistent difference in reduction of symptoms between beta-carotene and placebo.

Treatment of polymorphous light eruption with nicotinamide: a pilot study. Neumann R, Rappold E, Pohl-Markl H. Br J Dermatol 1986; 115(1): 77–80.

This was reported to be moderately effective in an uncontrolled trial of 42 patients, who also used topical sunscreens of SPF 6–17. When taken at a dose of 2–3 g daily before sun exposure, 60% of patients reported complete abolition of symptoms despite continued sun exposure, while 26% reported no benefit. Apart from mild fatigue in some patients, the treatment was well tolerated.

Dietary fish oil reduces basal and ultraviolet B-generated PGE2 levels in skin and increases the threshold to provocation of polymorphic light eruption. Rhodes LE, Durham BH, Fraser WD, et al. J Invest Dermatol 1995; 105(4): 532–5.

In 13 patients taking 10 g mixed ω -3 PUFAs (MaxEPA, Seven Seas, Hull, UK), taken as five capsules twice daily for 3 months, significantly increased the MED to UVB, and significantly increased the threshold for UVA-provocation of rash.

Topical liposomal DNA-repair enzymes in polymorphic light eruption. Hofer A, Legat FJ, Gruber-Wackernagel A, et al. Photochem Photobiol Sci 2011; 10(7): 1118–28.

This within-patient study of 18 participants showed that an aftersun lotion (containing plankton extract and DNA-repair enzymes) significantly reduced PLE severity on artificial provocation compared with placebo. The relatively short study period and use of provocation rather than in-use assessment make firm conclusions difficult.

Randomized, double blinded placebo-controlled intra-individual trial on topical treatment with a 1,25 dihydroxyvitamin D₃ analogue in polymorphic light eruption. Gruber-Wackernagel A, Bambach F, Legat FJ, et al. Br J Dermatol 2011; 165(1): 152–63.

This within-patient study of 13 participants showed that 1,25-dihydroxyvitamin D₃ (calcipotriol cream) reduced PLE severity on artificial provocation compared with placebo. The relatively short study period and use of provocation rather than in-use assessment make firm conclusions difficult.

Porokeratoses

Chapman Wei, Adam J. Friedman



The porokeratoses are uncommon disorders of keratinization presenting as keratotic papules or plaques, often pruritic, with hallmark raised keratotic rims histologically characterized as cornoid lamella. The main recognized clinical variants are (1) classic porokeratosis of Mibelli (PM); (2) disseminated porokeratoses (DSP) and (3) disseminated superficial actinic porokeratosis (DSAP); (4) palmoplantar porokeratosis et plantaris disseminata (PPPD); (5) linear porokeratosis (LP); and (6) punctate porokeratosis (PP). PM, LP, and PP are localized porokeratoses, while DSP, DSAP, and PPPD are extensive porokeratoses. Porokeratoses are genodermatoses with an autosomal dominant mode of inheritance that has incomplete penetrance. Porokeratotic lesions are progressive and can undergo malignant degeneration, especially with large, longstanding lesions and linear variants. Overexpression of the p53 tumor suppressor is observed in cornoid lamella as porokeratotic lesions hypersensitive to radiation. Heterozygous germline mutations in the mevalonate pathway, a signaling pathway crucial for tumorigenesis and tumor growth, have been identified in familial and sporadic porokeratoses. Additionally, these lesions can be problematic cosmetically, causing distress for some patients.

MANAGEMENT STRATEGY

Given the familial disposition of porokeratosis, a thorough family history needs to be retrieved. The patient's immune function needs to be assessed, particularly with disseminated forms. Discontinuation of immunosuppression has led to resolution of lesions in some patients.

Treatment of porokeratoses may be indicated not only for cosmetic benefit and symptomatic relief, but also to prevent malignant transformation. Thus, treatment is dependent on the type and extent of porokeratosis and malignancy potential. Management should always include counseling avoidance of irradiation (ultraviolet or X-rays) and surveillance for signs of malignant transformation (squamous cell carcinoma, basal cell carcinoma, Bowen disease), particularly in immunocompromised patients.

Porokeratotic lesions are usually asymptomatic and may go unnoticed until presenting with symptoms, including pain and pruritus. Palmoplantar porokeratosis may cause functional disability due to pain and discomfort from mechanical stress on the lesions. Symptomatic relief can be achieved with *topical corticosteroids*, *topical retinoids*, and *topical diclofenac*. Pruritus associated with disseminated lesions is often responsive to topical corticosteroids.

Localized porokeratoses can be responsive to 'surgical' methods such as *cryotherapy*, *laser*, *curettage and cautery*, or *excision*, but these can leave patients with significant scarring and recurrence is common, especially when numerous porokeratoses are present. *Topical 5-fluorouracil*, *imiquimod*, and *vitamin D analogs* are helpful, but response rates are partial in DSAP. *5-Fluorouracil* and *imiquimod* can induce marked inflammatory reactions, which are necessary for efficacious response. Thus, it might be more efficacious to use these modalities under occlusion, treating one area at a time.

Systemic retinoids have been effective in localized and extensive porokeratoses, but there have been reports of exacerbation in preexisting lesions. Recurrence is common on discontinuation of therapy, and a long-term maintenance dose may be required. This might also reduce the potential for malignant transformation.

Few reports on the use of *topical ingenol mebutate* show a great response for both PM and DSAP. *Topical diclofenac* does provide some pruritus relief in DSAP and genital porokeratosis, but only partial improvement has been observed with limited benefit. A recent report on the use of *topical cholesterol/lovastatin* for DSAP may prove to be promising if the results are found to be consistent. There are also reports on the effectiveness of *topical retinoids*, *dermabrasion*, *ultrasonic surgical aspiration*, *radiofrequency surgery*, *various lasers*, and *intense pulse light (IPL)*, *cantharidin*, *corticosteroids*, *tacrolimus*, and *topical photodynamic therapy*. Treatments in combination have included *CO₂ laser and photodynamic therapy*, *5-fluorouracil and imiquimod*, and *calcipotriol with adapalene*.

Specific Investigations

- Biopsy
- Dermoscopy
- Assessment of immune function

Treatment of porokeratosis: a systematic review. Weidner T, Illing T, Miguel D, et al. *Am J Clin Dermatol* 2017; 18: 435–49.

Biopsy of a porokeratosis lesion's hyperkeratotic edge will show a column of parakeratosis within the epidermis with interruption of the granular layer, which is the histologic hallmark of the cornoid lamella.

Dermoscopy for the diagnosis of porokeratosis. Delfino M, Argenziano G, Nino M. *Eur Acad Dermatol Venereol* 2004; 18: 194–5.

Dermoscopic examination of DSAP showed a characteristic central scarlike area with a single or double 'white track' structure at the margin. The histopathologic correlate of the linear structure was shown to be the cornoid lamella.

First-Line Therapy

- Cryotherapy

D

Porokeratosis of Mibelli: successful treatment with cryosurgery. Dereli T, Ozyurt S, Osturk G. *J Dermatol* 2004; 31: 223–7.

Eight patients with 20 lesions received treatment with 30-second cycles of cryospray followed by sharp dissection of the lesion border.

Most lesions resolved after one treatment; two required one further treatment.

Cryosurgery of porokeratosis plantaris discreta. Limmer BL. Arch Dermatol 1979; 115: 582–3.

Twenty-one lesions of porokeratosis in 11 patients were treated with cryotherapy, resulting in a cure rate of 90.5%. The lesions were pared before treatment. There was no evidence of recurrence over an average follow-up period of 22 months.

Second-Line Therapies

• 5-Fluorouracil	D
• Imiquimod	D
• Vitamin D analogs	D

Fluorouracil ointment treatment of porokeratosis of Mibelli. Goncalves JC. Arch Dermatol 1973; 108: 131–2.

Six patients with facial lesions were treated with 5% fluorouracil ointment three times daily. The treatment was maintained for 8–10 days after a strong inflammatory response occurred. There was no recurrence at 9-month follow-up.

Disseminated superficial porokeratosis: a rapid therapeutic response to 5-fluorouracil. Shelley WB, Shelley ED. Cutis 1983; 32: 139–40.

Resolution of DSP was observed after 3 weeks of daily application of 5% 5-fluorouracil cream. There was no recurrence at 5-month follow-up.

Disseminated superficial actinic porokeratosis treated effectively with topical imiquimod 5% cream. Arun B, Pearson J, Chalmers R. Clin Exp Dermatol 2011; 3: 509–11.

One patient with DSAP responded to imiquimod 5% cream five times a week for 6 weeks.

Porokeratosis of Mibelli: involution and resolution with 5% imiquimod cream. Gajic B, Tang K, Whitfield M. Australas J Dermatol 2011; 52: 301–3.

Resolution and involution of PM was observed after 26 weeks of applying 5% imiquimod cream five times per week. There was no recurrence at 3-year follow-up.

Successful treatment of disseminated superficial actinic porokeratosis with calcipotriol. Bakardzhiev I, Kavak S, Pehlivanov G. Int J Dermatol 2012; 51: 1139–42.

Resolution of DSAP was seen applying 0.005% calcipotriol cream twice daily for 3 months with no recurrence at follow-up 6 months after.

Disseminated superficial actinic porokeratosis responding to calcipotriol. Harrison PV, Stollery N. Clin Exp Dermatol 1994; 19: 95.

Three patients were treated with topical calcipotriol daily for 6–8 weeks. An overall improvement of 50–75% was noted and maintained for up to 6 months in two patients.

Third-Line Therapies

• Systemic retinoids	D
• Topical retinoids	D
• CO ₂ laser	D
• Er:YAG laser	E
• Nd:YAG laser	E
• Pulsed dye laser	E
• Ruby laser	E
• Fractional photothermolysis	E
• Grenz rays	E
• Intense pulse light (IPL)	D
• Photodynamic therapy	C
• Dermabrasion	E
• Ultrasonic surgical aspiration	E
• Radiofrequency surgery	E
• Chemical peel	D
• Corticosteroids	E
• Diclofenac 3% gel	C
• Ingenol mebutate	E
• Tacrolimus	E
• Cholesterol/lovastatin	D
• 5-Fluorouracil with imiquimod cream	E
• Photodynamic therapy with CO ₂ laser	E
• Excision and skin graft	E
• Cantharidin	E

Generalized linear porokeratosis: a rare entity with excellent response to acitretin. Garg T, Ramchander Varghese B, Barara M, et al. Dermatol Online J 2011; 17: 3.

A patient with generalized LP was treated with acitretin 0.5 mg/kg. There was marked flattening of the lesions after 6 weeks but not complete resolution after 5 months of treatment.

Acitretin for treatment of familial porokeratosis palmaris disseminate. Skroza N, Proietti I, Bernardini N, et al. Eur J Dermatol 2012; 22: 699–70.

Near total resolution was seen in a patient with PPPD after treatment with acitretin 0.5 mg/kg/day for 4 months.

A case of extensive linear porokeratosis with evaluation of topical tretinoin versus 5-fluorouracil as treatment modalities. Grover C, Goel A, Nanda S, et al. J Dermatol 2005; 32: 1000–4.

One patient with LP was treated with topical tretinoin and 5-fluorouracil. Both agents were efficacious, but tretinoin was better tolerated.

Calcipotriol and adapalene therapy for disseminated superficial actinic porokeratosis. Nakamura Y, Yamaguchi M, Nakamura A, et al. Indian J Dermatol Venereol Leprol 2014; 80: 373–4.

Calcipotriol 0.005% ointment was applied in the morning and adapalene (0.1%) gel at night. After 3 months the skin lesions improved substantially, leaving only slight hyperpigmentation.

Treatment of porokeratosis of Mibelli with CO₂ laser vaporization versus surgical excision with split-thickness skin graft. Rabin PE, Baldwin HE. *J Dermatol Surg Oncol* 1993; 19: 199–202.

CO₂ vaporization resulted in better cosmetic and functional improvement than split-skin grafting in the same patient.

Successful treatment of porokeratosis with ablative fractional carbon dioxide laser and vitamin C, E, and ferulic acid serum. Nguyen JK, Mancebo S, Bleicher B, et al. *J Drugs Dermatol* 2019; 18L: 1174–6.

CO₂ laser ablation with vitamins C, E, and ferulic acid serum applied twice daily for two days post-laser treatment resulted in complete clearance of PM with no recurrence at follow-up.

Erbium laser for the treatment of disseminated superficial actinic porokeratosis: a case report. Rosenblum J. *Dermatol Surg* 2013; 39: 1543–5.

A patient received 13 Er:YAG treatments to more than 100 DSAP lesions with treatments spaced 2–4 weeks apart resulting in significant improvement over a 1-year follow-up.

Treatment of lichen amyloidosis (LA) and disseminated superficial porokeratosis (DSP) with frequency-doubled Q-switched Nd:YAG laser. Liu HT. *Dermatol Surg* 2000; 26: 958–62.

A patient's face and arms were treated four times, 1 month apart, resulting in marked improvement but not complete clearance of the lesions.

Successful treatment of porokeratosis with 585 nm pulsed dye laser irradiation. Alster TS, Nanni CA. *Cutis* 1999; 63: 265–6.

This is a case of LP that responded to a series of 585-nm pulsed dye laser treatments.

Treatment of disseminated superficial actinic porokeratosis (DSAP) with the Q-switched ruby laser. Lolis MS, Marmur ES. *J Cosmet Laser Ther* 2008; 10: 124–7.

This patient received three treatments with Q-switched ruby laser (694 nm) with good improvement.

Fractional photothermolysis: a novel treatment for disseminated superficial actinic porokeratosis. Chrastil B, Glaich AS, Goldberg LH, et al. *Arch Dermatol* 2007; 143: 1450–2.

Two patients received three to six courses of fractionated photothermolysis (erbium-doped fiber laser). Both patients reported 50% improvement.

Bullous and pruritic variant of disseminated superficial actinic porokeratosis: successful treatment with grenz rays. Ricci C, Rosset A, Panizzon RG. *Dermatology* 1999; 199: 328–31.

Good response to grenz ray treatment, 2 Gy once a day for 5 days. Grenz ray therapy has a low carcinogenic risk but needs to be used with caution in a condition with a potential for malignant transformation.

Unconventional use of intense pulsed light. Piccolo D, Di Marcantonio D, Crisman G, et al. *Biomed Res Int* 2014: 1–10.

Successful use of IPL in a series of 10 cases. Split 550-nm filter pulses, of 5–10 msec, with a 10-msec delay, and fluence of 10–12 J/cm² of broadband red light (Waldmann 1200). Resolution of two lesions of DSAP was observed in one case, but the response could not be reproduced in this or two other cases.

A retrospective analysis of real-life practice of off-label photodynamic therapy using methyl aminolevulinate (MAL-PDT) in 20 Italian dermatology departments. Part 1: inflammatory and aesthetic indications. Calzavara-Pinton PG, Rossi MT, et al. and The Italian Group For Photodynamic Therapy. *Photochem Photobiol Sci* 2013; 12: 148–57.

Of 13 DSAP, 1 LP, and 2 PM patients, six had some improvement. Lesions were irradiated with 37 J/cm² of red light (635 ± 18 nm) for a mean of two treatments at intervals of 14 ± 11.7 days.

Successful treatment of porokeratosis of Mibelli with diamond fraise dermabrasion. Spencer JM, Katz BE. *Arch Dermatol* 1992; 128: 1187–8.

No recurrence observed at 15-month follow-up in a 79-year-old Filipino woman, but the lesion healed with slight hyperpigmentation and mild hypertrophy.

Vulvar porokeratosis: case report and review of literature. Robinson JB, Im DD, Jockle G, et al. *Int J Gynecol Pathol* 1999; 18L: 169–73.

Ultrasonic surgical aspiration of the perineum of vulvar porokeratosis resulted in pruritus relief and good cosmesis.

Porokeratosis of Mibelli induced by topical corticosteroid. Yazkan F, Turk BG, Dereli T, et al. *J Cutan Pathol* 2006; 33: 516–8.

Radiofrequency surgery successfully treated the patient's PM with no recurrence at 6-month follow-up.

Effective treatment of disseminated superficial actinic porokeratosis with chemical peels – customary treatment for a rare disease. Lang BM, Peveling-Oberhag A, Zimmer S, et al. *J Dermatolog Treat* 2019; 1–17.

Five DSAP patients had moderate improvement with glycolic acid 50%-salicylic acid 25% in a two-layer technique for a mean of three cycles every 6 weeks. Patients were very satisfied with their treatment.

Dexamethasone pulse treatment in disseminated porokeratosis of Mibelli. Verma KK, Singh OP. *J Dermatol Sci* 1994; 7: 71–2.

A familial case of progressive porokeratosis received pulses of 100 mg dexamethasone in 5% dextrose intravenously on 3 consecutive days in a month. No new lesions appeared after the first pulse, and clinical improvement was noted after four pulses. There was an 80% improvement after 18 pulses. The patient was then lost to follow-up.

Diclofenac sodium 3% gel as a potential treatment for disseminated superficial actinic porokeratosis. Marks S, Varma R, Cantrell W, et al. *Eur Acad Dermatol Venereol* 2009; 23: 42–5.

An open-label, multicenter trial; 17 patients were treated with 3% diclofenac applied twice daily for 3–6 months to get a target area. The areas treated progressed less than the untreated areas.

Disseminated superficial actinic porokeratosis treated with ingenol mebutate gel 0.05%. Anderson I, Routt, ET, Shelbi C, On J. *Cutis* 2017; 99: E36–9.

The patient was treated with ingenol mebutate gel 0.05% for 2 days resulting in notably reduced scaling and erythema after 60 days, follow-up.

Long-term clearance of linear porokeratosis with tacrolimus, 0.1%, ointment. Parks AC, Conner KJ, Armstrong CA. *JAMA Dermatol* 2014; 150: 194–6.

A patient with LP had 0.1% tacrolimus ointment applied twice daily added with her current treatments of betamethasone dipropionate 0.05% after failed response to acitretin. She had a near-complete resolution after a 2.5-year follow-up.

Topical cholesterol/lovastatin for the treatment of porokeratosis: a pathogenesis-directed therapy. Atzmony L, Lim YH, Hamilton C, et al. *J Am Acad Dermatol* 2020; 82: 123–31.

Near-complete resolution was seen in SAP patients and moderate improvement was seen in patients with PPPD or LP when using topical 2%-cholesterol/2%-lovastatin ointment twice daily for as long as 3 months with up to 3 months of follow-up.

Porokeratosis of Mibelli: successful treatment with 5 percent topical imiquimod and topical 5 percent 5-fluorouracil. Venkatarajan S, LeLeux TM, Yang D, et al. *Dermatol Online J* 2010; 16: 10.

A patient with PM was treated with 5-fluorouracil twice a day and 5% imiquimod cream once a day for 12 weeks, leading to resolution of the lesion.

Photodynamic therapy combined with CO₂ laser vaporization on disseminated superficial actinic porokeratosis: a report of 2 cases on the face. Kim HS, Baek JH, Park YM, et al. *Ann Dermatol* 2011; 23: S211–3.

Two patients were treated with CO₂ laser to the cornoid lamella followed by photodynamic therapy. There was a marked response after four treatments.

Recalcitrant digital porokeratosis of Mibelli: a successful surgical treatment. Shahmoradi Z, Sadeghiyan H, Pourazizi M, et al. *N Am J Med Sci* 2015; 7: 295–6.

A case successfully treated by excision and split-thickness skin graft.

Treatment of porokeratosis of Mibelli with cantharidin. Levitt JO, Keeley BR, Phelps RG. *J Am Acad Dermatol* 2013; 69: e254–5.

Two cases of PM treated successfully with one application of a thin film of cantharidin to the circumference of the lesion.

Porphyria cutanea tarda

Maureen B. Poh-Fitzpatrick



From Lebwohl MG. Atlas of the Skin and Systemic Disease. Churchill Livingstone: Elsevier, 1995.

The term *porphyria cutanea tarda* (PCT) encompasses several related inherited or acquired disorders in which deficient hepatic uroporphyrinogen decarboxylase (UROD) enzyme activity (reduced to <20% of normal) causes overproduction of polycarboxylated porphyrins. These porphyrins can mediate cutaneous photosensitivity manifested as fragility, bullae, hypertrichosis, dyspigmentation, sclerodermoid features, and scarring. PCT usually presents in adults but occasionally in children. Genetic and other diverse factors or circumstances that may cause, influence, or aggravate its expression include mutations of UROD or hemochromatosis (HFE) genes, other predisposing genetic determinants, ethanol abuse, smoking, medicinal estrogen, iron overload, hepatitis C virus (HCV), and/or human immunodeficiency virus (HIV) infections, chronic dialysis treatment, toxic aromatic hydrocarbon exposure, and, rarely, hepatic tumors. Increased tissue iron, a common feature of alcoholism, HCV infection, hemochromatosis, and therapeutic iron supplementation, plays a central role in the pathogenesis of PCT. Iron-dependent partial oxidation of uroporphyrinogen to uroporphomethene, a competitive inhibitor of UROD, may be the mechanism reducing its activity sufficient to provoke manifest PCT (Phillips et al. Proc Natl Acad Sci USA 2007; 104: 5079–84). Iron-enhanced complete oxidation of porphyrinogens accumulated due to inhibited UROD activity yields photoactive porphyrins. Hepatic siderosis or porphyrin crystallization in hepatocytes may lead to fibrosis, cirrhosis, and hepatocellular carcinoma in long-term active PCT. Ferrodepletion by serial phlebotomy is the preferred first-line therapy for PCT patients with iron overload.

MANAGEMENT STRATEGY

Precise diagnosis is essential; optimal management calls for induction of remissions using strategies that are inappropriate for other porphyrias or pseudoporphyrias. Concurrent conditions that may influence management (viral infections, hemochromatosis,

or other causes of iron overload, lupus erythematosus, diabetes mellitus, anemias, pregnancy, glucose-6-phosphate deficiency, renal disease) should be identified. Sun exposure and mechanical skin trauma should be minimized until full clinical remission is achieved. Eliminating contributory factors and pursuing ferrodepletion by serial phlebotomy, iron chelation, or erythropoiesis stimulation, or increasing porphyrin excretion with chloroquine or hydroxychloroquine, can reproducibly induce biochemical and clinical remissions. Phlebotomy and hydroxychloroquine protocols adjusted for pediatric parameters are available. Highly effective antiviral drugs may benefit PCT coincident with HCV or HIV infections. Other therapies are less well established (e.g., increasing porphyrin excretion by enteric sorbents or metabolic alkalization, vitamins E and C, plasmapheresis or plasma exchange, high-flux hemodialysis, cimetidine). Hepatoerythropoietic porphyria, caused by coinheritance of two UROD gene mutations, resists induction of remission and thus requires lifelong vigilant photoprotection. Photothermolysis using light with selected wavelengths may reduce persistent hypertrichosis.

Specific Investigations

- Porphyrin concentrations and types in erythrocytes, serum or urine, feces
- Hematologic and iron profiles, serum ferritin, HFE gene analysis
- Liver function profile; liver imaging and elastography, liver biopsy if clinically indicated
- Hepatitis A, B, C, and HIV serologies
- Fasting blood glucose
- Serum antinuclear antibody
- Mutation analysis of the UROD gene

Porphyria cutanea tarda: recent update. Singal AK. Mol Genet Metab 2019; 128: 271–81.

Overview of PCT pathophysiology, diagnosis, and therapeutic management with an expansive bibliography.

Hepatitis C, porphyria cutanea tarda and liver iron: an update. Ryan Caballes F, Sendi H, Bonkovsky HL. Liver Int 2012; 32: 880–93.

A review emphasizing pathophysiologic roles of HCV, iron-facilitated oxidative stress, and hepcidin (a key regulator of iron absorption and metabolism that is downregulated in PCT). Treatment guidelines are offered.

Porphyria cutanea tarda, hepatitis C, and HFE gene mutations in North America. Bonkovsky HL, Poh-Fitzpatrick MB, Pimstone N, et al. Hepatology 1998; 27: 1661–9.

Of 70 American patients with PCT, 53% had evidence of HCV infection, and 43% of 26 patients had HFE gene mutations.

Hepatocellular carcinoma risk in patients with porphyria cutanea tarda. Gisbert JP, Garcia-Buey L, Alonso A, et al. Eur J Gastroenterol Hepatol 2004; 16: 689–92.

Recommendations include viral hepatitis serologies and liver biopsy at initial evaluation, and monitoring PCT patients with HCV infection or advanced fibrosis/cirrhosis with semiannual ultrasonography.

The decision for liver biopsy should be made case-by-case. Patients without risk factors for hepatic siderosis or other liver pathology (e.g., women with estrogen use as the only PCT-inducing factor) may not need this invasive procedure.

First-Line Therapies

- Sunlight avoidance, opaque sunscreens, physical sunlight barriers **C**
- Contributory factor elimination (iron supplements, alcohol intake, smoking, medicinal estrogens, hepatotoxin exposure)
- Serial phlebotomies **B**
- Chloroquine, hydroxychloroquine **B**

Efficiency of opaque photoprotective agents in the visible light range. Kaye ET, Levin JA, Blank IH, et al. Arch Dermatol 1991; 127: 351–5.

Efficacy and quality of sunscreens containing zinc oxide, titanium dioxide, and iron oxide are described.

Minimizing sunlight exposure by lifestyle changes, opaque sunscreens, protective clothing, window glass barrier filters, etc., is essential until photosensitivity remits completely.

Treatment of porphyria cutanea tarda by phlebotomy. Ippen H. Semin Hematol 1977; 14: 253–9.

Repeated venesection resulted in reduction of porphyrins and serum iron, improvement of photocutaneous lesions, and normalization of liver function in the majority of 351 patients.

Phlebotomy schedules should be adjusted to the tolerance of individual patients; typically 200–500 mL of whole blood is withdrawn at twice-weekly to fortnightly or monthly intervals. Keeping hemoglobin over 10–11 g/dL minimizes symptoms of iatrogenic anemia.

Childhood-onset familial porphyria cutanea tarda: effects of therapeutic phlebotomy. Poh-Fitzpatrick MB, Honig PJ, Kim HC, et al. J Am Acad Dermatol 1992; 27: 896–900.

Pediatric phlebotomy guidelines are described.

Plasma ferritin levels as a guide to the treatment of porphyria cutanea tarda by venesection. Ratnaike S, Blake D, Campbell D, et al. Australas J Dermatol 1988; 29: 3–8.

Phlebotomies can be terminated when iron stores, as reflected by plasma ferritin concentration, have fallen to low-normal levels.

Reduction of porphyrins in plasma (or serum or urine) and clinical improvement typically begin during therapy and continue for weeks to months after venesection stops. Clinical improvement precedes full biochemical normalization.

Treatment of porphyria cutanea tarda with chloroquine. Kordač V, Semrádová M. Br J Dermatol 1974; 90: 95–100.

Twenty-one adults received oral chloroquine 125 mg twice weekly until cutaneous blistering and fragility ceased and urinary uroporphyrins fell below three times the normal limit. Mean duration of treatment was 8.5 months (range 4–11 months) in 19 patients. Serum transaminases and urinary uroporphyrins rose during initial weeks of therapy and then progressively diminished.

Chloroquine risks include irreversible retinopathy after large cumulative doses (>100–300 g), but this is infrequent at dose rates <4 mg/kg daily (<6.5 mg/kg daily for hydroxychloroquine). Ophthalmologic examination is recommended at baseline; if normal, no further testing is needed unless treatment continues beyond 5 years (unlikely for PCT). The risk of hemolysis can be minimized by pretreatment testing for glucose-6-phosphate dehydrogenase deficiency and interval monitoring of hematologic profiles during therapy.

Childhood-onset porphyria cutanea tarda: successful therapy with low-dose hydroxychloroquine (Plaquenil). Bruce AJ, Ahmed I. J Am Acad Dermatol 1998; 38: 810–4.

A 4-year-old child given hydroxychloroquine 3 mg/kg twice weekly for 14 months, plus vitamin E 200 U/day, achieved remission without adverse side effects.

Choice of therapy in porphyria cutanea tarda. Adjarov D, Naydenova E, Ivanov E, et al. Clin Exp Dermatol 1996; 21: 461–2.

The effectiveness of phlebotomy (500 mL weekly for 4 weeks, then monthly) versus oral chloroquine 250 mg twice weekly alone vs. combined phlebotomy/chloroquine therapies was retrospectively analyzed in unequal groups totaling 115 patients. Remissions occurred more quickly and reliably with phlebotomy than with chloroquine. Combined therapy shortened the mean total treatment course by approximately 1.5 months only when initial urinary uroporphyrin levels exceeded 3000 nmol/24 hours.

Others found remissions more rapid with chloroquine than with venesection (10.2 months in 24 patients, 12.5 months in 15 patients, respectively). Combination therapy was quickest (3.5 months in 20 patients) (Seubert S, Seubert A, Stella AM, et al. Z. Hautkr. 1990; 65: 223–5). In another study, urinary porphyrin excretion significantly improved in 22 of 30 hydroxychloroquine-treated subjects (200 mg twice weekly), but in only eight of 31 phlebotomy-treated subjects (400 mL whole blood twice monthly) after 1 year, while clinical improvement was similar in both groups. (Cainelli T, Di Padova C, Marchesi L, et al. Br J Dermatol 1983; 108: 593–600). Low-dose hydroxychloroquine (13 subjects) was similarly effective as biweekly phlebotomy (17 subjects) in inducing normal plasma porphyrin levels (6.1 and 6.9 months, respectively) (Singal AK, Kormos-Hallenberg C, Lee C, et al. Clin Gastroenterol Hepatol 2012; 10: 1402–9).

Hemochromatosis (HFE) gene mutations and response to chloroquine in porphyria cutanea tarda. Stolzel U, Kostler E, Schuppan D, et al. Arch Dermatol 2003; 139: 379–80.

Chloroquine was effective in heterozygotes with one of the major HFE mutations (C282Y, H63D) or in compound heterozygotes, but C282Y homozygotes failed to improve. Serum iron markers decreased after treatment only in patients with PCT and wild-type HFE. Phlebotomy was the recommended first-line therapy for patients with PCT and HFE gene mutations.

Second-Line Therapies

- Iron chelators (parenteral, oral) **C, E**
- Erythropoietin **E**

Liver iron overload and desferrioxamine treatment of porphyria cutanea tarda. Rocchi E, Cassanelli M, Borghi A, et al. Dermatologica 1991; 182: 27–31.

Ferrodepletion by desferrioxamine 1.5 g subcutaneous pump infusions 5 days/week (18 patients) or 200 mg/kg infused intravenously once weekly (5 patients) or by serial phlebotomies (22 patients) led to clinical remission after nearly 6 months with all treatments. Normalization of serum ferritin and uroporphyrins occurred at approximately 11 months with chelation and approximately 13 months with venesection; liver function improved with both modalities.

Subcutaneous chelation is expensive and cumbersome and thus is best reserved for cases in which first-line therapies are inadequate or inappropriate.

Successful treatment of haemodialysis-related porphyria cutanea tarda with deferoxamine. Pitche P, Corrin E, Wolkenstein P, et al. *Ann Dermatol Venereol* 2003; 130: 37–9.

Intravenous deferoxamine 40 mg/kg weekly for 6 weeks led to normalization of clinical and biological signs of PCT in one patient, persisting for 12 months in the setting of end-stage renal disease and chronic hemodialysis.

Successful treatment of hemodialysis-related porphyria cutanea tarda with deferoxamine. Stockenhuber F, Kurz R, Grimm G, et al. *Nephron* 1990; 55: 321–4.

Deferasirox for porphyria cutanea tarda. Pandya AG, Neza-fati KA, Ashe-Randolph M, et al. *Arch Dermatol* 2012; 148: 898–901.

Among eight patients considered to have PCT treated with oral deferasirox 250–500 mg/day for 6 months, reductions in blistering (8), urinary porphyrins (6), and serum ferritin levels (8) resulted.

Although true PCT was questionable in two cases, these promising results encourage larger confirmatory trials.

Erythropoietin for the treatment of porphyria cutanea tarda in a patient on long-term hemodialysis. Anderson KE, Goeger DE, Carson RW, et al. *N Engl J Med* 1990; 322: 315–7.

An end-stage renal disease patient treated with chronic hemodialysis received erythropoietin 150 U/kg after every dialysis session, plus several low-volume phlebotomies. Reticulocytosis and lowered serum ferritin and plasma porphyrin levels followed; blistering resolved.

Management of porphyria cutanea tarda in the setting of chronic renal failure: a case report and review. Shieh S, Cohen JL, Lim HW. *J Am Acad Dermatol* 2000; 42: 645–52.

High-dose erythropoietin (80–360 U/kg thrice weekly) plus 100-mL phlebotomies weekly for several months was followed by clinical remission, normalized serum ferritin, and 10-fold lower plasma porphyrin levels in one patient. Positive and negative aspects of alternative treatment for PCT in the context of renal failure are reviewed, including several third-line therapies listed next.

Third-Line Therapies

• Highly effective antiviral therapies for HCV or HIV	E
• Vitamin E, vitamin C	D
• Plasmapheresis, plasma exchange	D
• High-flux hemodialysis	D
• Enteric sorbents (cholestyramine, activated charcoal)	D
• Metabolic alkalization by oral sodium bicarbonate	D
• Cimetidine	E
• Phototherapy	E

Highly active antiretroviral therapy leading to resolution of porphyria cutanea tarda in a patient with AIDS and hepatitis C. Rich JD, Mylonakis E, Nossa R, et al. *Dig Dis Sci* 1999; 44: 1034–7.

The association between PCT and HIV infection is less well established than that of PCT and HCV. Coinfection with HCV may trigger PCT in patients with HIV infection.

Treatment of chronic hepatitis with boceprevir leads to remission of porphyria cutanea tarda. Aguilera M, Laguno M, To-Figueras J. *Br J Dermatol* 2014; 171: 1595–6.

A patient with both HIV and HCV infections, whose PCT had not improved with chloroquine and phlebotomy, achieved biochemical and clinical remission 2 months after boceprevir was added to a pegylated interferon/ribavirin regimen to which he had been previously unresponsive.

Direct-acting antivirals for hepatitis C virus induce a rapid clinical and biochemical remission of porphyria cutanea tarda. Combalia A, To-Figueras J, Laguno M, et al. *Br J Dermatol* 2017; 177: e183–4.

In this study, 15 patients with both active PCT and HCV (most coinfecting with HIV, but with ‘undetectable’ viral loads <37 copies/mL) were treated with various combinations of newer, highly effective anti-HCV agents, resulting in undetectable RNA-HCV levels. Urinary porphyrin excretion subsequently normalized, followed by clinical remissions of PCT in all 15.

High-dose vitamin E lowers urine porphyrin levels in patients affected by porphyria cutanea tarda. Pinelli A, Trivulzio S, Tomasoni L, et al. *Pharmacol Res* 2002; 45: 355–9.

Oral vitamin E (1 g daily) reduced urinary uroporphyrin levels and attenuated skin lesions during a 4-week trial in five subjects, who continued to imbibe at least 1.5 L of red wine each day.

Although urinary porphyrin levels were lower during vitamin E treatment, they remained very abnormal. Convincing confirmatory studies are needed.

Porphyria cutanea tarda: a possible role for ascorbic acid. Anderson KE. *Hepatology* 2007; 45: 6–8.

Deficiencies of vitamin C (ascorbic acid) and perhaps other antioxidants may facilitate development of PCT. Adequate dietary or supplemental vitamin C and other nutrients should be ingested by patients with PCT but should not usually be used as primary therapy instead of phlebotomy or chloroquine/hydroxychloroquine.

Removal of plasma porphyrins with high-flux hemodialysis in porphyria cutanea tarda associated with end stage renal disease. Carson RW, Dunnigan EJ, DuBose TD Jr, et al. *J Am Soc Nephrol* 1992; 2: 1445–50.

High-flux hemodialysis removes porphyrins more effectively than conventional techniques.

Treatment of hemodialysis related porphyria cutanea tarda with plasma exchange. Disler P, Day R, Burman N, et al. *Am J Med* 1982; 72: 989–93.

This may aid patients with PCT and chronic renal failure for whom other treatments are unavailable.

The adsorption of porphyrins and porphyria precursors by sorbents: a potential therapy for the porphyrias. Tishler PV, Gordon RJ, O'Connor JA. *Meth Find Exp Clin Pharmacol* 1982; 4: 125–31.

Metabolic alkalization therapy in porphyria cutanea tarda. Perry HO, Mullanax MG, Weigand SE. *Arch Dermatol* 1970; 102: 359–67.

Cimetidine in the treatment of porphyria cutanea tarda. Horie Y, Tanaka K, Okano J, et al. Intern Med 1996; 35: 717–9.

Cimetidine therapy reduced porphyrin levels within 2 weeks. This benign treatment might be offered to patients unwilling or unable to try standard therapeutic approaches.

Convincing confirmatory reports are needed.

Successful and safe treatment of hypertrichosis by high-intensity pulses of noncoherent light in a patient with hepatoerythropoietic porphyria. Garcia-Bravo M, Lopez-Gomez S, Segurado-Rodriguez MA, et al. Arch Dermatol Res 2004; 296: 139–40.

Hypertrichosis was almost completely removed after seven sessions, without development of skin lesions.

Port wine stain (‘nevus flammeus’)

Dawn Z. Eichenfield, Lawrence F. Eichenfield



Courtesy of Herbert Goodheart and Bob Rudolf

A port wine stain (PWS), also known as *nevus flammeus*, is a benign capillary malformation (CM) of the superficial cutaneous vasculature. These lesions are almost always congenital, though they may be acquired secondary to trauma and, thus, may rarely develop in adolescence or adulthood. The head and neck are sites of predilection, but any part of the integument can be affected. Morphologically, PWS present as light pink to red patches that typically grow proportionately with the child's growth. Unlike the salmon patch (also known as *nevus simplex* or *angel kiss*), which usually disappears during childhood untreated, PWS persist throughout a patient's life and tend to darken with time. Confusing this clinical picture is that PWS may appear to lighten during the first 3–6 months of life, a physiologic change likely due to a decrease in blood hemoglobin concentration (typically 15–17 g/dL at birth to a nadir of 8–10 g/dL by 3 months of age) and should not be interpreted as a sign of clinical resolution. Skin thickening and development of surface irregularities (nodules or 'blebs') and soft tissue hypertrophy may occur, especially in the V2 distribution. PWS may also present with an inflammatory component consisting of scaling, excoriations, oozing, and crusting, which resembles an eczematous dermatitis.

In addition to being cosmetically distressing and its risk for long-term deformation, PWS may be associated with physical, social, and psychological sequelae. The presentation of a PWS on the face in the V1 distribution, for example, has been classically linked to the development of ocular and/or neurologic

complications in the form of glaucoma or Sturge-Weber syndrome (SWS), especially with complete unilateral involvement of V1, bilateral involvement of V1, or a combination of V1, V2, and V3. Of note, anatomic variation in the distribution of V1 and V2 at the medial and lateral canthus (the so-called *watershed areas*) has resulted in considerable difficulty in definitively defining distribution of a PWS occurring in these areas. Several papers have posited alternative methods of characterizing facial PWS and risk of SWS, highlighting segmental patterns that differ from traditional dermatomal designations. Two papers show that the distribution of facial PWS appears to follow the embryonic vasculature of the face instead of following the traditional delineation of the trigeminal nerve, with hemifacial (upper quarter and cheek involvement) and median (forehead) patterns representing the strongest predictor of SWS and possible later neural and ophthalmologic complications.

PWS may also be associated with overgrowth and complex vascular malformations (e.g., capillary-venous, capillary-venous-lymphatic, capillary-arteriovenous). Evaluation of non-facial PWS for limb overgrowth or evidence of complex malformations may warrant consideration of magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) and/or referral to genetics or multidisciplinary vascular lesion clinics for diagnostic evaluation and management.

Although our understanding of the exact molecular pathogenesis of these CMs is evolving, it is believed that complex, localized defects in pathways controlling embryogenesis and angiogenesis play crucial roles. Whole genome sequencing of paired affected and normal tissue showed that GNAQ mutations are commonly associated with both SWS and non-syndromic PWS, as well as phakomatosis pigmentovascularis and diffuse CM with mild overgrowth. Evolving work has elucidated somatic mutations in other G proteins (e.g., *GNA14*, *GNA11*), and the PTEN-PI3K-AKT-mTOR (e.g., *PTEN*, *PIK3CA*, *AKT*) and RAS-RAF-MEK-ERK (e.g., *NRAS*, *KRAS*, *RASA1*, *MAP3K3*, *MAP2K1*) pathways. Many of these mutations are seen with PWS occurring concurrently with overgrowth syndromes, as well as PWS associated with arteriovenous malformations (e.g., *RASA1* and *EBH4* mutations) and Parkes Weber syndrome. The potential for gene-directed therapy based on genetic targets is under investigation.

MANAGEMENT STRATEGY

Because of the well-recognized physical and psychosocial comorbidities associated with PWS, many specialists advocate for treatment as soon as possible after birth. Support for early intervention is based on the observation that early lesions are physically smaller in size and comprise smaller and more superficial vessels. Early treatment may improve responsiveness, decrease the overall number of treatments, and reduce the likelihood of long-term adverse outcomes.

Many therapeutic modalities have been utilized to treat PWS, including surgical excision and grafting, dermabrasion, cryotherapy, sclerotherapy, radium implants, X-ray therapy, electrocautery, tattooing, vascular-targeted photodynamic therapy and intense-pulsed light, and cosmetic camouflage.

Various *lasers* have been used, including CO₂, neodymium:yttrium-aluminum-garnet (Nd:YAG), argon, and copper vapor lasers, but results have been unsatisfactory, with the risk of scarring unacceptably high. Consequently, the *flashlamp-pumped pulsed dye laser* (PDL) is considered by most authorities to be the gold standard of treatment for PWS. Treatment settings should be based on therapeutic end points, e.g., purpura. More recently, dynamic optical coherence tomography and in vivo reflectance

confocal microscopy have been used to provide quantitative visualization and guidance for tailored laser treatment protocols, but these techniques remain experimental. Lightening and/or reduction in size of the stain is directly related to the number of treatments. Initial treatments usually give the highest percentage of improvement. Generally, the smaller, more superficial vessels are targeted with the PDL, and deeper, larger-caliber vessels may require longer pulse durations or longer wavelength lasers. Other modalities have been used for refractory PWS, including long-pulsed alexandrite and Nd:YAG lasers, intense-pulsed light, and photodynamic therapy.

Swelling, erythema, and pain are frequently present immediately after treatment with PDL. Other potential adverse events include postinflammatory dyspigmentation (especially in darker-skinned patients), immediate postlaser purpura, and recurrence of the lesion itself. Rarely, blistering, crusting, scarring, and infection may occur. For these reasons, a test area may be performed before a full treatment session. Sun exposure can drastically affect pigmentary changes, and sun avoidance/protection should be optimized prior to and between treatment sessions. Before and after photos are a helpful tool for demonstrating clinical efficacy and for assuaging patient and family fears.

Cooling the skin via an attached device utilizing a targeted cryogenic spray or by application of a cool air machine is crucial to minimizing damage to surrounding tissues and reducing the risk of postoperative complications. Cold compresses and/or bags of ice applied immediately to the treated area are also useful for preventing postoperative complications.

Measures to overcome pain and anxiety associated with laser use include topical anesthetics such as lidocaine 4% gel, eutectic mixture of 2.5% lidocaine and 2.5% prilocaine, local lidocaine infiltration, cold air chiller devices, nerve block, sedation, and general anesthesia. Concerns about general anesthesia and potential neurotoxic effects in young children have been raised and should be considered in discussions about approaches to therapy, though not negating the utility and effectiveness of early laser therapy.

Topical daily treatment with 1% rapamycin cream after laser treatment may improve responsiveness to laser therapy through an unknown mechanism, possibly by decreasing vascular proliferation through the mTOR and HIF-1 α pathway.

Specific Investigations

- Ophthalmologic examination in infants with V1 PWS (or equivalent facial pattern)
- MRI/MRA may be considered in infants with V1 PWS, hemifacial, median patterns, or suspected SWS to delineate the extent of central nervous system (CNS) abnormalities and in PWS that may be associated with complex vascular malformations or overgrowth syndromes. Computed tomography (CT) is an alternative, but not preferred, imaging method
- Genetic testing for mutation analysis can be considered

Facial port wine stains and Sturge-Weber syndrome. Enjolras O, Riche MC, Merland JJ. *Pediatrics* 1985; 76: 48–51.

SWS was present in 28.5% of patients with PWS covering the V1 trigeminal sensory area alone or in association with V2 and V3, and 9.5% had glaucoma.

Sturge-Weber syndrome in patients with facial port-wine stain. Piram M, Lorette G, Sirinelli D, et al. *Pediatr Dermatol* 2012; 29: 32–7.

This cross-sectional study of 259 patients with facial PWS included 15 patients with a diagnosis of SWS. All patients with SWS showed involvement of the V1 trigeminal cutaneous area. SWS was significantly associated with bilateral topography of the PWS, its extension to another territory, and involvement of the upper eyelid.

This study provides valuable data to support risk stratification of a facial PWS for SWS and glaucoma based on anatomic distribution.

Facial port-wine stain: when to worry? Melancon JM, Dohil MA, Eichenfield LF. *Pediatr Dermatol* 2012; 29: 131–3.

A 'comment' on the aforementioned article by Piram et al. discussing the anatomic variations that have made direct comparison of the available literature difficult and providing insight in terms of management.

Location of port-wine stains and the likelihood of ophthalmic and/or central nervous system complications. Tallman B, Tan OT, Morelli JG, et al. *Pediatrics* 1991; 87: 323–7.

Among patients with trigeminal PWS, 8% had evidence of eye and/or CNS involvement. PWS of the eyelids, bilateral distribution, and unilateral PWS involving all three branches of the trigeminal nerve were associated with a significantly higher likelihood of having eye and/or CNS complications.

Patients with such presentations should be screened for glaucoma, and the risk of CNS involvement should be discussed with the family and appropriate testing considered.

New vascular classification of port-wine stains: improving prediction of Sturge-Weber risk. Waelchli R, Aylett SE, Robinson K, et al. *Br J Dermatol* 2014; 171: 861–7.

Of 192 children with facial PWS seen in 2011 to 2013, PWS involving any part of the forehead, which corresponds well to the embryonic vascular development of the face, was the best predictor of adverse outcomes.

Children with PWS on any part of the forehead should undergo ophthalmologic evaluation and brain MRI.

A prospective study of risk for Sturge-Weber syndrome in children with upper facial port-wine stain. Dutkiewicz AS, Ezzedine K, Mazereeuw-Hautier J, et al. *J Am Acad Dermatol* 2015; 72: 473–80.

In this prospective multicenter study of 66 patients, 11 presented with SWS and four had suspected SWS without neurologic manifestations. These patients predominantly had hemifacial or median PWS patterns that were high risk for SWS.

Hemifacial or median PWS patterns conform to areas of somatic mosaicism and are high risk for SWS.

Sturge-Weber syndrome and dermatomal facial port-wine stains: incidence, association with glaucoma, and pulsed tunable dye laser treatment effectiveness. Hennedige AA, Quaba AA, Al-Nikib K. *Plast Reconstruct Surg* 2008; 121: 1173–80.

In this study of 874 patients, SWS occurred in 3% of all patients with facial PWS and 10% of those whose PWS were in a dermatomal distribution. Although both SWS and glaucoma occurred in patients with only V1 involvement, the risk increased substantially with V1 + V2 and V1 + V2 + V3 involvement. No patients with only V3 involvement had eye or CNS findings.

Children at risk of SWS should have ophthalmologic examination in the neonatal period and require ophthalmologic follow-up because glaucoma may develop subsequent to initial presentation.

Size of facial port-wine birthmark may predict neurologic outcome in Sturge-Weber syndrome. Dymerska M, Kirkorian AY, Offermann EA, et al. *J Pediatr* 2017; 188: 205–9.

The size of the port wine birthmark in Sturge-Weber syndrome predicts neurologic severity of disease.

Retrospective review of screening for Sturge-Weber syndrome with brain magnetic resonance imaging and electroencephalography in infants with high-risk port-wine stains. Zallmann M, Mackay MT, Leventer RJ, et al. *Pediatr Dermatol* 2018; 35(5): 575–81.

Children with PWS with positive screening MRI will almost certainly develop Sturge-Weber syndrome. Negative-screening MRI cannot exclude Sturge-Weber syndrome (in up to 23.1% of cases).

Analyzing the genetic spectrum of vascular anomalies with overgrowth via cancer genomics. Siegel DH, Cottrell CE, Streicher JL, et al. *J Invest Dermatol* 2018; 138(4): 957–67.

The authors assembled a 16-institution network to determine the genetic variants associated with the spectrum of vascular anomalies with overgrowth. Using tumor genetic profiling via next-generation sequencing, the authors found that most vascular anomalies with overgrowth harbor postzygotic gain-of-function mutations in oncogenes. Seventy-five percent of subjects harbored pathogenic or likely pathogenic variants in 10 genes, many of which contained variants previously described in cancer settings and not described in vascular malformations. The authors conclude that this methodology can be applied to study other benign developmental disorders that may also contain gain-of-function mutations in oncogenes.

First-Line Therapy

- Pulsed dye laser

B

Anatomic differences of port-wine stains in response to treatment with pulsed dye laser. Renfro L, Geronemus RG. *Arch Dermatol* 1993; 129: 182–8.

Centrofacial lesions and lesions involving dermatome V2 responded less favorably than lesions located elsewhere on the head and neck.

Facial port wine stains in childhood: prediction of the rate of improvement as a function of the age of the patient, size and location of the port wine stain and the number of treatments with the pulsed dye (585 nm) laser. Nguyen CM, Yohn JJ, Huff C, et al. *Br J Dermatol* 1998; 138: 821–5.

Major determinants of treatment response, in order of decreasing importance, are PWS location, size, and patient age. The most successful responses are seen in young patients (under 1 year of age) with small PWS (<20 cm²) located over bony areas of the face, such as the central forehead. The greatest percentage of size reduction occurred after the first five treatments. There was less reduction in size with subsequent treatments.

Why do port-wine stains (PWS) on the lateral face respond better to pulsed dye laser (PDL) than those located on the central face? Yu W, Ma G, Qiu Y, et al. *J Am Acad Dermatol* 2016; 74: 527–35.

In 13 patients with PWS who underwent PDL treatments in both central and lateral areas of the face, lateral facial PWS responded better to PDL treatments than did PWS located in the central face.

Efficacy of early treatment of facial port wine stains in newborns: a review of 49 cases. Chapas AM, Eickhorst K, Geronemus RG. *Lasers Surg Med* 2007; 39: 563–8.

Patients who received treatment with the cryogen spray-cooled 595-nm PDL before 6 months of age achieved a mean 88.6% clearance after 1 year after an average of nine treatments. Higher clearance rates were observed for smaller lesions and V1 dermatome lesions.

Treatment of port-wine stains (capillary malformations) with the flash lamp pumped pulsed dye laser. Goldman MP, Fitzpatrick RE, Ruiz-Esparza J. *J Pediatr* 1993; 122: 71–7.

Initial treatment in children with PWS results in approximately 50% improvement, and each subsequent treatment up to six adds a further increment of 10% improvement. Treatments should be continued as long as there is incremental improvement.

High-fluence modified pulsed dye laser photocoagulation with dynamic cooling of port-wine stains in infancy. Geronemus RG, Quintana AT, Lou WW, et al. *Arch Dermatol* 2000; 136: 942–3.

Early intervention using a modified PDL with a longer wavelength (595 nm), broader pulse width (1.5 ms), dynamic cooling spray, and high-energy fluences can result in lightening or clearing of PWS with minimal risk of adverse effects.

Redarkening of port-wine stains 10 years after pulsed-dye-laser treatment. Huikeshoven M, Koster PH, deBorgie CA, et al. *N Engl J Med* 2007; 356: 1235–40.

After follow-up for a median of 9.5 years, PWS, on average, were darker than when measured after the last of the five initial treatments, although still lighter than when measured before treatment.

Patients should be counseled that due to progressive ectasia of PWS vessels, 'recurrence', or redarkening of the stain, is a possibility.

Effects of percutaneous local anesthetics on pain reduction during pulse dye laser treatment of port wine stains. McCafferty DE, Woolfson AD, Handley J, et al. *Br J Anaesth* 1997; 78: 286–9.

Both EMLA and 4% tetracaine gel were statistically superior to placebo in reducing pain caused by the laser treatment.

Effect of the topical anesthetic EMLA on the efficacy of pulsed dye laser treatment of port wine stains. Ashinoff R, Geronemus RG. *J Dermatol Surg Oncol* 1990; 16: 1008–11.

The use of topical anesthetic creams or sedating agents has been shown not to interfere with laser therapy.

Cryogen spray cooling and higher fluence pulsed dye laser treatment improve port wine stain clearance while minimizing epidermal damage. Chang CJ, Nelson JS. *Dermatol Surg* 1999; 25: 767–72.

The retrospective study of 196 patients with head and neck PWS showed the statistically significant advantage of using a cryogen spray-cooling device with PDL by permitting higher light dosages and a subsequently higher clearance rate without increasing the rate of complications.

General anesthesia for pediatric dermatologic procedures: risks and complications. Cunningham BB, Gigler V, Wang K, et al. *Arch Dermatol* 2005; 141: 573–6.

In a review of 881 cases performed on 269 pediatric patients, 88% were PDL treatment of vascular lesions, including PWS; there were no life-threatening events; and the mortality rate was zero.

The use of general anesthesia for dermatologic procedures performed in a children's hospital setting is safe with a low rate of complications.

Anesthetic neurotoxicity—clinical implications of animal models. Rappaport BA, Suresh S, Hertz S, et al. *N Engl J Med* 2015; 372: 796–7.

A perspective paper discussing possible animal studies and ongoing clinical studies in children undergoing prolonged or repeated general anesthesia.

US Safety Warning: about using general anesthetics and sedation drugs in young children. <https://www.fda.gov/downloads/Drugs/DrugSafety/UCM533197.pdf>

The US Food and Drug Administration (FDA) has communicated that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years may affect the development of children's brains. Healthcare professionals should balance the benefits of appropriate anesthesia in young children against the potential risks. Discuss with parents, caregivers, and pregnant women the benefits, risks, and appropriate timing of surgery or procedures requiring anesthetic and sedation drugs. Anesthetic and sedation drugs are necessary for infants, children, and pregnant women who require surgery or other painful and stressful procedures, especially when they face life-threatening conditions requiring surgery that should not be delayed. In addition, untreated pain can be harmful to children and their developing nervous systems.

Neurodevelopmental outcome at 5 years after general anesthesia or awake-regional anesthesia in infancy (GAS): an international, multicenter, randomized, controlled equivalence trial. McCann ME, de Graaff JC, Dorris L, et al. *Lancet* 2019; 393(10172): 664–77.

In this international, randomized, controlled trial conducted at 28 hospitals, the authors found that ≈1 hour of general anesthesia in early infancy does not affect neurodevelopmental outcome at age 5 years when compared with awake-regional anesthesia.

Pulsed dye laser treatment of port-wine stains in infancy without the need for general anesthesia. Jeon H, Bernstein LJ, Belkin DA, et al. *JAMA Dermatol* 2019; 155(4): 435–41.

In this retrospective cohort study, the authors evaluated 197 children who underwent PDL treatment without general anesthesia. The mean improvement was 3.65 (on a 5-point visual analog scale), corresponding to excellent clearance.

Early use of laser for port-wine stains: timing, efficacy, and shared decision making. Mathews EF, Frieden IJ. *JAMA Dermatol* 2019; 155(4): 421–3.

A 'comment' on the aforementioned article by Jeon et al. emphasizing the importance of shared decision making with parents (and children, if age appropriate), and consideration of the psychosocial consequences of treatment, non-treatment, pain control, and the risks and benefits of general anesthesia, as well as the issue of redarkening and potential need for future treatment courses.

Second-Line Therapies

- Alexandrite 755-nm laser **B**
- Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser **B**
- Intense-pulsed light source **B**

Split-face comparison of intense pulsed light with short- and long-pulsed dye lasers for the treatment of port-wine stains. Babilas P, Schreml S, Eames T, et al. *Lasers Surg Med* 2010; 42: 720–7.

This study evaluated the efficacy and side effects of intense-pulsed light (IPL) treatment of PWS in a direct comparison to short-pulsed dye laser (SPDL) and long-pulsed dye laser (LPDL). Test spots were applied with IPL, SPDL, or LPDL in a side-by-side modus. Subjects included those with both untreated ($n=11$) and previously treated ($n=14$) PWS. Lesion clearance was evaluated by three blinded investigators based on follow-up photography 6 weeks after treatment. In both untreated and previously treated PWS, IPL treatments were rated significantly better than SPDL; however, IPL and LPDL treatment results did not differ significantly.

Intense pulsed light source for the treatment of dye laser resistant port-wine stains. Bjerring P, Christiansen K, Troilius A. *J Cosmet Laser Ther* 2003; 5: 7–13.

A greater than 50% reduction was achieved after four treatments with IPL in 46.7% of 15 patients with PWS previously treated by PDL. None of the lesions located in the V2 distribution responded.

There are several case reports of successful treatment of resistant PWS with IPL source. However, controlled studies are needed to confirm this observation.

Treatment of hypertrophic and resistant port wine stains with a 755 nm laser: a case series of 20 patients. Izikson L, Nelson JS, Anderson RR. *Lasers Surg Med* 2009; 41: 427–32.

Many PWS that respond initially to PDL treatment may reach a response plateau, and many hypertrophic PWS are generally less responsive to PDL. Based on the theory of selective photothermolysis, deoxyhemoglobin and oxyhemoglobin located in deeper vessels within these lesions may be targeted with a 755-nm laser. This retrospective case review of 20 patients demonstrated the utility of the 755-nm laser for improving hypertrophic and treatment-resistant PWS in both adult and pediatric patients. Most commonly encountered complications included pain, edema, bullae, crusting, and rare scarring.

Some scarring with the 755-nm laser is inevitable if one uses the laser enough; however, the technique for PWS is difficult enough that these authors recommend its use by experienced laser specialists only.

Treatment endpoints for resistant port wine stains with a 755 nm laser. Izikson L, Anderson RR. *J Cosmet Laser Ther* 2009; 11: 52–5.

Deeper vessels may be targeted with the near-infrared light from the 755-nm laser. Because it is more difficult to assess laser-induced changes (the laser end point) within the deeper dermis, adverse effects may include deep dermal burns. The authors treated a resistant PWS with a 755-nm laser at high fluences with a dynamic cooling device. Mild-to-moderate lightening of the PWS was associated with the immediate clinical end point of a transient gray color that gradually evolved into persistent deep purpura within several minutes. The authors recommend judicious use of 755 nm for resistant PWS.

Long-pulsed neodymium:yttrium-aluminum-garnet laser treatment for port wine stains. Yang MU, Yaroslavsky AN, Farinelli WA, et al. *J Am Acad Dermatol* 2005; 52: 480–90.

Treatment achieved similar 50–75% clearing with both the PDL and the Nd:YAG laser at minimum purpura dose (MPD). The PDL performed significantly better than the Nd:YAG at fluences lower than 1 MPD, and scarring occurred in only one patient who was treated with the laser at a fluence greater than 1 MPD.

Nd:YAG may be an alternative treatment option, although there is a narrow margin at which this laser is both safe and effective.

Combined 595 nm and 1064 nm laser irradiation of recalcitrant and hypertrophic port-wine stains in children and adults. Alster TS, Tanzi EL. *Dermatol Surg* 2009; 35: 914–9.

This study evaluated the safety and efficacy of a novel device that delivers sequential pulses of 595-nm and 1064-nm wavelengths in the treatment of recalcitrant and hypertrophic PWS. Twenty-five subjects (aged 2–75) with skin types I to III were identified showing incomplete clearance after 10+ (mean = 16.9) prior PDL treatments. Nineteen had a PWS in a trigeminal location and six on the extremities. Subjects were treated at 6- to 8-week intervals. Continued improvement was noted in these resistant lesions. Side effects included transient erythema, edema, mild purpura, and rare vesicle formation.

A direct comparison of pulsed dye, alexandrite, KTP and Nd:YAG lasers and IPL in patients with previously treated capillary malformations. McGill DJ, MacLaren W, Mackay IR. *Lasers Surg Med* 2008; 40: 390–8.

Patients with PWS previously treated with PDL were treated using the alexandrite, KTP (potassium titanyl phosphate), and Nd:YAG lasers, as well as IPL, with additional PDL patches as a control. Fifty-five percent of patients achieved some lightening with the alexandrite laser, although a high percentage also developed hyperpigmentation or scarring. Thirty-three percent achieved some lightening with IPL; 11% achieved improvement with the KTP and Nd:YAG lasers, and 28% with further PDL pulses.

Third-Line Therapies

• Potassium titanyl phosphate laser	B
• Imiquimod (as antiangiogenic therapy)	B
• Photodynamic therapy	B
• Rapamycin (as antiangiogenic therapy)	B

Potassium titanyl phosphate laser treatment of resistant port-wine stains. Chowdhury MU, Harris S, Lanigan SW. *Br J Dermatol* 2001; 144: 814–7.

A greater than 50% reduction was seen in 17% of 30 patients with PWS previously treated by PDL; 20% of patients experienced side effects, including scarring or hyperpigmentation.

Pilot study examining the combined use of pulsed dye laser and topical imiquimod versus laser alone for treatment of port wine stain birthmarks. Chang CJ, Hsiao YC, Mihm MC Jr, et al. *Lasers Surg Med* 2008; 40: 605–10.

This retrospective review of 20 Asian subjects (aged 3–56 years) with PWS utilized three test sites on each subject for treatment assignments to the following regimens: (1) PDL + imiquimod; (2) PDL alone; and (3) imiquimod alone. For the PDL + imiquimod and imiquimod-alone test sites, subjects applied imiquimod topically once a day for 1 month after PDL exposure or alone. The primary efficacy measurement was a quantitative assessment of blanching response as measured by

a DermoSpectrometer. The authors report statistically significant differences in blanching responses over time favoring PDL + imiquimod compared with either PDL alone or imiquimod alone. Some evidence of redarkening, thought to be related to revascularization of blood vessels, was noted at 12 months at test sites treated with PDL + imiquimod and PDL alone. Transient hyperpigmentation was noted but had resolved on all sites without medical intervention within 6 months. The authors note that clinical validation in larger patient samples is necessary.

Enhanced port-wine stain lightening achieved with combined treatment of selective photothermolysis and imiquimod. Tremaine AM, Armstrong J, Huang YC, et al. *J Am Acad Dermatol* 2012; 66: 634–41.

Twenty-four patients with PWS were treated with PDL and randomized to apply posttreatment placebo cream or imiquimod 5% cream for 8 weeks. Chromameter measurements were taken at baseline and compared with measurements taken 8 weeks posttreatment. The change in erythema and the change in color between normal-appearing skin and PWS skin were the primary end points. Greater reduction in erythema and greater color improvement were noted with imiquimod. The authors note that the true clinical duration of effect is unknown. Minor skin irritation and other adverse events were noted.

Photodynamic therapy of port-wine stains: long-term efficacy and complication in Chinese patients. Xiao Q, Li Q, Yuan KH, et al. *J Dermatol* 2011; 38: 1146–52.

In this retrospective study, the authors studied 642 Chinese patients who had received photodynamic therapy (PDT) in a 5-year period (totaling 3066 treatment sessions; average of 2.6–8.2 sessions per patient). Seventy percent of patients had more than 25% clearing, and over 5% of patients had complete clearing. Ten percent of patients experienced complications that included hyperpigmentation (4.3%), scabbing (2.2%), blistering (1.4%), hypopigmentation (1.2%), prolonged blistering that persisted for >2 months (<0.7%), photoallergy (0.6%), and eczematous dermatitis (0.4%).

Retrospective study of photodynamic therapy for pulsed dye laser-resistant port-wine stains. Han Y, Ying H, Zhang X, et al. *J Dermatol* 2020; 47(4): 348–55.

The authors retrospectively evaluated the efficacy and safety of photodynamic therapy for treating pulsed dye laser-resistant PWS. Objective measures utilizing colorimetric changes and subjective evaluations, as well as patient satisfaction, were utilized, with 46.2% of patients showing excellent or good levels of improvement.

Topical rapamycin combined with pulse dye laser in the treatment of capillary vascular malformations in Sturge-Weber syndrome: phase II, randomized, double-blind, intraindividual placebo-controlled clinical trial. Marques L, Nunez-Cordoba JM, Aquado L, et al. *J Am Acad Dermatol* 2015; 72(1): 151–8.

In 23 patients with SWS and facial PWS, four interventions were evaluated: placebo, PDL + placebo, rapamycin, and PDL + rapamycin. PDL + rapamycin showed a statistically significant improvement on a visual scale and had a lower percentage of vesicles in histologic analysis.

Topical daily treatment with 1% rapamycin cream after laser treatment may improve responsiveness to laser therapy by decreasing vascular proliferation.

Postinflammatory hyperpigmentation and other disorders of hyperpigmentation

Seemal R. Desai, Adrienne Joseph



INTRODUCTION

Hyperpigmentation is a common condition encountered in dermatologic practice. It is defined as darkening of natural skin color and can have a significant impact on quality of life. Hyperpigmentation results from increased melanocyte activity resulting in increased deposition of melanin in the epidermis or dermis. Alternatively, hyperpigmentation is due to deposition of endogenous or exogenous non-melanin pigments. Pigmentary disorders may be congenital or acquired. Acquired disorders can be divided into localized dermatoses such as postinflammatory hyperpigmentation, melasma, etc., or generalized dermatoses such as those resulting from autoimmune disease, metabolic disorders, or malignancy. Clinically, conditions with primarily epidermal hypermelanosis present with tan to dark brown pigmentation whereas dermal hypermelanosis presents with dark gray to blue-gray pigmentation. This chapter will focus on acquired dermatoses and give a brief summary of treatment.

POSTINFLAMMATORY HYPERPIGMENTATION

Postinflammatory hyperpigmentation (PIH) is defined as excess melanin in the epidermis or dermis that occurs as a result of cutaneous inflammation or injury. It is more common in patients with darker skin types, possibly due to increased epidermal melanin. Epidermal melanosis occurs when melanocytes are stimulated by inflammatory mediators resulting in increased melanin production. This melanin is then transferred to surrounding

keratinocytes. Dermal melanosis occurs when inflammation disrupts the basal layer of the epidermis releasing melanin into the dermis. Macrophages can then phagocytize released melanin in the dermis and form melanophages. Alternatively, macrophages can migrate to the epidermis, engulf epidermal melanosomes, and return to the dermis. Melanin can remain in dermal macrophages for years.

OTHER DISORDERS OF HYPERPIGMENTATION

There are numerous other hyperpigmentary disorders that affect people of all skin phototypes. Sun or light exposure, aging, hormones, medications, cosmetics, fragrances, and genetics are often implicated in the pathogenesis of these conditions. We will briefly address a few of these disorders below.

Freckles, or ephelides, are small, hyperpigmented macules present on sun-exposed areas such as the face, hands, and upper trunk. Freckles tend to get darker with sun exposure. Lentigines are clinically similar to freckles, but in contrast to freckles, the color of lentigines are not affected by the sun. Both are more prevalent in those with lighter skin phototypes but can occur in all individuals.

Melasma is a common condition typically affecting women of reproductive age and is most prevalent in those with darker skin phototypes. The word *melasma* is derived from the Greek word *melas*, meaning 'black'. Melasma that occurs during pregnancy is referred to as chloasma or the mask of pregnancy. The condition appears as well-defined irregular hyperpigmented macules and patches. Three types of clinical patterns have been described: centrofacial, malar, and mandibular. The pathogenesis of melasma is multifactorial and includes genetic and environmental factors.

Phototoxic dermatitis occurs when a photosensitizing substance is applied to the skin followed by exposure to ultraviolet radiation. Systemic medications, topically applied cosmetics, fragrances, and plants containing furocoumarins are all phototoxic substances that have been implicated in phototoxic dermatitis. Berloque dermatitis is a condition that results from the use of bergamot oil in fragrances and colognes. Hyperpigmentation is often present after the acute inflammatory phase subsides.

Erythema dyschromicum perstans (EDP), also called ashy dermatosis or gray dermatosis, presents as hyperpigmented ovoid gray-brown macules, mainly affecting the face, trunk, and proximal extremities. Early lesions may have a more pronounced border, which can be erythematous and slightly raised. Lichen planus pigmentosus (LPP) is a variant of lichen planus. It presents similarly to EDP. In contrast to EDP, LPP lacks an inflammatory phase and thus lacks the presence of an inflammatory border.

MANAGEMENT STRATEGY

First-Line Therapy

Photoprotection

- Sunscreen

B

The use of a broad-spectrum sunscreen is essential in the prevention and treatment of these disorders. Physical sunscreens, those containing iron oxide, zinc oxide, or titanium oxide, are preferred to chemical sunscreens, which are often preferred in those with darker skin since physical sunscreens often leave a chalky white cast on the skin. Sunscreen that blocks both ultraviolet light and visible light is ideal in preventing the exacerbation of hyperpigmentation and in improving its appearance. The use of sunscreen

is widely accepted as a key component in the management of hyperpigmentary disorders; however, large, randomized, placebo-controlled studies are lacking.

Near-visible light and UV photoprotection in the treatment of melasma: a double-blind randomized trial. Castaneda-Cazares JP, Hernandez-Blanco D, Carlos-Ortega B, et al. *Photodermatol Photoimmunol Photomed* 2014; 30(1): 35–42.

Sixty-eight women ages 18 and older were included in this study. All patients received 4% topical hydroquinone cream. The patients were randomized to receive sunscreen that blocked ultraviolet radiation only (UV-only) or sunscreen that blocked ultraviolet radiation and visible light (UV-VL). The UV-only sunscreen was 50+ SPF and contained Mexoryl SX, XL, titanium dioxide, octocrylene, Tinosorb S, avobenzene, and ethylhexyl triazone as active ingredients. The UV-VL product was labeled SFP 60 and included benzophenone-3, octinoxate, octocrylene, titanium dioxide, zinc oxide, and iron oxide as active ingredients. All participants were instructed to apply sunscreen to melasma lesions every 2–3 hours between 8 a.m. and 5 p.m. using 2 mg/cm² dosing. Use of facial cosmetics and daily skin care products were not allowed. Other photoprotective habits were not modified. Patients were followed at 2, 4, 6, and 8 weeks. The study outcomes were improvement in Melasma Area and Severity Index (MASI) score, changes in lightness values based on colorimetric measurements, and histological evaluation of melanin content between the start and end of the study. Sixty-one women completed the trial. Both groups showed improvement in melasma, but the UV-VL group showed 15%, 28%, and 4% greater improvement than the UV-only group in MASI score, lightness value, and melanin assessments, respectively. This study demonstrates that UV-VL sunscreens can enhance the efficacy of depigmenting agents when compared with UV-only sunscreen and reveals the importance of visible light in the pathogenesis of melasma.

Depigmenting Agents

See Table 200.1.

- Hydroquinone and triple-combination therapy **B**
- Naturally derived depigmenting agents **B**

Hydroquinone is considered the gold standard depigmenting agent and the efficacy of any new depigmenting agent is compared with hydroquinone. It is commonly used in triple-combination formulas containing hydroquinone, retinoids, and corticosteroids, which are more effective than monotherapy. Short-term side effects include irritant contact dermatitis, while long-term side effects include ochronosis and confetti-like depigmentation. Hydroquinone works by increasing the breakdown of melanosomes in melanocytes by inhibition of tyrosinase. Due to concerns that hydroquinone may increase risk for malignancy, it is not US Food and Drug Administration (FDA) approved and is banned in Europe, Australia, and Japan. Despite these concerns there has been no confirmation in either clinical practice or human research that suggests hydroquinone is carcinogenic, and it continues to be the mainstay of treatment for hyperpigmentary disorders in many countries including the United States.

A randomized controlled trial of the efficacy and safety of a fixed triple combination (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) compared with hydroquinone 4% cream in Asian patients with moderate to severe melasma. Chan R, Park KC, Lee MH, et al. *Br J Dermatol* 2008; 159: 697–703.

Table 200.1 Mechanism of action of commonly used depigmenting agents

Mechanism of action	Depigmenting agent
Tyrosinase inhibition	Hydroquinone
	Kojic acid
	Arbutin
	Azelaic acid
	Licorice
	Ellagic acid
Reactive oxygen scavengers	Flavonoids
	Ascorbic acid
Skin turnover acceleration	Retinoic acid
	Lactic acid
	Glycolic acid
	Salicylic acid
Inhibition of melanosome transfer	Niacinamide
	Soya/milk extracts
Prostaglandin inhibition	Tranexamic acid

This was a multicenter trial in nine centers (Korea, Philippines, Singapore, and Hong Kong) on 260 Southeast Asian patients with melasma. The study population was randomized into two groups: one group received triple combination (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) and the other group received 4% hydroquinone for a total of 8 weeks. A questionnaire-based assessment for patient satisfaction was done. The participants in the triple-combination group reported significantly more improvement (71%) compared with the hydroquinone group (50%) ($p=0.005$). Physician-reported improvement using static global assessment score confirmed those results. Significantly more patients in the triple-combination group (87/125) reported a score of 0 (clear) or 1 (mild hyperpigmentation) compared with the 4% hydroquinone group (57/129). The triple-combination group reported earlier onset of response with significant differences in score from 4 weeks onward. The cutaneous side effects reported, such as erythema, itching, and discomfort, were significantly more in the triple-combination group compared with the hydroquinone group. An assessment was also made among the participants on how much they were bothered by the treatment side effects. A total of 43% of patients in the triple-combination group were not bothered by treatment side effects compared with 77% (significantly more) in the hydroquinone group.

Efficacy and safety of a new triple-combination agent for the treatment of facial melasma. Taylor SC, Torok H, Jones T, et al. *Cutis* 2003; 72: 67–72.

Participants ($n=641$) were randomly divided into four groups: triple-combination cream (4% hydroquinone, tretinoin 0.05%, and fluocinolone acetonide 0.01%; $n=161$), dual combination agent (tretinoin 0.05% and 4% hydroquinone; $n=158$), dual combination agent (tretinoin 0.05% and fluocinolone acetonide 0.01%; $n=161$), or dual combination agent (4% hydroquinone and fluocinolone acetonide 0.01%; $n=161$), each applied daily at night for 8 weeks. Of those receiving the triple-combination cream, 26.1% had complete clearing of melasma compared with 9.5%, 1.9%, and 2.5%, respectively, in each of the dual combination creams. Side effects were more common in the tretinoin hydroquinone group (80%) followed by the tretinoin fluocinolone acetonide (65%) group, triple-combination (63%) group, and hydroquinone fluocinolone group (34%).

Botanical and naturally derived depigmenting agents are increasing in popularity as an alternative to hydroquinone. These agents act via various mechanisms to decrease melanocyte activity and disrupt the melanogenic pathway. Multiple ingredients can be used together to increase their effectiveness. Although natural ingredients serve as promising depigmenting agents, there is a paucity of long-term, randomized controlled clinical trials assessing their effectiveness and safety.

Asplit-face evaluation of a novel pigment-lightening agent compared with no treatment and hydroquinone. Draelos ZD. *J Am Acad Dermatol* 2015; 72(1): 105–7. <https://doi.org/10.1016/j.jaad.2014.09.011>

Lignin peroxidase is an enzyme derived from fungi that acts by oxidizing and breaking down melanin. This study recruited 60 patients with mild-to-moderate dyspigmentation. Participants were randomized to two cohorts. Cohort 1 applied lignin peroxidase to one half of the face and no treatment to the other half of the face for 12 weeks. Cohort 2 applied lignin peroxidase to one half of the face and 4% hydroquinone to the other half of the face. Efficacy was assessed via dermospectrophotometer, MASI score, and subject and investigator evaluation of improvement in overall dyspigmentation, texture, roughness, clarity, radiance, irritation, and overall appearance. In cohort 1, lignin peroxidase was superior when compared with no treatment in all measured parameters. In cohort 2, lignin peroxidase and hydroquinone were comparable when it came to skin lightening, but lignin peroxidase was superior in the evaluation of skin texture, roughness, lack of clarity, radiance, and overall appearance.

Second-Line Therapy

Systemic Agents

- Tranexamic acid

A

Systemic agents such as tranexamic acid have gained recognition in the treatment of hyperpigmentation. Tranexamic acid; is an antifibrinolytic that can reduce prostaglandin formation in keratinocytes and thus decrease tyrosinase activity. Thromboembolic events are a rare, but serious, side effect of tranexamic acid; therefore, all patients should be screened for hypercoagulability before starting treatment. Topical applications of tranexamic acid are also being explored with some success. It is important to remember that, currently, tranexamic acid is considered to be an FDA off-label treatment for melasma and hyperpigmentation, similar to many other treatment options.

Randomized, placebo-controlled, double-blind study of oral tranexamic acid in the treatment of moderate-to-severe melasma. Del Rosario E, Florez-Pollack S, Zapata L Jr, et al. *J Am Acad Dermatol* 2018; 78(2): 363–9. <https://doi.org/10.1016/j.jaad.2017.09.053>

Forty-four patients were enrolled and randomized to receive 250 mg of oral tranexamic acid or placebo twice daily for 3 months followed by 3 months of sunscreen only. The primary outcome measure was the modified MASI (mMASI) score. Of the 44 patients enrolled, 39 completed the study. At 3 months, there was a 49% reduction in mMASI score in the tranexamic acid group compared with an 18% reduction in the placebo group. At 6 months, 3 months after cessation of treatment, there was 26% reduction in mMASI score from baseline versus a 19% reduction in the placebo group.

Adjuvant Therapies

Chemical peels, laser therapy, and microdermabrasion are used as adjuvants to topical or systemic therapy. They should never be used as monotherapy. This is due to increased risk of dyschromia with these methods.

Chemical peels cause controlled exfoliation of the epidermis. Superficial and medium-depth peels are used for treatment of pigmentation. Prolonged use of medium-depth peels carries a risk of dyschromia, especially in darker-skinned individuals. Choosing the right patient with adequate priming, strict sun protection, and concomitant topical therapy forms the backbone of a good peeling regimen.

Salicylic acid peeling combined with vitamin C mesotherapy versus salicylic acid peeling alone in the treatment of mixed type melasma: a comparative study. Balevi A, Ustuner P, Ozdemir M. *J Cosmet Laser Ther* 2017; 19(5): 294–9.

This study included 50 adult females between the ages of 18 and 65 years old with moderate-to-severe mixed-type melasma. Patients were randomized to receive 30% salicylic acid peel and intralesional vitamin C (Group A) or 30% salicylic acid peel alone (Group B) every 2 weeks for 2 months. Patients were followed for 6 months. Improvement was evaluated via the MASI. Patients also completed the melasma quality of life questionnaire to assess satisfaction after treatment. Of 50 participants, 41 completed the study. After the treatment period, there was a statistically significant improvement in quality of life in both groups, with Group A having greater improvement than Group B. At the end of the treatment period, both groups showed a significant decrease in MASI scores. Group A had greater improvement in MASI score (68.11%) than Group B (13.17%), but at the end of the follow-up period, there was no statistically significant difference between the groups.

Adjuvant Therapies

• Chemical peels	B
• Laser	B
• Microdermabrasion	B

Q-switched, fractional, intense pulsed light, and combination lasers are used in the treatment of pigmentary dermatosis with variable results. Individuals with higher Fitzpatrick skin types carry a risk of postinflammatory hyperpigmentation after the procedure. Other side effects reported include rebound hyperpigmentation, physical urticaria, acneiform eruption, etc.

Microdermabrasion is a procedure where abrasive crystals scrape the skin's surface within a controlled vacuum. It leads to exfoliation of the top layer of the skin. This can be beneficial for superficial pigmentation. Side effects include skin irritation, scarring, and postinflammatory hyperpigmentation.

Successful treatment of melasma using a combination of microdermabrasion and Q-switched Nd:YAG lasers. Kauvar AN. *Lasers Surg Med* 2012; 44(2): 117–24. <https://doi.org/10.1002/lsm.21156>.

In this study, 27 female patients with melasma refractory to conventional therapy were treated with Nd:YAG laser sessions after microdermabrasion. Low fluence laser treatment was used with 5–6 mm spot size and energy of 1.6–2 J/cm².

Postprocedure, patients were discharged on sunscreen and topical preparation containing hydroquinone with tretinoin or vitamin C. Treatment was repeated at monthly intervals. About 50% of the patients reported improvement after 1 month of

starting the treatment. Remission was noted for 6 months. Side effects reported included mild postprocedural erythema and exacerbation of lesions, which resolved in a few weeks after topical treatment.

Pregnancy dermatoses

Lauren E. Wiznia, Miriam Keltz Pomeranz



Dermatoses specifically associated with pregnancy and the puerperium include polymorphic eruption of pregnancy (PEP), pemphigoid gestationis (PG), intrahepatic cholestasis of pregnancy, and atopic eruption of pregnancy. In addition to these classic dermatoses of pregnancy, pregnant women can develop all of the same pruritic dermatoses as non-pregnant women. There are also many skin changes during pregnancy that are normal physiologic changes. Because some pregnancy-related dermatoses may adversely affect the fetus, it is important to correctly diagnose and treat these diseases. Pustular psoriasis of pregnancy (previously impetigo herpetiformis), which we will not address in this chapter as it is discussed elsewhere, can have a detrimental effect on pregnancy outcome as well.

POLYMORPHIC ERUPTION OF PREGNANCY

Polymorphic eruption of pregnancy (PEP), also known as *pruritic urticarial papules and plaques of pregnancy (PUPPP)*, is an intensely pruritic dermatosis that usually begins in the third trimester of first pregnancies or in the immediate postpartum period. Pruritic urticarial papules are often the initial lesions. The immediate periumbilical area, face, palms, and soles are commonly uninvolved. Many patients develop polymorphic lesions, including erythema, vesicles, target lesions, and eczematous plaques. PEP tends not to recur in subsequent pregnancies.

MANAGEMENT STRATEGY

PEP has no increased risk of fetal or maternal morbidity, and the eruption resolves over an average of 4 weeks or within a few days of delivery. Treatment is often required to provide relief from intense itching. If PG is in the clinical differential, then consider a perilesional biopsy for direct immunofluorescence microscopy,

which has non-specific patterns in PEP (but is pathognomonic in PG). Contact dermatitis, drug eruptions, erythema multiforme, insect bites, and urticaria should be considered in the differential diagnosis.

In women with localized disease, application of *midstrength topical corticosteroids* provides symptomatic relief in most cases. Most patients benefit from emollients and topical antipruritics with additives such as menthol. Treatment should be initiated with lower strength corticosteroids and escalated to a higher strength if the patient is not responding adequately. Use of clobetasol should not exceed 300 g during the course of a pregnancy. As the pregnancy continues, many patients require therapy only once a day or can stop treatment before delivery.

Oral first-generation H_1 antihistamines may offer some benefit in severely pruritic patients at bedtime. Hydroxyzine is avoided because of an increased risk (5.8%) of congenital anomalies.

In more widespread cases and those that do not respond adequately to topical corticosteroids, a systemic corticosteroid treatment may be considered. Oral prednisone or prednisolone 40 mg daily or less over a taper of 1–2 weeks is very effective. Currently, PEP is not considered an indication for early delivery.

Specific Investigations (only if PG is being considered)

- Biopsy for direct immunofluorescence (DIF)
- Serum for indirect immunofluorescence (IIF) or enzyme-linked immunosorbent assay (ELISA) BP 180

A prospective study of 200 women with dermatoses of pregnancy correlating clinical findings with hormonal and immunopathological profiles. Vaughan Jones SA, Hern S, Nelson-Piercy C, et al. Br J Dermatol 1999; 141: 71–81.

A prospective study of 200 women with dermatoses of pregnancy, 44 of whom had PEP. IIF was negative in all 44 cases of PEP, and DIF showed non-specific findings. The most common histopathologic features on lesional skin biopsy were papillary dermal edema and a perivascular infiltrate, often with numerous eosinophils. Epidermal changes were common, with focal spongiosis and, less frequently, parakeratosis or hyperkeratosis.

Usefulness of BP180 NC16a enzyme-linked immunosorbent assay in the serodiagnosis of pemphigoid gestationis and in differentiating between pemphigoid gestationis and pruritic urticarial papules and plaques of pregnancy. Powell AM, Sakuma-Oyama Y, Oyama N, et al. Arch Dermatol 2006; 141: 705–10.

A study of 412 women, 82 with PG and 164 with PEP and 166 age- and sex-matched controls, demonstrated that the NC16a ELISA is 96% sensitive and specific in differentiating PG from PEP.

First-Line Therapies

• Topical corticosteroids	D
• Antihistamines	D

Pruritic urticarial papules and plaques of pregnancy. Clinical experience in 25 patients. Yancey KB, Hall RP, Lawley TJ. J Am Acad Dermatol 1984; 10: 473–80.

Of 25 patients, 22 were successfully treated with frequent applications of high-potency topical corticosteroids, providing

relief from pruritus and controlling the eruption. Three patients were treated with brief courses of systemic corticosteroids, ranging from 10 to 40 mg daily. Seven patients self-administered antihistamines or received them from referring physicians; two used cocoa butter, one used calamine lotion, and one used emollients; the authors noted that these agents were unsuccessful in controlling pruritus and lesion formation.

Pruritic urticarial papules and plaques of pregnancy (PUPPP). A clinicopathologic study. Callen JP, Hanno R. *J Am Acad Dermatol* 1981; 5: 401–5.

Of 15 cases, PEP cleared before delivery (5 cases), within 1 week of delivery (9 cases), and at 6 weeks postpartum (1 case). Treatment included various potent topical corticosteroids and diphenhydramine in all cases except one.

Safety of topical corticosteroids in pregnancy. Chi CC, Wang SH, Wojnarowska F, et al. *Cochrane Database Syst Rev* 2015; 10: CD007346.

A Cochrane review that assessed the effects of topical corticosteroids in pregnant women on pregnancy outcomes identified a probable association between low birth weight and maternal use of potent to very potent topical steroids, especially with very large cumulative dosage. Maternal exposure to topical corticosteroids of any potency was not associated with an increase in adverse pregnancy outcomes, including mode of delivery, congenital abnormality, preterm delivery, fetal death, or low Apgar score.

Safety of dermatologic medications in pregnancy and lactation: part I. Pregnancy. Murase JE, Heller MM, Butler DC. *J Am Acad Dermatol* 2014; 70: 401. e1–14.

Fetal growth restriction has been reported with potent topical steroid use during the third trimester, particularly when using >300g. Guidelines recommend mild-to-moderate over potent corticosteroids, which should be used only for short periods. First-generation antihistamines are preferred over second-generation. Among second-generation antihistamines, loratadine remains first choice, and cetirizine second choice. Hydroxyzine is avoided because of an increased risk (5.8%) of congenital anomalies. Antihistamine use within 2 weeks of delivery in neonates born prematurely has been reported to double the risk of retinopathy of prematurity (previously retrolental fibroplasia). Overdose and intravenous use of antihistamines can stimulate uterine contractions and increase the risk of fetal hypoxia.

Polymorphic eruption of pregnancy: clinicopathology and potential trigger factors in 181 patients. Rudolph CM, Al-Fares S, Vaughan-Jones SA, et al. *Br J Dermatol* 2006; 154: 54–60.

A retrospective analysis of 181 patients with PEP reported symptoms to be controlled in most patients with emollients and topical steroids. Systemic therapy with antihistamines was required in 25%. Systemic corticosteroids (prednisone and prednisolone) were required in 9%.

Second-Line Therapy

- Systemic corticosteroids

D

Pruritic urticarial papules and plaques of pregnancy. Clinical experience in twenty-five patients. Yancey KB, Hall RP, Lawley TJ. *J Am Acad Dermatol* 1984; 10: 473–80.

Please see previous section for discussion of systemic corticosteroid use.

Polymorphic eruption of pregnancy: clinicopathology and potential trigger factors in 181 patients. Rudolph CM, Al-Fares S, Vaughan-Jones SA, et al. *Br J Dermatol* 2006; 154: 54–60.

Please see previous section for discussion of systemic corticosteroid use.

Although only a limited number of severe cases of PEP that required oral corticosteroids are reported in the literature, it is generally accepted that this treatment is effective and safe if prednisone or prednisolone are chosen and used in the third trimester. However, larger series and prospective studies are lacking.

PEMPHIGOID GESTATIONIS

PG, previously herpes gestationis, is a rare dermatosis of pregnancy seen in 1 in 1700 to 1 in 50,000 pregnancies. It presents with urticarial followed by vesicular lesions on the trunk and extremities in mid- to late pregnancy or the early postpartum period. It occurs in the presence of paternally derived tissue (fetus, hydatidiform mole, or choriocarcinoma). Unlike PEP, PG involves periumbilical skin.

MANAGEMENT STRATEGY

An important part of managing PG is making the diagnosis. Patients in whom PG is suspected usually require biopsy for histology and DIF. DIF with C3 in a linear band at the dermal–epidermal junction is pathognomonic for PG. Circulating autoantibodies are directed against the same target antigens as in bullous pemphigoid, more commonly against BP180 than BP230. The ELISA can be sent (with specificity and sensitivity as high as 96%) or, if available, IIF studies for the BP180 antigen.

Treatment can begin with topical steroids and a systemic antihistamine. *First-generation antihistamines* are favored over second-generation (see also discussion earlier about the use of antihistamines in PEP). Most patients require *systemic corticosteroid* treatment. Initially doses of prednisolone or its equivalent in the range of 0.5 mg/kg body weight may be tried, but in severe cases, 1 mg/kg of prednisolone may be necessary.

Many women will improve and may decrease doses of, or even discontinue, steroids. In cases that do not respond satisfactorily to prednisolone alone or in cases where prolonged treatment with corticosteroids is contraindicated, plasmapheresis or intravenous immunoglobulins may be considered.

The maternal prognosis is very good, with most cases resolving within a few months postpartum; however, it may take weeks, months, or even years until complete remission. 75% of women flare postpartum, requiring treatment. Exacerbations may occur postpartum with oral contraceptives and during the menstrual cycle. PG often recurs and is commonly more severe in subsequent pregnancies.

Newborns of mothers with PG may develop bullous lesions, which are transient and require no therapy. PG is associated with premature delivery and a risk of low birth weight, and the risk of these fetal complications correlates with maternal disease severity. Therefore patients with PG should be followed more carefully by the obstetrician.

Specific Investigations

- Biopsy for histopathology and DIF
- Serum for enzyme-linked immunosorbent assay (immunoblot) and/or IIF

Clinical and immunologic profiles of 25 patients with pemphigoid gestationis. Tani N, Kimura Y, Koga H, et al. *Br J Derm* 2015; 172: 120–9.

Clinical and immunologic profiles were performed on 25 patients with PG. DIF showed C3 deposition in the basement membrane zone in all patients, and IIF revealed circulating immunoglobulin G (IgG) anti-basement membrane zone auto-antibodies in 92% of patients. Immunoblotting and ELISA of the NC16a domain of BP180 recombinant protein were positive in 96% and 92% of patients, respectively. Only four patients had a positive ELISA for BP230.

First-Line Therapies

• Topical corticosteroids	D
• Systemic corticosteroids	D
• Antihistamines	D

Clinical features and management of 87 patients with pemphigoid gestationis. Jenkins RE, Hern S, Black MM. *Clin Exp Dermatol* 1999; 24: 255–9.

A review of 142 pregnancies in 87 patients with PG. Only 69 patients had documented treatment information. Thirteen of these 69 patients (18.8%) were treated with topical corticosteroids without systemic therapy. Chlorpheniramine suppressed pruritus in most patients. Fifty-six out of 69 (81.2%) required systemic corticosteroids with initial doses of prednisolone of 5–110 mg daily, with suppression of blistering in most patients. Two patients' eruptions were not controlled with high-dose systemic corticosteroids, with disease persistence for more than 10 years.

Pregnancy outcome after first trimester exposure to corticosteroids: a prospective controlled study. Gur C, Diav-Citrin O, Shechtman S, et al. *Reprod Toxicol* 2004; 18: 93–101.

This study, which was powered to find a 2.5-fold increase in teratogenicity, supports that glucocorticosteroids do not represent a major teratogenic risk in humans.

Second-Line Therapies

• Plasmapheresis	E
• High-dose intravenous immunoglobulin (IVIG)	E

Plasma exchange in herpes gestationis. Van de Wiel A, Hart HC, Flinterman J, et al. *Br Med J* 1980; 281: 1041–2.

A case report of a 40-year-old patient with PG initially treated with antihistamines and pyridoxine, both of which were ineffective. Systemic corticosteroid treatment was thought inadvisable, and the patient received three exchanges during the 26th week of pregnancy. Within 24 hours of the first exchange, the patient's pruritus subsided, and no new lesions developed. After three exchanges, the lesions had largely resolved. After delivery, an exacerbation occurred that required four additional exchanges within 1 week. A flare 3 weeks postpartum required two more exchanges.

Pemphigoid gestationis and intravenous immunoglobulin therapy. Yang A, Uhlenhake E, Murrell DF. *Int J Womens Dermatol* 2018; 4(3): 166–9.

Two cases of PG treated with IVIG, resulting in clinical remission. Each patient was initiated on monthly IVIG

therapy at 2 g/kg divided over 3 days. The clinical improvement noted corresponded with declining Bullous Pemphigoid Disease Activity Index activity scores.

Antepartum intravenous immunoglobulin therapy in refractory pemphigoid gestationis: case report and literature review. Doiron P, Pratt M. *J Cutan Med Surg* 2010; 14: 189–92.

A case report of a 34-year-old woman who developed PG with three pregnancies. The PG in her first two pregnancies was managed with oral prednisone and topical agents. PG in the patient's third pregnancy was initially treated with prednisone but ultimately required monthly infusions of IVIG (40 g IV for 3 consecutive days). A healthy baby was delivered at 37.5 weeks.

Pemphigoid gestationis successfully treated with intravenous immunoglobulin. Almeida FT, Sarabando R, Pardal J, et al. *BMJ Case Rep* 2018 Apr 7; 2018: bcr2018224346.

A more recent case of PG treated successfully with IVIG, her first dose of which was 25/day for 5 days. She was treated with six mensal IVIG cycles.

Third-Line Therapies

• Azathioprine	E
• Cyclophosphamide	E
• Ciclosporin	E
• Dapsone	D
• Sulfapyridine	E
• Pyridoxine	E
• Rituximab	E

A severe persistent case of pemphigoid gestationis treated with intravenous immunoglobulin and cyclosporine. Hern S, Harman K, Bhogal BS, et al. *Clin Exp Dermatol* 1998; 23: 185–8.

A report of a patient with severe PG that persisted for 1.5 years postpartum. The patient was treated with prednisolone (initially at 80 mg daily) and two doses of IVIG (5-day course at 0.4 g/kg daily) and then required ciclosporin (initially at 100 mg and then tapered).

Chronic herpes gestationis and antiphospholipid antibody syndrome successfully treated with cyclophosphamide. Castle SP, Mather-Mondrey M, Bennion S, et al. *J Am Acad Dermatol* 1996; 34: 333–6.

A report of a patient with PG treated postpartum with pulse-dose intravenous cyclophosphamide (1.245 g, 0.75 g/m²). The patient was initially treated at 19 weeks of gestation with oral prednisone with no effect; increasing dosages of prednisone were administered (up to 120 mg/day) with no effect. The patient continued to have lesions postpartum, despite continued oral prednisone. Azathioprine treatment was initiated 8 months postpartum but was discontinued within 1 month secondary to increased liver enzyme values. Pulsed intravenous cyclophosphamide was administered 9 months postpartum. The patient received two doses during a 2-month period with resolution of skin lesions and associated symptoms. A mild recurrence 5 months later was treated with an additional dose.

Cytotoxic agents such as cyclophosphamide for the treatment of PG can only be used in the postpartum period while the mother is not breastfeeding.

Clinical features and management of 87 patients with pemphigoid gestationis. Jenkins RE, Hern S, Black MM. *Clin Exp Dermatol* 1999; 24: 255–9.

A review of 142 pregnancies in 87 patients with PG. Azathioprine, dapsone, sulfapyridine, and pyridoxine were used as adjunctive therapy with oral corticosteroids (in 2, 6, 2, and 5 out of 56 patients, respectively).

Severe persistent pemphigoid gestationis: long-term remission with rituximab. Cianchini G, Masini C, Lupi E, et al. *Br J Dermatol* 2007; 157: 388–9.

A case report of a 31-year-old woman who, during the fifth month of her third pregnancy, developed PG resistant to systemic corticosteroid therapy. A male infant was born at 32 weeks, 2 days after which the patient flared. After 5 months of unsuccessful corticosteroid therapy with azathioprine daily, she was treated with dapsone for 3 months. IVIG was then initiated, followed by rituximab (375 mg/m² weekly for 4 consecutive weeks). Azathioprine was discontinued and prednisone tapered. Clinical remission lasted for 2 months, at which time another four infusions of rituximab (375 mg/m² at 2-month intervals) were given.

The benefit of these drugs on the course of the disease remains questionable.

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Intrahepatic cholestasis of pregnancy (ICP; previously pruritus gravidarum and prurigo gravidarum) is a rare, reversible cholestasis that typically occurs in late pregnancy. Patients present with dramatic pruritus that may initially involve the palms and soles; jaundice can occur in 10% of patients. ICP is the only pregnancy dermatosis that presents without primary skin lesions. A reduced excretion of bile acids likely contributes to severe maternal pruritus that typically resolves soon after delivery. More concerning are harmful effects on the fetus, including an increase in premature births, intrapartum fetal distress, and fetal death.

MANAGEMENT STRATEGY

ICP must be differentiated from other causes of pruritus during pregnancy. The differential diagnosis can include scabies, eczema, urticaria, and drug eruptions, as well as early cases of PEP and PG. Total serum bile acid levels greater than 11 micromol/L are consistent with ICP. Liver function tests may be abnormal as well, often with an elevated alkaline phosphatase. The maternal pruritus and cholestasis usually resolve within a few days of delivery. ICP may recur with subsequent pregnancies and oral contraceptive pill use.

First-line treatment includes *ursodeoxycholic acid* (either a dose of 15 mg/kg/day or, independent of body weight, 1 g/day is administered either as a single dose or divided into two or three doses until delivery), which is thought to correct the maternal serum bile acid profile, relieve symptoms, and improve fetal prognosis. Early delivery at 38 weeks or before is frequently advocated by obstetricians to reduce the risk of intrauterine fetal demise.

In mild disease, pruritus may improve with the adjuvant use of topical treatments such as *cooling lotions or creams* and antihistamines. *Phototherapy* may also be of benefit. These adjuvant treatments will not affect fetal outcome.

Specific Investigations

- Liver function tests, total serum bile acid
- Hepatitis C serologies

Specific pruritic disease of pregnancy. A prospective study of 3192 pregnant women. Roger D, Vaillant L, Fignon A, et al. *Arch Dermatol* 1994; 130: 734–9.

A prospective study of pregnant women presenting with pruritus identified 17 patients with ICP. The increase in mean values of alanine aminotransferase, aspartate aminotransferase, total serum bile salt, serum cholestyglycine, serum 5'-nucleotidase, and total alkaline phosphatase was statistically significant compared with the control group.

Intrahepatic cholestasis of pregnancy: relationships between bile acid levels and fetal complication rates. Glantz A, Marschall HU, Mattsson LA. *Hepatology* 2004; 40: 287–8.

Prospective cohort study that identified 693 ICP cases. The probability of preterm delivery, asphyxia events, and green staining of placenta and membranes did not increase until bile acid levels exceeded 40 micromol/L, and the probability of meconium staining of amniotic fluid started to rise when bile acid levels exceeded 20 micromol/L.

The importance of serum bile acid level analysis and treatment with ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: a case series from central Europe. Ambros-Rudolph CM, Glatz M, Trauner M, et al. *Arch Dermatol* 2007; 143: 757–62.

A retrospective study of 13 patients with ICP reported elevated total serum bile acid levels in all patients. Pregnancies complicated by fetal distress or prematurity demonstrated higher total bile acid levels than those with normal fetal outcome. Other hepatic function test abnormalities were noted in 77% of patients, with elevated serum aspartate aminotransferase in 62%, alanine aminotransferase in 46%, gamma-glutamyl transferase in 23%, total serum bilirubin in 15%, and alkaline phosphatase in 100%.

Intrahepatic cholestasis of pregnancy in hepatitis C virus infection. Paternoster DM, Fabris F, Palu G, et al. *Acta Obstet Gynecol Scand* 2002; 81: 99–103.

A prospective study of the prevalence of hepatitis C virus (HCV) infection and incidence of ICP reported 56 patients to have developed ICP, 12 of whom were HCV-RNA positive. ICP was observed more commonly in HCV-RNA-positive women than in HCV-RNA-negative women, leading the authors to conclude that ICP during the third trimester should prompt assessment of patients' HCV status.

Intrahepatic cholestasis of pregnancy: maternal and fetal outcomes associated with elevated bile acid levels. Brouwers L, Koster MP, Page-Christiaens GC, et al. *Am J Obstet Gynecol* 2015; 212: 100. e1.

A retrospective study of 215 ICP patients studied the correlation of bile acid levels and pregnancy outcome. The group was divided into mild (bile acid levels 10–39 micromol/L), moderate (40–99 micromol/L), and severe (≥ 100 micromol/L) ICP. Higher bile acid levels were significantly associated with spontaneous preterm birth, meconium-stained amniotic fluid, and perinatal death. Gestational age at diagnosis and delivery was significantly lower in the severe compared with the mild ICP group.

Fetal outcomes in pregnancies complicated by intrahepatic cholestasis of pregnancy in a Northern California cohort. Rook M, Vargas J, Caughey A, et al. *PLoS One* 2012; 7: e28343.

A study of 101 women with ICP reported fetal complications in 33% of deliveries, with respiratory distress accounting for the majority of complications. The study found no statistically

significant clinical or biochemical predictors of increased risk of fetal complications.

First-Line Therapies

- Ursodeoxycholic acid (UDCA) – not helpful **A**
- Early delivery **D**

Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): a randomised controlled trial. Chappell LC, Bell JL, Smith A, et al.; PITCHES study group. *Lancet* 2019; 394(10201): 849–60.

A double-blind, randomized, placebo-controlled trial of 605 women with ICP showed that treatment with ursodeoxycholic acid did not reduce adverse perinatal outcomes. The authors concluded that UDCA's routine use for ICP should be reconsidered.

Is it necessary to perform the pharmacological interventions for intrahepatic cholestasis of pregnancy? A Bayesian network meta-analysis. Shen Y, Zhou J, Zhang S, et al. *Clin Drug Investig* 2019; 39(1): 15–26.

A network meta-analysis of 13 randomized controlled trials with 625 participants comparing maternal and fetal outcomes after UDCA, S-adenosylmethionine, or both showed no favorable effect on symptoms including pruritus in ICP patients.

Therapeutic plasma exchange as a novel treatment for severe intrahepatic cholestasis of pregnancy: case series and mechanism of action. Ovadia C, Lövgren-Sandblom A, Edwards LA, et al. *J Clin Apher* 2018; 33(6): 638–44.

A case series of four patients reported management of ICP with therapeutic plasma exchange. Given the potential complications and limited experience, the authors recommended restricting the use of therapeutic plasma exchange to women with the most severe disease who failed other treatments.

Intrahepatic cholestasis of pregnancy: review of six national and regional guidelines. Bicocca MJ, Sperling JD, Chauhan SP. *Eur J Obstet Gynecol Reprod Biol* 2018; 231: 180–7.

A review of medical association guidelines regarding diagnosis and management of ICP. The authors note that there is heterogeneity in the literature. All six of the guidelines recommend treatment with UDCA for maternal benefit, although the dosing regimens differ; only one national organization recommended treatment with UDCA for fetal benefit.

Efficacy of ursodeoxycholic acid in treating intrahepatic cholestasis of pregnancy: a meta-analysis. Bacq Y, Sentilhes L, Reyes HB, et al. *Gastroenterology* 2012; 143: 1492–501.

A meta-analysis of nine randomized controlled trials comprising data from 454 ICP patients compared the effects of UDCA with other drugs, placebo, or no specific treatment. UDCA (given in doses ranging from 450 to 1000 mg/day) was associated with reduced or resolved pruritus, normalization of liver function tests, fewer premature births, reduced fetal distress, less frequent respiratory distress syndrome, and fewer neonates in the intensive care unit in analyses of UDCA compared with all controls. In analyses of UDCA compared with placebo, UDCA reduced pruritus and normalized liver function tests.

Interventions for treating cholestasis in pregnancy. Gurung V, Middleton P, Milan SJ, et al. *Cochrane Database Syst Rev* 2013; 6: CD000493.

A Cochrane review of randomized controlled trials compared intervention strategies for patients with ICP. Twenty-one trials involving 1197 women were included, with 11 different interventions resulting in 15 different comparisons. UDCA showed improvement in pruritus in five out of seven trials. There were significantly fewer total preterm births with UDCA and fewer (although not statistically significant) instances of fetal distress/asphyxia events in the UDCA groups compared with placebo.

The risk of infant and fetal death by each additional week of expectant management in intrahepatic cholestasis of pregnancy by gestational age. Puljic A, Kim E, Page J, et al. *Am J Obstet Gynecol* 2015; 212: 667. e1.

A retrospective study of 1,604,386 singleton pregnancies of women between 34 and 40 weeks' gestation with and without ICP. Among women with ICP, the mortality risk of delivery is lower than the risk of expectant management at 36 weeks' gestation. The authors concluded that delivery at 36 weeks' gestation would reduce perinatal mortality risk compared with expectant management.

Primum non nocere: how active management became modus operandi for intrahepatic cholestasis of pregnancy. Henderson CE, Shah RR, Gottimukkala S, et al. *Am J Obstet Gynecol* 2014; 211: 189–96.

To evaluate ICP as an indication for early term delivery, the authors divided 16 articles based on whether or not obstetric care included active management. They found no evidence to support active management for ICP, noting that the stillbirth rates in both groups were similar to their respective national stillbirth rate.

Second-Line Therapies

- Phototherapy **E**
- Emollients and topical antipruritic agents **D**
- Antihistamines **D**

Dermatoses of pregnancy. Shornick JK. *Semin Cutan Med Surg* 1998; 17: 172–81.

Review indicating that broadband ultraviolet B (UVB) phototherapy may be useful for symptomatic treatment of ICP.

Specific pruritic disease of pregnancy. A prospective study of 3192 pregnant women. Roger D, Vaillant L, Fignon A, et al. *Arch Dermatol* 1994; 130: 734–9.

A prospective study of pregnant women presenting with pruritus identified 17 patients with ICP. Thirteen patients received emollients and oral antihistamines (hydroxyzine dihydrochloride). Pruritus did not resolve until after delivery (though within 2 weeks).

ATOPIC ERUPTION OF PREGNANCY

Atopic eruption of pregnancy (AEP; previously prurigo of pregnancy, prurigo gestationis, early onset prurigo of pregnancy, pruritic folliculitis of pregnancy, and eczema in pregnancy) is the most common pregnancy dermatosis. It is a benign pruritic disorder that presents early in pregnancy (in 75% of patients before the third trimester) with eczematous and/or papular lesions in patients with an atopic diathesis. For approximately 80% of AEP patients, the eruption is the first occurrence of atopy, whereas it represents an exacerbation for the remaining 20%. AEP tends to recur in subsequent pregnancies.

MANAGEMENT STRATEGY

There are no fetal or maternal risks associated with AEP other than significant maternal pruritus. *Topical corticosteroids* with or without *systemic antihistamines* are often sufficient for resolution of lesions and improvement of pruritus. Emollients and topical antipruritic agents also play a role. Severe cases may require a short course of systemic corticosteroids and antihistamines, and secondary bacterial infections may require oral antibiotics. *Phototherapy* (UVB) is an additional option, particularly for severe cases in early pregnancy. Biologic therapies like *dupilumab* are emerging as therapeutic options.

Specific Investigations

- None

The specific dermatoses of pregnancy revisited and reclassified: results of a retrospective two-center study on 505 pregnant patients. Ambros-Rudolph CM, Müllegger RR, Vaughan-Jones SA, et al. J Am Acad Dermatol 2006; 54: 395–404.

A retrospective study of 505 pregnant patients proposed a reclassification of eczema in pregnancy, prurigo of pregnancy, and pruritic folliculitis of pregnancy into the category of AEP.

First-Line Therapies

- Topical corticosteroids
- Antihistamines

For their use in pregnancy, see the discussion earlier in the section discussing PEP.

Second-Line Therapy

- UVB

Third-Line Therapy

- Dupilumab

A case of atopic eczema treated safely with dupilumab during pregnancy and lactation. Kage P, Simon JC, Treudler R. J Eur Acad Dermatol Venereol 2020 Jan 28 [Epub ahead of print].

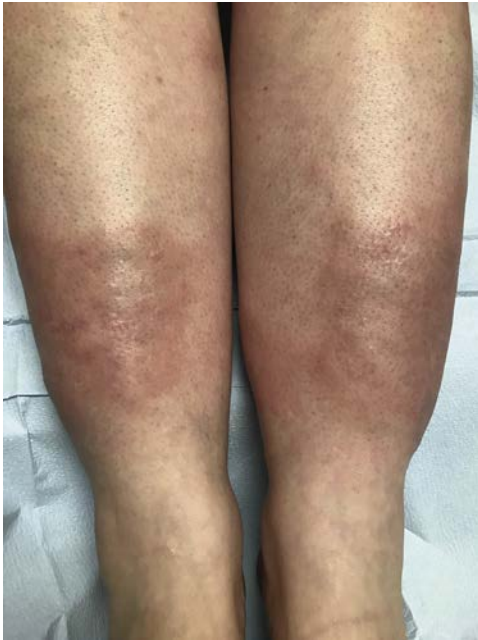
To date, there are only animal studies that have not identified a birth defect associated with dupilumab; but considering the severity of atopic dermatitis in some pregnant women, we will likely see more cases.

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Pretibial myxedema

Michael A. Renzi Jr., Warren R. Heymann



Pretibial myxedema (PM), more accurately termed *thyroid dermopathy*, is characterized by non-pitting edema and skin-colored to violaceous nodules or plaques. These are most commonly distributed pretibially but can sometimes be seen over the arms, shoulders, head, and neck. The differential diagnosis of thyroid dermopathy includes lymphedema, lipodermatosclerosis, and the newly described *obesity-associated lymphedematous mucinosis*.

MANAGEMENT STRATEGY

PM is an autoimmune response to the expression of thyrotropin (TSH)-receptor antigen in skin fibroblasts, resulting in secretion and accumulation of glycosaminoglycans in the dermis and subcutaneous tissue. Autoantibodies inhibiting the binding of TSH to its receptor (TBI) has also been described.¹ Usually occurring after treatment of Graves disease, PM may develop in hypothyroid and euthyroid patients. Exophthalmos is the commonest association. Other clinical signs of thyroid disease, including thyroid acropachy (characterized by clubbing of the fingers and toes, periosteal proliferation of the phalanges and long bones, and swelling of the soft tissue overlying bony structures) and the presence of a goiter may occur. Goals of treatment include cosmesis and the prevention of long-term sequelae such as elephantiasis, decreased range of motion, or foot drop from neural entrapment. Resolution may occur without treatment.

Patients with significant thyroid dermopathy should start a trial of *high-potency topical corticosteroids*, alone or under occlusion, for at least 2 months. If symptoms persist, *intralesional corticosteroids* may be effective. A combination of these methods in conjunction with *compression bandages* can be beneficial when monotherapy

proves inadequate. Both *oral* and *intravenous corticosteroids* have also been shown to improve lesions in several patients. However, their use is limited by systemic side effects.

Pentoxifylline has shown efficacy and can also be used in conjunction with topical and/or intralesional corticosteroids. Despite conflicting data, *intravenous immunoglobulin (IVIG)* may improve PM. Subcutaneous or intralesional *octreotide*, a somatostatin analog, yields conflicting results. Intralesional hyaluronidase has emerged as a promising treatment option. *Plasmapheresis* has been reported to be beneficial in improving severe cases, especially when combined with rituximab.

Temporary improvement with *cytotoxic agents* has been observed. PM is not a life-threatening condition, and so the use of such agents should be limited to severe, debilitating cases. *Surgical excision* has been shown to be effective in a minority of cases. The high risk of recurrence makes surgical intervention an infrequently used modality; however, postoperative intralesional steroids can minimize this risk. *Complete decongestive physiotherapy* has shown some success in treating the elephantiasic form of PM.

Pretibial ultrasonography, with or without digital infrared thermal imaging, to measure skin thickness may be useful in assessing treatment response. Measuring serum hyaluronic acid levels to follow therapeutic response may also be of value.

Specific Investigations

- Thyroid function tests
- Antithyroglobulin and antithyroid peroxidase antibodies
- Antithyroid-stimulating hormone receptor antibodies
- Pretibial ultrasound and/or digital infrared thermal imaging

Pretibial myxedema. Fatourehchi V. In: Heymann WR, ed. *Thyroid Disorders with Cutaneous Manifestations*. London: Springer Verlag, 2008; 103–19.

Pretibial myxedema: case presentation and review of treatment options. Kim WB, Mistry N, Alavi A, et al. *Int J Low Extrem Wounds* 2014; 13: 152–4.

A classic case of PM in a 57-year-old woman treated for Graves disease is presented.

This article details how to differentiate PM from lymphedema and lipodermatosclerosis.

Pretibial myxedema as the initial manifestation of Graves' disease. Georgala S, Katoulis AC, Georgala CJ. *Eur Acad Dermatol Venereol* 2002; 16: 380–3.

A 28-year-old woman presented initially with asymptomatic PM, which ultimately led to a diagnosis of Graves disease. This patient had elevated anti-TSH-receptor antibodies.

An assessment of thyroid function is warranted because most patients with PM have clinical or laboratory evidence of autoimmune thyroid disease.

Observing pretibial myxedema in patients with Graves' disease using digital infrared thermal imaging and high-resolution ultrasonography: for better records, early detection and further investigation. Shih SR, Lin MS, Li HY, et al. *Eur J Endocrinol* 2011; 164: 605–11.

Digital infrared thermal imaging (DITI) detects surface temperature, and sonography reflects composition changes in soft tissue. In all patients with PM, DITI showed abnormally low focal temperatures over the lesions. In Graves disease patients with

mild diffuse non-pitting edema and in Graves disease patients with normal appearance of the lower legs, DITI showed abnormally low focal temperature in 90.9% and 65.2% of the patients, respectively. Areas of clinically visible PM and low focal temperature detected by DITI were sonographically characterized with increased skin thickness, hypoechoic substance deposition in the cutaneous tissue, and blurred boundary lines between dermis and subcutaneous tissue.

First-Line Therapies

• Topical corticosteroids with or without occlusion	C
• Intralesional corticosteroids	D
• Compression	D

Dermopathy of Graves disease (pretibial myxedema): review of 150 cases. Fatourechi V, Pajouhi M, Fransway AE. *Medicine* 1994; 73: 1–7.

Treatment with topical 0.05–0.1% triamcinolone acetonide cream under occlusion for 2–10 weeks led to partial remission in 29 of 76 patients in this retrospective study; 1% had complete remission.

Intralesional triamcinolone therapy for pretibial myxedema. Lang PG, Sisson JC, Lynch PJ. *Arch Dermatol* 1975; 111: 197–202.

Seven of nine patients treated with monthly injections of 8 mL or less of intralesional triamcinolone acetonide solution (5 mg/mL, 1 mL per injection site) had complete remission of PM after three to seven visits. The other two patients showed a partial improvement.

Pretibial myxedema: a review of the literature and case report. Frisch DR, Roth I. *J Am Podiatr Med Assoc* 1985; 75: 147–52.

A 29-year-old woman with PM was treated with rest, elevation, and weekly intralesional Celestone Soluspan injections followed by topical 0.05% fluocinonide cream under occlusion and compression dressings with an Unna boot left on for a week. After 2 months the lesions were greatly improved.

Compression stockings may also be beneficial. Unless contraindicated, compression should be used in conjunction with any therapeutic approach for this disorder.

Treatment of pretibial myxedema with intralesional immunomodulating therapy. Ren Z, He M, Deng F, et al. *Ther Clin Risk Manag* 2017; 13: 1189–94.

A group of 32 PM patients were treated prospectively with intralesional compounded betamethasone solution (betamethasone sodium phosphate 2 mg and betamethasone dipropionate 5 mg mixed with 5 mL of 5% lidocaine) injected at 1-cm intervals (total volume of 0.5–1 mL per treatment). All 32 patients achieved clinical remission at different intervals; 21.7% patients after one treatment, 34.8% with two treatments, 17.4% with three treatments, 4.3% with four treatments, and 4.3% with five treatments.

Second-Line Therapies

• Pentoxifylline	E
• Pentoxifylline with topical and/or intralesional steroids	E

Pentoxifylline inhibits the proliferation and glycosaminoglycan synthesis of cultured fibroblasts derived from

patients with Graves' ophthalmopathy and pretibial myxedema. Chang CC, Chang TC, Kao SC. *Acta Endocrinol* 1993; 129: 322–7.

Pentoxifylline caused an in vitro dose-dependent decrease in fibroblast proliferation and glycosaminoglycan synthesis in fibroblast cultures taken from pretibial sites. A preliminary trial with a dose of 400 mg intravenously and 800 mg orally daily of pentoxifylline reduced the size of PM lesions within 1 week.

Successful combined pentoxifylline and intralesional triamcinolone acetonide treatment of severe PM. Engin B, Gümüşel M, Özdemir M. *Dermatol Online J* 2007; 13: 16.

A 32-year-old man achieved partial remission with clobetasol under occlusion combined with pentoxifylline 400 mg three times daily and intralesional triamcinolone (5 mg/mL).

Third-Line Therapies

• Intravenous immunoglobulin	D
• Systemic corticosteroids (including pulse corticosteroid therapy)	D
• Octreotide	E
• Plasmapheresis	D
• Plasmapheresis with rituximab	E
• Cytotoxic therapy	E
• Surgery	E
• Complete decongestive physiotherapy	E
• UVA1 in combination with topical and intralesional steroids	D
• Radiotherapy	E
• Intralesional hyaluronidase	E
• Teprotumumab	E

Pretibial myxedema and high-dose intravenous immunoglobulin treatment. Antonelli A, Navarranne A, Palla R, et al. *Thyroid* 1994; 4: 399–408.

Improvement of PM began after a few weeks in six patients treated with 400 mg/kg daily of high-dose IVIG given over 3–4 hours on 5 consecutive days. The cycle was repeated three times every 21 days. Maintenance therapy of 400 mg/kg for 1 day was then administered for 7–15 more cycles every 21 days. Total treatment ranged from 7 to 12 months, with maximum response occurring after an average of 6 months.

Lack of response of elephantiasic pretibial myxoedema to treatment with high-dose intravenous immunoglobulins. Terheydem P, Kahaly GJ, Zillikens D, et al. *Clin Exp Dermatol* 2003; 28: 224–6.

IVIG did not significantly improve the lesions of a patient with elephantiasic PM.

Corticoid therapy for pretibial myxedema: observations on the long-acting thyroid stimulator. Benoit FL, Greenspan FS. *Ann Intern Med* 1967; 66: 711–20.

Oral prednisolone, begun at 60 mg and then tapered, and methylprednisolone starting at 40 mg cleared the pretibial lesions of four patients and improved the lesions of two others. Of the various corticosteroid treatments studied, the best results were obtained with high-dose systemic corticosteroids for 2 weeks.

Refractory pretibial myxoedema with response to intralesional insulin-like growth factor 1 antagonist (octreotide): downregulation of hyaluronic acid production by the

lesional fibroblasts. Shinohara M, Hamasaki Y, Katayana I. Br J Dermatol 2000; 143: 1083–6.

Intralesional octreotide 200 mcg daily improved the lesions of PM in a male patient with Graves disease after 4 weeks of therapy.

Octreotide inhibits insulin-like growth factor-1-induced hyaluronic acid secretion by lesional fibroblasts, which may play a role in the pathogenesis of PM.

Octreotide and Graves' ophthalmopathy and pretibial myxedema. Chang TC, Kao SC, Huang KM. Br Med J 1992; 304: 158.

Three patients with PM were successfully treated with 100 mcg of octreotide three times daily.

The authors do not comment on the route of administration of the octreotide acetate. According to the Physicians' Desk Reference, the drug may be administered either by subcutaneous injection or intravenously.

Lack of effect of long-term octreotide therapy in severe thyroid-associated dermatopathy. Rotman-Pikielny P, Brucker-Davis F, Turner ML, et al. Thyroid 2003; 13: 465–70.

Three women did not show a statistically significant benefit from octreotide 300 mcg.

The conflicting results from these small studies regarding the use of octreotide for thyroid dermatopathy mandates that only larger, controlled studies will verify whether it is a useful modality for this condition.

Effect of plasmapheresis and steroid treatment on thyrotropin binding inhibitory immunoglobulins in a patient with exophthalmos and a patient with PM. Kuzuya N, DeGroot LJ. J Endocrinol Invest 1982; 5: 373–8.

Two patients, one with elephantiasis-like lesions, were treated with 16 exchanges over 4–5 months with 1–2 L of the patients' plasma removed and replaced with 1300 mL of purified protein fraction and 700 mL 0.9% saline. Immunoglobulin G fraction was separated out, thereby reducing total thyrotropin-binding inhibitory immunoglobulin (TBII) activity per unit of serum. The PM was partially and temporarily improved with plasmapheresis, and abnormal antibodies were reduced.

Beneficial effects of plasmapheresis followed by immunosuppressive therapy in pretibial myxedema. Noppen M, Velkeniers B, Steenssens L, et al. Acta Clin Belg 1988; 43: 381–3.

A patient with PM unresponsive to topical corticosteroids was cured after 5 days of plasmapheresis followed by 100 mg of azathioprine twice daily for 3 months. Azathioprine was tapered to 50 mg twice daily and continued for a year, at which time no recurrence was noted.

Pretibial myxedema (elephantiasis form): treatment with cytotoxic therapy. Hanke CW, Bergfeld WF, Guirguis MN, et al. Cleve Clin Q 1983; 50: 183–8.

Fibroblasts from PM sites of a 44-year-old man showed reduced DNA content in vitro with the use of cytotoxic agents. Melphalan, which reduced hyaluronic acid levels to the greatest extent, was given orally (8 mg daily) for 4 days and repeated monthly for 6 months. This regimen provided transient improvement, but the patient's condition then worsened.

Successful combined surgical and octreotide treatment of severe pretibial myxoedema reviewed after 9 years. Felton J, Derrick EK, Price ML. Br J Dermatol 2003; 148: 825–6.

A 56-year-old man with PM was treated with surgical shave removal followed by daily subcutaneous octreotide injections for 6 months. His lesions did not recur over a 9-year follow-up period.

Electrosurgical debulking of pretibial myxedema of the foot. Alia E, Feit EJ, Levitt JO. Dermatol Online J 2019; 25(2).

Two cases of PM successfully treated electrosurgical debulking. One patient was treated under general anesthesia, the other with local.

Treatment-resistant elephantiasic thyroid dermatopathy responding to rituximab and plasmapheresis. Heyes C, Nolan R, Leahy M, et al. Australas J Dermatol 2012; 53: e1–4.

A 55-year-old woman underwent plasmapheresis once every 6 days and received rituximab infusions once per week for 1–7 weeks on seven occasions for a total of 29 doses of rituximab and 241 episodes of plasmapheresis over 3.5 years. She remained clear 6 months after completion of treatment.

Clinical experience with rituximab and intravenous immunoglobulin for PM: a case series. Kotwal A, Turcu AF, Sonawane V, et al. Thyroid 2019; 29(5): 692–9.

Retrospective chart review of three patients treated with IVIG and five patients treated with rituximab (RTX) for PM. Of the patients treated with IVIG, one developed subjective and objective improvement, one patient's disease remained stable, and the third experienced worsening after a brief initial improvement. Among those treated with RTX, subjective improvement occurred in two patients, one of whom achieved almost complete resolution of PM (PTM) after 9 months. Subjective and objective stability was reported in two patients, while the fifth patient experienced subjective and objective worsening. There were no serious adverse events reported.

Elephantiasic pretibial myxedema: a novel treatment for an uncommon disorder. Susser WS, Heermans AG, Chapman MS, et al. J Am Acad Dermatol 2002; 46: 723–6.

A 67-year-old woman with elephantiasic PM had a 47% reduction of leg edema after 6 weeks of intensive complete decongestive physiotherapy. This response was sustained for 2 years after treatment.

Complete decongestive physiotherapy consists of manual massage of the lower extremities to promote lymphatic drainage, followed by compressive bandages, exercise, and skin care.

Efficacy of trimodality therapy for pretibial myxoedema: a case series of 20 patients. Chen X, Zhao X, Li X, et al. Acta Derm Venereol 2016; 96: 714–5.

Severe thyroid dermatopathy was treated for 12 weeks. The triple therapy comprised intralesional injections of betamethasone dipropionate 5 mg and betamethasone disodium phosphate 2 mg for a total of 4–6 mL, topical 0.1% mometasone furoate cream under occlusive dressing, and UVA1 at a dose of 80 J/cm² per treatment three times a week for 2 weeks, twice a week for 2 weeks, and once a week for 8 weeks. At the end of the trimodality treatment, 8 and 12 patients achieved complete and partial remission, respectively. Dermal thickness was decreased as detected by ultrasound.

Radiation therapy as part of the therapeutic regimen for extensive multilocular myxedema in a patient with exophthalmos, myxedema and osteoarthropathy syndrome: a case report. Elsayad K, Kriz J, Bauch J, et al. Oncol Lett 2015; 9: 2404–8.

A 48-year-old male patient was diagnosed with thyroid dermatopathy in the setting of proptosis and acropathy. Radiation therapy was commenced to treat the lower left leg and foot at a total dose of 5 Gy. Simultaneously, radiotherapy of the lower

right leg and foot was commenced, with the administration of ≤ 20 Gy. Radiotherapy was well tolerated, with the exception of skin edema and slight erythema. Results were maintained with follow-up excision, pentoxifylline, and repeat radiation.

PM successfully treated with intralesional hyaluronidase. Hoesly PM, Tolaymat LM, Sluzevich JC, et al. *JAAD Case Rep* 2018; 4(9): 874–6.

Two cases of pretibial myxedema treated with intralesional hyaluronidase (150 U/mL) at 6-week intervals over the course of 18 weeks. In one case, the amount of hyaluronidase administered varied at each treatment with a maximum dose of 150 U in 10 aliquots. The second patient received 150 U in 10 equal aliquots each treatment. Both patients experienced substantial plaque flattening and regression over 24 weeks. No adverse events occurred in either case.

Resolution of pretibial myxedema with teprotumumab in a patient with Graves disease. Varma A, Rheeman C, Levitt J. *JAAD Case Rep* 2020; 6(12): 1281–2.

Case report documenting the use of α -lipoic acid and teprotumumab initially administered intravenously for thyroid eye disease at 10 mg/kg week 1, then 20 mg/kg every 3 weeks. The patient received a total of 7 infusions. Improvement of PM was noted after two infusions and continued with subsequent treatments.

Reference

1. Fatourehchi V. Pretibial myxedema: pathophysiology and treatment options. *Am J Clin Dermatol*. 2005;6:295–309.

Prurigo nodularis

Fikki Orekoya, Junie Li Chun Wong, Niall Wilson



Nodular prurigo (NP; also known as *prurigo nodularis* [of Hyde]) is a chronic condition characterized by the presence of highly pruritic, hyperkeratotic papules or nodules, ranging from a few to hundreds in numbers. Accompanying features include severe excoriation, crusting, lichenification, and the presence of postinflammatory hyperpigmentation or hypopigmentation. Lesions are often distributed symmetrically over extensor surfaces of the limbs; the sacral area, abdomen; the face, palms, and genitalia may be affected.

NP may arise at any age but more commonly develops in middle age with a slight female preponderance. It is often regarded as a secondary reaction to chronic pruritus and scratching rather than as a primary cutaneous disease. In over 80% of patients, an underlying cause can be found. This is most commonly atopy, which is present in just under 50% of cases. Cutaneous disorders associated with the development of NP include atopic eczema, venous eczema, allergic contact eczema, dermatitis herpetiformis, Grover disease, lichen planus, and cutaneous lymphoma.

Metabolic diseases have been identified in up to 40% of cases. Diabetes mellitus, thyroid diseases, food (sorbitol, lactose, and fructose) intolerance and malabsorption, iron deficiency, and renal and hepatic failure have all been described. Infections with *Helicobacter pylori*, hepatitis C and human immunodeficiency virus (HIV), underlying malignancies, and neurologic causes such as neuropathy and chronic pain syndrome have also been reported. Concomitant psychosocial disorders can be found; anxiety and depression may be primary associations or secondary to the chronic pruritus of NP.

MANAGEMENT STRATEGY

Management should be holistic and directed toward treating the symptoms of pruritus and identifying and correcting any underlying cause. A thorough medical history and physical examination, in combination with relevant investigations, are needed to determine any driver(s) of the itching, whether cutaneous, systemic, or psychological.

General measures such as *clipping the fingernails* and recommending the *use of gloves* and mittens can help reduce excoriation.

Patients should be encouraged to apply *emollients* regularly, as xerosis can worsen pruritus. Preparations containing *menthol*, *camphor*, or *phenol* can be useful.

Oral *antihistamines* are effective for symptom control, and the use of sedating antihistamines such as promethazine 25–75 mg may be helpful at night. Potent *topical or intralesional corticosteroid injections* (triamcinolone acetonide 40 mg/mL injected in amounts of 0.1 mL/nodule and repeated every 6 weeks) can be used to treat individual lesions. Topical *calcineurin inhibitors* or topical *vitamin D3* analogs may be used as adjuncts or substitutes for topical corticosteroids to ameliorate the risk of skin atrophy associated with prolonged use of the latter. The use of *occlusive bandaging or dressings* such as hydrocolloid pads, preferably in combination with a topical medication, can interrupt the itch-scratch cycle and facilitate the healing of lesions.

Other oral antipruritic agents include *pregabalin* 25 mg or *gabapentin* 300 mg three times a day, or *tricyclic antidepressants*, such as amitriptyline started at a low dose of 10–25 mg at night. *Naltrexone*, an opioid receptor antagonist, has been reported to have a potent antipruritic effect in patients with NP. These agents may be more useful for cases with underlying neurologic or psychological causes.

In cases with more widespread involvement, phototherapy with *narrowband ultraviolet B (UVB)*, *broadband UVB*, *psoralens and ultraviolet A (PUVA)*, or *long-wavelength ultraviolet A (UVA1)* may be helpful. In severe cases that have failed to respond to topical treatment or phototherapy, systemic immunosuppressive agents such as *ciclosporin*, *azathioprine*, and *methotrexate* can be considered. These may be particularly effective for NP associated with atopic eczema. Thalidomide, due to its side effect profile, should be reserved for patients with debilitating disease in whom all other conventional treatment options have failed.

Recent studies have identified novel therapeutic agents that may effectively treat NP but are still under investigation. These include *interleukin (IL)-4 receptor-α inhibitor (dupilumab)*, *opioid receptor antagonist (nalbuphine)*, *the neurokinin 1 receptor (NK1r) antagonist (serlopitant)*, and *the anti-IL-31 receptor A agent nemolizumab*.

In cases of NP with an identifiable underlying cause, treatment should be directed toward correcting this; for example, prescribing iron supplements in iron-deficiency anemia.

Specific Investigations

- Full blood count
- Blood urea, creatinine, and electrolytes
- Liver function tests
- Hematinics (iron studies, vitamin B₁₂ and folate)
- Calcium
- Thyroid function tests
- Erythrocyte sedimentation rate
- Hemoglobin A1c
- Consider hepatitis B and C and HIV serology
- Consider chest X-ray
- Consider serum immunoglobulin levels and electrophoresis
- Consider total serum IgE
- Consider indirect immunofluorescence
- Consider biopsies for histopathology and direct immunofluorescence to exclude differential diagnoses such as pemphigoid nodularis and squamous cell carcinoma in cases with lone or a small number of lesions

Diagnostic and treatment algorithm for chronic nodular prurigo. Ständer HE, Elmariah S, Zeidler C, et al. *J Am Acad Dermatol* 2020; 82: 460–8.

A review of the diagnostic assessment, workup, and treatment algorithm for patients with chronic NP.

First-Line Therapies

• Topical corticosteroid	A
• Topical calcineurin inhibitor	A
• Topical corticosteroids with occlusion	C
• Occlusion	E
• Antihistamines	D
• Intralesional corticosteroids	E

Evaluation of the antipruritic effects of topical pimecrolimus in nonatopic prurigo nodularis: results of a randomized, hydrocortisone-controlled, doubled-blind phase II trial. Siepmann D, Lotts T, Blome C, et al. *Dermatology* 2013; 227: 353–60.

The antipruritic effects of 1% hydrocortisone and 1% pimecrolimus creams are compared in this within-participant, right-left, controlled trial involving 30 patients. A significant reduction in pruritus intensity was achieved on both pimecrolimus- and hydrocortisone-treated sites. No therapeutic difference between pimecrolimus and hydrocortisone was found. Dermatology Life Quality Index scores among subjects improved significantly after treatment.

This is one of very few comparative trials of topical therapies for NP. Although this study looked at the relative efficacy of hydrocortisone, other studies had employed the use of at least potent-strength topical corticosteroids. The highly pruritic nature of NP is such that the use of potent or superpotent topical corticosteroids is often necessary and should be used as first-line treatment.

Treatment of pruritic diseases with topical calcineurin inhibitors. Ständer S, Schurmeyer-Horst F, Luger TA, et al. *Ther Clin Risk Manag* 2006; 2: 213–8.

Eleven patients were treated with twice-daily application of topical pimecrolimus or tacrolimus. Five patients achieved 70% or greater reduction of itch with healing or major improvement of lesions.

Topical calcineurin inhibitors are known to have antipruritic and immunosuppressive effects in atopic eczema and, as demonstrated in this study, in non-atopic NP. They represent an effective and non-atrophogenic alternative to topical steroids and may potentially be a safer option for long-term use.

An occlusive dressing containing betamethasone valerate 0.1% for the treatment of prurigo nodularis. Saraceno R, Chiricozzi A, Nistico SP, et al. *J Dermatolog Treat* 2010; 21: 363–6.

A bilateral-paired comparison study involving 12 patients comparing 0.1% betamethasone valerate tape against a moisturizing itch-relief cream containing feverfew. Occlusion enhanced the efficacy of treatment, preventing scratching, and the side treated with betamethasone valproate 0.1% tape demonstrated a higher clinical response.

Use of occlusive membrane in prurigo nodularis. Meyers LN. *Int J Dermatol* 1989; 28: 275–6.

Four patients with NP responded to weekly application of an occlusive hydrocolloid pad, which also served as a negative reinforcer of scratching.

The use of adhesive occlusive pads, dressings, or bandaging can serve as a deterrent to repetitive scratching of the skin that perpetuates the disease and can disrupt the itch-scratch cycle.

Second-Line Therapies

• Topical vitamin D ₃ analogs	A
• PUVA and UVB	B
• Narrowband UVB	C
• PUVA or bath PUVA	B
• UVA1 phototherapy	D
• Monochromatic excimer light	C
• Modified Goeckerman regimen	E

Double-blind, right/left comparison of calcipotriol ointment and betamethasone ointment in the treatment of prurigo nodularis. Wong SS, Goh CL. *Arch Dermatol* 2000; 136: 807–8.

A randomized, double-blind, right/left comparative study evaluating the efficacy of calcipotriol ointment vs. 0.1% betamethasone valerate ointment in 30 patients. Calcipotriol was found to be more effective than betamethasone valerate after 8 weeks of treatment, with a greater reduction in number and size of nodules from baseline.

Topical vitamin D3 (tacalcitol) for steroid-resistant prurigo. Katayama I, Miyazaki Y, Nishioka K. *Br J Dermatol* 1996; 135: 237–40.

Nine of 11 patients treated with twice-daily application of topical tacalcitol showed a significant clinical response within 4 weeks.

Phototherapy in nodular prurigo. Divekar PM, Palmer RA, Keefe M. *Clin Exp Dermatol* 2003; 28: 99–100.

The responses of 14 patients treated with a total of 19 courses of phototherapy (8 courses of broadband UVB, 4 courses of bath PUVA, and 7 courses of oral PUVA) are reported. Partial resolution was achieved in 68% of treatment courses. Complete resolution occurred in three patients, but two relapsed within 1 year.

Narrow-band ultraviolet B phototherapy in patients with recalcitrant nodular prurigo. Tamagawa-Mineoka R, Katoh N, Ueda E, et al. *J Dermatol* 2007; 34: 691–5.

Ten patients with recalcitrant NP received once-weekly narrow-band UVB therapy. Complete or marked clearance was achieved in all patients after a mean cumulative dose of 23.88 J/cm² over a mean of 24 sessions. At 1-year follow-up, only one patient had relapsed.

Phototherapy of generalized prurigo nodularis. Bruni E, Caccialanza M, Piccinno R. *Clin Exp Dermatol* 2010; 35: 549–50.

Nineteen patients with generalized NP who had failed a range of previous therapies, including topical corticosteroids, coal tar, oral antihistamines, and ciclosporin, were treated with phototherapy mainly in the UVA range with a spike at 390 nm. A median number of 23 sessions, with a mean total dose of 6.07 J/cm², was required. Out of 15 patients who improved with treatment, two patients achieved complete remission, and eight patients achieved marked improvement.

Long-term results of topical trioxsalen PUVA in lichen planus and nodular prurigo. Karoven J, Hannuksela M. *Acta Derm Venereol* 1985; 120: 53–5.

Bath and ointment trioxsalen PUVA (primary treatment episode of 2–4 weeks, with mean cumulative dose of 7 J/cm²) was initiated in 63 patients with NP. Good results were achieved in 81% of patients. At follow-up over 1–6 years,

18% of patients were totally healed, although the majority of patients relapsed and further treatments were required to maintain results.

Efficacy of UVA1 phototherapy in 230 patients with various skin diseases. Rombold S, Lobisch K, Katzer K, et al. Photodermatol Photoimmunol Photomed 2008; 24: 19–23.

UVA1 was given to 17 patients with NP, with a mean cumulative dose of 650J/cm² given over a mean of 13.9 irradiations. Improvement was observed in 82% of patients, with 41% of patients achieving a marked improvement.

Monochromatic excimer light (308 nm) in the treatment of prurigo nodularis. Saraceno R, Nistico SP, Capriotti E, et al. Photodermatol Photoimmunol Photomed 2008; 24: 43–5.

A study of 11 patients treated with weekly monochromatic excimer light (MEL). Partial or complete clinical and histologic remission was observed in all nine patients who completed an average of eight treatment sessions.

UVB 308-nm excimer light and bath PUVA: combination therapy is very effective in the treatment of prurigo nodularis. Hammes S, Hermann J, Roos S, et al. J Eur Acad Dermatol Venereol 2011; 25: 799–803.

The efficacy of bath PUVA alone versus combination of PUVA and UVB excimer was compared in this randomized, unblinded study involving 22 patients. Adding UVB sped up the healing process and required 30% less PUVA radiation. There was no significant difference in the proportion of patients achieving complete clearance.

Successful use of a modified Goeckerman regimen in the treatment of generalized prurigo nodularis. Sorenson E, Levin E, Koo J, et al. J Am Acad Dermatol 2015; 72: 40–2.

Four patients were treated with an outpatient modified Goeckerman regimen consisting of 5 days per week broadband UVB therapy followed by application of crude coal tar and topical corticosteroids under occlusion for 4 hours. After a mean 45.5 sessions of modified Goeckerman therapy, patients continued with three sessions of broadband UVB per week with topical steroids applied to recalcitrant nodules. Remission lengths between 2.5 and 8 months were observed.

Third-Line Therapies	
• Cryotherapy	E
• Capsaicin	B
• Pulsed dye laser	E
• Fexofenadine and montelukast	C
• Naltrexone	C
• Pregabalin	B
• Gabapentin	E
• Ciclosporin	C
• Azathioprine	E
• Methotrexate	C
• Thalidomide	C
• Lenalidomide	E
• Oral tacrolimus	E
• Intravenous immunoglobulin	E
• Fire needle therapy combined with conventional treatments	B
• Dupilumab	C
• Serlopitant	A

Cryotherapy improves prurigo nodularis. Waldinger TP, Wong RC, Taylor WB, et al. Arch Dermatol 1984; 120: 1598–600.

A patient with corticosteroid- and phototherapy-resistant NP was treated successfully with blistering cryotherapy.

Cryotherapy to the point of blistering may cause scarring and hypopigmentation, as it did in this patient.

Treatment of prurigo nodularis with topical capsaicin. Ständer S, Luger T, Metze D. J Am Acad Dermatol 2001; 44: 471–8.

Topical capsaicin (0.025%–0.3%) was administered to 33 patients four to six times daily, over periods ranging from 2 weeks to 10 months. Pruritus resolved in all patients within 12 days but returned in 16 of 33 patients within 2 months of discontinuation of therapy.

Nodular prurigo successfully treated with the pulsed dye laser. Woo PN, Finch TM, Hindson C, et al. Br J Dermatol 2000; 143: 215–6.

A patient with NP unresponsive to topical and intralesional steroids and PUVA improved after six sessions of treatment with pulsed dye laser (595 nm), spaced 6 weeks apart. He remained symptom free 18 months after discontinuation of treatment.

Combination therapy of fexofenadine and montelukast is effective in prurigo nodularis and pemphigoid nodularis. Shintani T, Ohata C, Koga H, et al. Dermatol Ther 2014; 27: 135–9.

Nine of 12 patients with NP improved after 4 weeks of treatment with 10 mg montelukast once a day and 240 mg fexofenadine twice a day.

Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatologic diseases. Metze D, Reimann S, Beissert S, et al. J Am Acad Dermatol 1999; 41: 533–9.

Naltrexone 50 mg once daily was initiated in 17 patients with NP. Nine patients achieved greater than 50% improvement in pruritus, which contributed to healing of skin lesions. Two of these patients experienced tachyphylaxis after 1 and 7 months but improved when the dose of naltrexone was doubled to 50 mg twice daily.

Treatment of prurigo nodularis with pregabalin. Mazza M, Guerriero G, Marano G, et al. J Clin Pharm Ther 2013; 38: 16–8.

Thirty patients were treated with pregabalin 25 mg three times a day for 3 months. In 23 patients, a complete resolution of pruritus with reduction of lesions was seen; only one patient failed to improve. Treatment was generally well tolerated, and only six patients reported side effects.

Therapeutic hotline: treatment of prurigo nodularis and lichen simplex chronicus with gabapentin. Gencoglan G, Inanir I, Gunduz K. Dermatol Ther 2010; 23: 194–8.

Four patients with NP were treated with gabapentin and achieved at least partial remission.

Antipruritic effect of cyclosporine microemulsion in prurigo nodularis: results of a case series. Siepmann D, Luger TA, Ständer S. J Dtsch Dermatol Ges 2008; 6: 941–6.

Monotherapy with oral ciclosporin (3–5 mg per kg daily) was initiated in 14 patients. Ten patients experienced at least 80% reduction of pruritus, and in three patients, pruritus reduced by 40% to 70%, with healing of prurigo nodules during treatment. Maximal antipruritic effect was observed after 2 weeks to

12 months. Fifty percent of patients described side effects. One patient developed angioedema, and another patient had to abort treatment after embolism of the popliteal artery.

Nodular prurigo responsive to azathioprine. Lear JT, English JS, Smith AG. *Br J Dermatol* 1996; 134: 1151.

The responses of two patients treated with azathioprine 50 mg twice daily for 6 and 12 months are described. After 2–3 months of treatment, pruritus improved and lesions became less prominent. Disease relapse occurred after 2 months of treatment cessation in one patient and after 3 years in another.

Treatment of prurigo with methotrexate: a multicentre retrospective study of 39 cases. Klejtman T, Beylot-Barry M, Joly P, et al. *J Eur Acad Dermatol Venereol* 2018; 32: 437–40.

A multicenter retrospective study of 39 patients with refractory NP receiving methotrexate 5–25 mg weekly demonstrated a response rate of 91% and 94% at 3 and 6 months, respectively. Fifteen patients experienced side effects including gastrointestinal symptoms and transaminitis.

Thalidomide in 42 patients with prurigo nodularis Hyde. Anderson TP, Fogh K. *Dermatology* 2011; 223: 107–12.

A retrospective study of 42 patients treated with an average dose of thalidomide 100 mg daily over a mean period of 105 weeks. Clinical improvement was observed in 32 patients. Side effects, such as neuropathy and sedation, were the most common reason for discontinuation of treatment.

Thalidomide is one of the most reported and studied treatments of NP. However, side effects are common and can be serious and unpredictable. These include fatigue, constipation, sedation, dizziness, teratogenicity, and peripheral neuropathy. As such, thalidomide should be reserved for exceptional circumstances, in debilitating disease, and when other treatment options have been exhausted.

Treatment of prurigo nodularis with lenalidomide. Ossorio-García L, Jiménez-Gallo D, Rodríguez-Mateos ME, et al. *Dermatol Ther* 2017; 30: e12451.

A patient with refractory NP, who failed to respond to thalidomide, was treated with lenalidomide 10 mg/day. Her lesions and pruritus completely remitted after 2 months of treatment, and she remained in remission after a year of treatment.

Oral tacrolimus treatment of pruritus in prurigo nodularis. Halvorsen JA, Aasebo W. *Acta Derm Venereol* 2015; 95: 866–7.

A patient with NP achieved good response to ciclosporin but experienced hypertrichosis as a side effect. She started periodic treatment with oral tacrolimus 10–20 mg daily, alternating with ciclosporin. Monotherapy with tacrolimus led to a reduction of itch but without the side effect of hypertrichosis.

Atopic prurigo nodularis responds to intravenous immunoglobulins. Feldmeyer L, Werner S, Kamarashev J, et al. *Br J Dermatol* 2012; 166: 461–2.

A patient with refractory NP achieved dramatic improvement with intravenous immunoglobulins (IVIG; 2 g/kg monthly, given intravenously over 3 days) in combination with methotrexate. After three therapy cycles with IVIG, she experienced sustained improvement on methotrexate and topical steroids.

Efficacy and safety of fire needle therapy for nodular prurigo: a quantitative study. Luo Y, Kuai L, Song N, et al. *Evid Based Complement Alternat Med* 2019; Article ID 8797056. <https://doi.org/10.1155/2019/8797056>.

A randomized controlled trial showing that fire needle therapy (a type of hot needle acupuncture) combined with conventional treatments may be more effective than conventional therapies alone for NP, with a similar adverse event rate.

Effectiveness and safety of dupilumab for the treatment of prurigo nodularis in a French multicenter adult cohort of 16 patients. Calugareanu AN, Jachiet M, Tauber M, et al. *J Eur Acad Dermatol Venereol* 2020; 34: e74–6.

Sixteen patients with refractory NP were treated with dupilumab. At 3 months, 14 patients achieved at least a partial clinical improvement in pruritus symptoms and number of lesions. There was no difference in the overall response rate among atopic and non-atopic patients.

Dupilumab is an IL-4 receptor- α inhibitor that is already licensed for treating atopic dermatitis and shows promise as a novel treatment for NP.

Serlopitant reduced pruritus in patients with prurigo nodularis in a phase 2, randomized, placebo-controlled trial. Ständer S, Kwon P, Hirman J, et al. *J Am Acad Dermatol* 2019; 80: 1395–402.

A randomized, double-blind, placebo-controlled trial involving 128 patients with refractory NP. Patients treated with serlopitant 5 mg/day, a NK1r antagonist, achieved a statistically significant greater reduction in pruritus intensity at 4 and 8 weeks compared with placebo. The most frequently reported side effects were nasopharyngitis, diarrhea, and fatigue.

Other novel therapeutic agents. A systematic review of evidence-based treatments for prurigo nodularis. Qureshi AA, Abate LE, Yosipovitch G, et al. *J Am Acad Dermatol* 2019; 80: 756–64.

Unpublished data (at time of submission) from recent randomized controlled trials (RCT) have revealed two new therapeutic agents which may effectively treat NP.

A multicenter, double-blind RCT (NCT02174419) suggests trends for efficacy of nalbuphine, a dual opioid κ -receptor agonist and μ -receptor antagonist, at a dose of 180 mg extended release twice daily in comparison to placebo with no serious adverse effects in the 62-patient sample.

In a separate trial, subcutaneous nemolizumab (an anti-IL-31 receptor- α antibody) at 0.5 mg/kg was associated with a greater improvement in pruritus at week 4, a significant improvement in skin lesions, and a similar safety profile compared to placebo in a multicenter phase 2 double-blind RCT with 70 patients (NCT03181503).

Prurigo pigmentosa

Yukiko Tsuji-Abe, Hiroshi Shimizu



Prurigo pigmentosa (PP) is a pruritic eruption that begins with urticarial papules or papulovesicles on the neck, chest, and back, followed by reticular pigmentation. It most commonly affects women in their twenties and thirties. PP is most frequently diagnosed in Japan, but it also has been described in various ethnicities worldwide.

MANAGEMENT STRATEGY

PP has a distinctive clinical course. Lesions initially start as pruritic, urticarial papules or papulovesicles. The lesions resolve spontaneously within a week, but repetition of the episode results in reticular pigmentation. The pathogenesis of PP remains unknown. Friction from clothing, especially in wet conditions such as sweating or swimming, can trigger the disease. In some cases, ketosis caused by diabetes mellitus, sudden weight loss from a low-carbohydrate diet, or anorexia nervosa precedes PP. Treatment of these conditions can lead to clinical resolution. Several case reports described individuals who developed this condition in association with other disorders, including contact allergic reactions to certain chemical agents, infection with *Helicobacter pylori* or spirochetes, an atopic diathesis, and pregnancy.

Minocycline (100–200 mg daily) is usually very effective for PP. The effects are mostly observed within 3–7 days after treatment and lead to reductions in itching and papular lesions. Minocycline is regarded as the first-line therapy because it produces fewer adverse reactions, and the remission is reportedly longer than other therapies. Topical or systemic corticosteroids and antihistamines are usually ineffective.

Specific Investigations

- History of low-carbohydrate diet, rapid weight gain/loss
- Consider blood or urine ketone levels

Prurigo pigmentosa induced by ketosis: resolution through dietary modification. Hartman M, Fuller B, Heaphy MR. *Cutis* 2019; 103: E10–3.

A 40-year-old white woman developed skin rash and elevated blood ketones coincided with an intentional weight loss, archived with low-carbohydrate diet. When carbohydrates were added back into her diet, both ketosis and eruption remarkably resolved.

Prurigo pigmentosa: a clinicopathologic study of 16 cases. Oh YJ, Lee MH. *J Eur Acad Dermal Venereol* 2012; 26: 1149–53.

Eight of 16 patients showed a chronological relationship between appearance of skin lesions and dieting or fasting.

Prurigo pigmentosa on a patient with soft-drink ketosis. Mitsuhashi Y, Suzuki N, Kawaguchi M, et al. *J Dermatol* 2005; 32: 767–8.

First-Line Therapies

• Minocycline	C
• Treatment of ketosis or any other potentially causative factors	D

Prurigo pigmentosa: clinicopathological study and analysis of 50 cases in Korea. Kim JK, Chung WK, Chang SE, et al. *J Dermatol* 2012; 39: 891–7.

Among 50 patients, 28 patients were treated with minocycline (100–200 mg daily), seven with dapsone (100 mg daily), and four with both minocycline and dapsone; all patients responded well to these therapies.

Prurigo pigmentosa: a clinical and histopathological study of nine Chinese cases. Zeng X, Li L, Cui BN. *J Eur Acad Dermatol Venereol* 2016; 30: 1794–8.

In this retrospective analysis, all nine patients responded well to minocycline treatment (100–200 mg daily) for the short duration of 8.62 days, and a lower recurrence rate was recorded after treatment.

Prurigo pigmentosa associated with diabetic ketoacidosis. Ohnishi T, Kisa H, Ogata E, et al. *Acute Derm Venereol* 2000; 80: 447–8.

Eighteen cases of PP were associated with diabetic ketoacidosis. Treatment of ketoacidosis improved eruptions in eight cases.

Second-Line Therapies

• Dapsone	D
• Doxycycline	D
• Roxithromycin	E
• Clarithromycin	E

Dapsone, doxycycline, and macrolide antibiotics such as roxithromycin and clarithromycin are reported to be effective for PP. These drugs are recommended for patients who respond poorly to first-line treatment and for whom dapsone and minocycline are contraindicated.

Prurigo pigmentosa in Korea: clinicopathological study. Shin JW, Lee SY, Lee JS, et al. *Int J Dermatol* 2012; 51: 152–7.

Dapsone and minocycline were used alone or in combination to treat 37 of 49 patients. Lesions and pruritus rapidly resolved in all patients.

Prurigo pigmentosa: a clinical and histopathologic study of 11 cases. Lin SH, Ho JC, Cheng YW, et al. *Chang Gung Med J* 2010; 33: 157–63.

Among 11 patients with PP, 10 patients were treated with doxycycline (200 mg daily) and exhibited a good response.

Prurigo pigmentosa: not an uncommon disease in the Turkish population. Baykal C, Buyukbabani N, Akinturk S, et al. *Int J Dermatol* 2006; 45: 1164–8.

Three of six patients with PP responded well to doxycycline 100 mg daily; another three responded well to tetracycline 500 mg daily.

The successful treatment of prurigo pigmentosa with macrolide antibiotics. Yazawa N, Ihn H, Yamane K, et al. *Dermatology* 2001; 202: 67–9.

Two patients with PP responded well to roxithromycin 300 mg daily; another two responded well to clarithromycin 400 mg daily. In all patients, the effect was quick, and pruritus and papules disappeared within 1 week.

Third-Line Therapies

• Isotretinoin	E
• Narrowband ultraviolet B (UVB) therapy	E

Most patients with PP respond well to first- or second-line therapies or achieve spontaneous remission, but these treatment alternatives might be useful in unusual cases.

Vesiculous prurigo pigmentosa in a 13-year-old girl: good response to isotretinoin. Requena Caballero C, Nagore E, Sanmartín O, et al. *Int J Eur Acad Dermatol Venereol* 2005; 19: 474–6.

The initial diagnosis was a vesiculobullous form of Darier disease, and the patient was started on isotretinoin 40 mg/day, which resulted in a good response in 10 days. The lesion relapsed 5 months later, and treatment with minocycline 100 mg/day resulted in resolution within 7 days.

Prurigo pigmentosa successfully treated with low-dose isotretinoin. Akoglu G, Boztepe G, Karaduman A. *Dermatology* 2006; 213: 331–3.

An 18-year-old woman was successfully treated with isotretinoin 20 mg daily (0.3 mg/kg/day). Pruritus and erythematous macules resolved within 1 month of the start of therapy.

Successful treatment with narrowband UVB phototherapy in prurigo pigmentosa associated with pregnancy. Jang MS, Baek JW, Kang DY, et al. *Eur J Dermatol* 2011; 21: 634–5.

A woman in the 13th week of pregnancy was treated with narrowband UVB for PP. Pruritus decreased significantly after the first irradiation, and erythema resolved after the fifth session.

Pruritus

Kayla Fourzali, Gil Yosipovitch



INTRODUCTION

Chronic pruritus or itch, defined as present for more than 6 weeks, is commonly encountered in the dermatologic clinic and is estimated to affect up to a fifth of the general population at some point during their lifetime. The causes of chronic itch are numerous and include primary dermatologic diseases, systemic illnesses, neuropathic conditions, psychologic and psychiatric conditions, or medication reactions. Evidence now suggests that chronic itch may be at least in part explained by hypersensitization or hyperinnervation of the neural itch pathways. The clinical presentation of itch may vary widely depending on the underlying etiology. Primary dermatologic conditions will most often have a recognizable manifestation in the skin ranging from a localized rash to erythroderma. Itch that is related to histaminergic activation (i.e., urticaria) may present as pruritic wheals. Neuropathic, systemic, or psychogenic etiologies may present with no rash or only secondary skin lesions due to scratching. Pruritus may be localized to a specific site on the body (i.e., scalp, groin, back, arms) or may be generalized.

MANAGEMENT STRATEGY

A thorough diagnostic workup is crucial in the determination of management of chronic itch, as the underlying cause of itch strongly informs treatment options. Special attention to the medical history, physical examination, laboratory testing, and additional specialized examinations (see Specific Investigations) is required. If a specific dermatologic condition is diagnosed, treatment of itch is ideally targeted to the underlying disease mechanism, such as inflammation or immune response. For neuropathic causes of itch, a variety of medications may be used to target the neural systems manifest in the skin. If a systemic or psychogenic condition is found to be the cause, treatment of the disease state must be addressed if possible along with symptomatic itch treatment. Chronic itch has known effects on patient quality of life and thus timely treatment targeted to the underlying etiology is of utmost importance.

Specific Investigations

Medical history

- Characteristics of itch (i.e., temporality, severity, aggravating vs. alleviating factors)
- Current medications (i.e., itch-inducing medications such as μ -opioid agonists, EGFR inhibitors, angiotensin-converting enzyme inhibitors)
- Medical illnesses
- Psychiatric history
- Environmental exposures

Physical exam

- Primary dermatologic lesions vs. secondary excoriations
- Distribution of lesions (i.e., generalized vs. localized, bodily locations)
- Signs of systemic disease or malignancy (i.e., weight loss, lymphadenopathy)

Core laboratory tests

- Complete blood count with differential
- Liver function tests (transaminases, bilirubin)
- Serum creatinine
- Thyroid function tests
- Erythrocyte sedimentation rate
- Human immunodeficiency virus test

Optional tests

- Skin biopsy with consideration of direct immunofluorescence/ELISA
- Chest X-ray
- Age appropriate malignancy screening (i.e., mammography, colonoscopy)

Referrals

- Malignancy workup or neurologic workup if indicated

CHRONIC PRURITUS OF UNKNOWN ORIGIN (CPUO)

Despite a thorough workup, many cases of chronic itch have no identifiable cause. CPUO is a diagnosis of exclusion that can be employed once an exhaustive workup has revealed no known primary dermatologic, medical, or psychiatric illness as the cause (see Specific Investigations). Medical therapy for CPUO can be challenging, as, by definition the underlying mechanism of disease cannot be targeted. Medications appropriate for empiric treatment of CPUO are discussed throughout this chapter for various etiologies of pruritus. First-line medications include the selective norepinephrine reuptake inhibitors (SNRIs) (i.e., mirtazapine) and gabapentinoids (gabapentin and pregabalin), which have antipruritic properties effective in various pruritic etiologies. Additional systemic therapies such as kappa opioid agonists (i.e., intranasal butorphanol), neurokinin 1 inhibitors (i.e., aprepitant), Janus kinase (JAK) inhibitors (i.e., abrocitinib, tofacitinib), and inhibitors of interleukins (ILs) 4, 13, and 31 (i.e., dupilumab, nemolizumab) have been shown effective in several disease states causing chronic pruritus and may provide relief for the patient with CPUO. Topical emollients including anesthetics such as pramoxine 1% or a formulation of ketamine (5–10%), amitriptyline (5%), and lidocaine (5%) (KAL) should be considered as adjunct therapies.

Table 205.1 Empiric therapy for CPUO

	Class of drug	Medication examples and recommended dosages	Notable adverse effects	Level of evidence for use in chronic itch etiologies
First-line medications	Serotonin-norepinephrine reuptake inhibitors	Mirtazapine 7.5–15 mg daily	Increased appetite, weight gain, dizziness and sedation, renal and hepatic dosing necessary	E (cholestasis, malignancy)
	Gabapentinoids	Gabapentin (300–600 mg at night, titration up to 3600 daily), pregabalin (75 mg twice daily, titration up to 400 mg daily) *Low dose gabapentin (100–300 mg) or pregabalin (25–50 mg) daily for renal disease or elderly	Somnolence, dizziness, increased appetite, weight gain, peripheral edema	A (uremic) C (neuropathic) E (malignancy)
Second-line medications	κ-opioid agonists	intranasal butorphanol 1–4 mg daily	Somnolence, dizziness, nausea, vomiting	A (uremic, cholestatic) E (malignancy)
Third-line and upcoming medications	NK-1 inhibitors	Aprepitant	Gastrointestinal upset, fatigue, vertigo, headache, drug–drug interactions	Aprepitant: C (malignancy), E (neuropathic)
	JAK inhibitors	Tofacitinib	Infection, neutropenia and lipid elevations, deep vein thrombosis	These medications have not been approved for use in chronic itch but are currently in clinical trials

Chronic pruritus of unknown origin (CPUO): uniform nomenclature and diagnosis as a pathway to standardized understanding and treatment. Kim BS, Berger TG, Yosipovitch G. *J Am Acad Dermatol* 2019; 81(5): 1223–4.

This article proposes preferred nomenclature for chronic itch and is a concise resource for the diagnostic workup of CPUO.

Clinical practice. Chronic pruritus. Yosipovitch G, Bernhard JD. *N Engl J Med* 2013; 368(17): 1625–34.

This review details the therapeutic approach to chronic itch.

British Association of Dermatologists' guidelines for the investigation and management of generalized pruritus in adults without an underlying dermatosis, 2018. Millington GWM, Collins A, Lovell CR, et al. *Br J Dermatol* 2018; 178(1): 34–60.

This article presents guidelines for treatment of pruritus based on the underlying etiology.

Chronic itch management: therapies beyond those targeting the immune system. Fowler E, Yosipovitch G. *Ann Allergy Asthma Immunol* 2019 Aug; 123(2): 158–65.

This is a comprehensive review of the underlying mechanisms of chronic itch and therapeutics that target the receptors, mediators, and pathways of the neural system.

Drugs on the horizon for chronic pruritus. McEwen MW, Fite EM, Yosipovitch G, et al. *Dermatol Clin* 2018; 36(3): 335–44.

A review of the newly developed therapies targeting the inflammatory and neural pathways implicated in chronic itch.

Itch: from mechanism to (novel) therapeutic approaches. Yosipovitch G, Rosen JD, Hashimoto T. *J Allergy Clin Immunol* 2018; 142(5): 1375–90.

This article gives an excellent overview on mechanisms of itch and neural sensitization as well as its treatments.

ITCH IN DERMATOLOGIC DISEASES

Itch is a predominant feature of numerous primary dermatologic diseases, most commonly atopic dermatitis (AD), psoriasis, and chronic urticaria. Other significant pruritic diseases include prurigo nodularis (PN), contact dermatitis, lichen simplex chronicus, lichen planus, bullous pemphigoid, and scabies. Xerosis, or dry skin, is multifactorial, and it may be the symptom of a primary dermatologic condition, but it has also been associated with aging skin and various systemic diseases. Treatment for specific dermatologic diseases is ideally targeted at the underlying etiology, which will in turn provide relief of itch. Symptomatic relief of mild itch associated with these conditions or xerosis may be achieved by topical therapy using emollients with anesthetics, cooling agents, or keratolytic agents. Topical medications targeting inflammation and immune function, such as topical corticosteroids or calcineurin inhibitors, are often first-line therapies. Systemic management using oral corticosteroids or oral immunosuppressants may better target the underlying cause of inflammation in refractory disease. Oral antihistamines provide relief for known histaminergic etiologies but are of limited use in chronic itch otherwise. Ultraviolet A and B (UVA and UVB) phototherapy has shown to be effective in various etiologies of itch. More recently, medications that target the known mediators of itch signaling and the neural system are being implemented, such as antidepressants, gabapentinoids, and NK-1 inhibitors. Biologic therapies have shown dramatic antipruritic effects in the treatment of various primary dermatologic conditions. The specifics regarding the treatment of primary dermatologic disease are discussed in detail in their

corresponding chapters of this text and is beyond the scope of the present chapter.

SYSTEMIC CAUSES OF CHRONIC ITCH

Neuropathic Itch

Neuropathic itch may result from peripheral neuropathy (i.e., diabetic polyneuropathy), infectious processes (i.e., postherpetic neuralgia [PHN]), or compression or inflammation of sensory nerve roots (i.e., brachioradial neuralgia [BRP], notalgia paresthetica [NP]). Neuropathic itch typically presents in the absence of primary dermatologic lesions and is often rated by patients as severe in quality, often with sleep disturbance and reduction in quality of life.

Treatment is often challenging, as neuropathic itch is non-histaminergically mediated and does not typically respond to antihistamines nor to corticosteroids. For mild or localized itch, topical emollients with anesthetics may provide rapid, targeted relief. Effective topical treatments include capsaicin 0.025%–0.075%, which acts through activating the TRPV1 receptors in the skin to desensitize local nerves, as well as anesthetics such as pramoxine 1%. A concentrated capsaicin patch (8%) has shown effectiveness in neuropathic itch, as has a topical formulation of ketamine (5–10%), amitriptyline (5%), and lidocaine (5%) (KAL).

For moderate-to-severe neuropathic itch, systemic treatments may be employed, including the gabapentinoid antiepileptics and antidepressants. Gabapentinoids have been found to be effective for several forms of neuropathic itch due to PHN, BRP, and NP, and spinal cord injury. Gabapentin starting dose suggested for neuropathic itch is 300–600 mg nightly, with increase to 3600 mg/day as tolerated. The corresponding suggested dose for pregabalin is 75 mg twice daily with increase to 400 mg daily as tolerated. Antidepressants, particularly the tricyclics (TCAs) such as amitriptyline, have been reported in cases to reduce pruritus due to neuropathic etiologies such as BRP, NP, and poststroke pruritus at dosage of 25 mg/day. Evidence for the role of NK-1 inhibitors such as aprepitant (dosage 80 mg daily) in neuropathic itch is limited, with a case report of success in refractory itch due to BRP. For neuropathic pruritus that is severe or resistant to topical or systemic therapies, more invasive management may be considered, such as intradermal botulinum toxin A injections (1 unit per cm²) or targeted nerve blocks.

First-Line Therapy

- Topical anesthetics

C

Diagnosis and management of neuropathic itch. Rosen JD, Fostini AC, Yosipovitch G. *Dermatol Clin* 2018; 36(3): 213–24.

This review details the pathophysiology and etiologies that underlie neuropathic forms of itch. It includes up-to-date evidence on therapies and a therapeutic ladder for neuropathic itch.

Topical capsaicin. The fire of a ‘hot’ medicine is reignited. Papoiu AD, Yosipovitch G. *Expert Opin Pharmacother* 2010; 11(8): 1359–71.

This article reviews the mechanism of action and clinical application of capsaicin in treating pruritus.

Topical capsaicin 8% for the treatment of neuropathic itch conditions. Andersen HH, Arendt-Nielsen L, Elberling J. *Clin Exp Dermatol* 2017; 42(5): 596–8.

A case-based article reviewing the mechanism of action, practical application, and clinical outcomes of use of a capsaicin 8% patch for treatment of chronic pruritus.

Successful treatment of refractory neuropathic pruritus with capsaicin 8% patch: a bicentric retrospective study with long-term follow-up. Misery L, Erfan N, Castela E, et al. *Acta Derm Venereol* 2015; 95(7): 864–5.

A series of seven cases of capsaicin 8% patch used in treatment of localized neuropathic itch (BRP, NP, small fiber neuropathy). All patients included in the series reported complete or near resolution of itch following a single patch application with no recurrence of symptoms at 6 months.

Topical ketamine-amitriptyline-lidocaine for chronic pruritus: a retrospective study assessing efficacy and tolerability. Lee HG, Grossman SK, Valdes-Rodriguez R, et al. *J Am Acad Dermatol* 2017; 76(4): 760–1.

A retrospective report of 96 patients prescribed topical KAL for treatment of chronic itch (29% neuropathic, 19% PN). Itch relief was experienced rapidly, with 58% of those surveyed reporting relief of pruritus to a great extent, and 35% to a moderate extent.

Second-Line Therapy

- Gabapentinoids

C

Use of antiepileptic mood stabilizers in dermatology. Gupta MA, Pur DR, Vujcic B, et al. *Clin Dermatol* 2018; 36(6): 756–64.

This article reviews the available evidence for the use of antiepileptic mood stabilizers such as gabapentin, pregabalin, and others in dermatologic conditions that are associated with neuropathic pain and itch such as PHN.

Gabapentin and pregabalin for the treatment of chronic pruritus. Matsuda KM, Sharma D, Schonfeld AR, et al. *J Am Acad Dermatol* 2016; 75(3): 619–25. e6.

This article reviews the evidence of use of gabapentin and pregabalin in the chronic pruritus conditions BRP and NP, among others.

- Antidepressants D
- NK-1 inhibitors E
- Botulinum toxin injection D
- Peripheral nerve block D

Use of oral antidepressants in patients with chronic pruritus: a systematic review. Kouwenhoven TA, van de Kerkhof PCM, Kamsteeg M. *J Am Acad Dermatol* 2017; 77(6): 1068–73. e7.

A systematic evaluation of 35 case reports and series, randomized controlled trials (RCTs), and retrospective cohort studies on the use of antidepressants in patients with chronic pruritus of various etiologies. The majority of studies showed improvement in pruritus with use of these medications, with mixed evidence of efficacy in neuropathic itch. Case reports and series demonstrate the antipruritic effects of amitriptyline.

The use of aprepitant in brachioradial pruritus. Ally MS, Gamba CS, Peng DH, et al. *JAMA Dermatol* 2013; 149(5): 627–8.

This case report of a patient with BRP treated with aprepitant 80 mg daily for 7 days shows improvement of pruritus within 2 days, but with relapse 2 days following discontinuation. Further treatment for 2 weeks resulted in partial improvement of symptoms.

Botulinum toxin type A for the treatment of localized recalcitrant chronic pruritus. Boozalis E, Sheu M, Selph J, et al. *J Am Acad Dermatol* 2018; 78(1): 192–4.

This article reviews the studies showing evidence for use of botulinum toxin as a treatment of chronic pruritus, including four studies of its use in NP, BRP, and other neuropathic itch etiologies.

Neuropathic scrotal pruritus: anogenital pruritus is a symptom of lumbosacral radiculopathy. Cohen AD, Vander T, Medvovsky E, et al. *J Am Acad Dermatol* 2005; 52(1): 61–6.

This case series included patients with anogenital pruritus with lumbosacral radiculopathy. Paravertebral injections at the L5–S1 level with a mixture of triamcinolone and lidocaine were performed and pruritus significantly decreased.

Brachioradial pruritus treated with computed tomography-guided cervical nerve root block: a case series. Weinberg BD, Amans M, Deviren S, et al. *JAAD Case Rep* 2018; 4(7): 640–4.

This case series in three BRP patients with cervical degenerative disease who had undergone epidural steroid injections. Complete relief of pruritus was reported in 2/3 upon first injection, while the third required repeat procedures to achieve relief of pruritus.

Renal/Uremic Itch

Pruritus is a commonly reported symptom in those with end-stage renal disease (ESRD) undergoing hemodialysis. The etiology of pruritus in ESRD is not fully understood but is proposed to be related to alterations in the Th1 vs. Th2 immune response, elevated dialysis-related substances, and an imbalance of endogenous opioids.

Topical treatments such as emollients with pramoxine 1% or capsaicin 0.025%–0.075% with topical anesthetic pretreatment (i.e., mixture of 2.5% lidocaine and 2.5% prilocaine) to avoid a burning sensation have been shown to be effective in uremic itch. Oral gabapentin in low doses ranging from 100 mg to 300 mg and pregabalin at 50–75 mg following hemodialysis have been shown in RCTs to be safe and effective treatment for ESRD-associated pruritus.

Butorphanol, a κ -opioid agonist with some μ -opioid antagonist properties, has Federal Drug Administration approval for use in the management of pain. Intranasal (1 mg or one spray in the nostril per day) administration has been successful in relieving cases of ESRD-related pruritus. Nalfurafine, also a κ -opioid agonist with partial μ -opioid agonism, only currently available in Japan, has been demonstrated in an RCT to reduce uremic itch, and newer drugs in this class in the pipeline, such as difelikefalin and nalbuphine, show promise in trials for uremic itch with a favorable safety profile.

Mirtazapine has shown success in cases of uremic itch at low doses of 15 mg nightly. Phototherapy with UVB has been used for years for treatment of uremic itch and has shown effectiveness in randomized trials in comparison to UVA phototherapy.

First-Line Therapies

- Topical anesthetics **A**
- Oral low dose gabapentinoids **A**

A pramoxine-based anti-itch lotion is more effective than a control lotion for the treatment of uremic pruritus in adult hemodialysis patients. Young TA, Patel TS, Camacho E, et al. *J Dermatol Treat* 2009; 20(2): 76–81.

A double-blind RCT of 28 ESRD patients undergoing hemodialysis with moderate-to-severe pruritus. Participants randomized to topical lotion of pramoxine 1% vs. placebo for 4 weeks. Results show the treatment lotion significantly reduced pruritus symptoms to a greater degree than placebo.

Topical capsaicin therapy for uremic pruritus in patients on hemodialysis. Makhloogh A, Ala S, Haj-Heydari Z, et al. *Iran J Kidney Dis* 2010; 4(2): 137–40.

This double-blind crossover RCT of 34 patients with ESRD-related itch on hemodialysis tested the treatment of topical capsaicin (0.03%) compared with placebo. Greater improvement in pruritus scores was demonstrated with treatment cream over placebo.

Effect of EMLA pre-treatment on capsaicin-induced burning and hyperalgesia. Yosipovitch G, Maibach HI, Rowbotham MC. *Acta Derm Venereol* 1999; 79(2): 118–21.

This single-blind study included healthy volunteers pretreated with EMLA vs. placebo prior to application of capsaicin 0.075% cream. Pretreatment with EMLA was shown to significantly reduce the burning sensation associated with capsaicin treatment.

Treatment of uremic pruritus: a systematic review. Simonson E, Komenda P, Lerner B, et al. *Am J Kidney Dis* 2017; 70(5): 638–55.

This comprehensive review of 44 RCTs evaluates the evidence available for treatment of uremic pruritus, including nine studies evaluating the gabapentinoids. The review concludes that current evidence favors a significant benefit of the use of gabapentinoids over placebo in the treatment of uremic pruritus.

Second-Line Therapy

- κ -opioid agonists and μ -opioid antagonists **A**

Butorphanol for treatment of intractable pruritus. Dawn AG, Yosipovitch G. *J Am Acad Dermatol* 2006; 54(3): 527–31.

Case series reporting the use of intranasal butorphanol, a κ -opioid and μ -opioid antagonist, for treatment of intractable pruritus, including one patient with ESRD. Butorphanol (1 mg daily) relieved that patient's pruritus within 1 day of starting treatment.

Effect of a novel kappa-receptor agonist, nalfurafine hydrochloride, on severe itch in 337 haemodialysis patients: a Phase III, randomized, double-blind, placebo-controlled study. Kumagai H, Ebata T, Takamori K, et al. *Nephrol Dial Transplant* 2010; 25(4): 1251–7.

This phase III double-blind RCT evaluated the efficacy and safety of nalfurafine hydrochloride at two doses vs. placebo for 14 days in 337 hemodialysis patients with uremic pruritus. Nalfurafine at doses 5 mcg and 2.5 mcg was shown to significantly reduce itch measured by visual analog scale (VAS) in these patients and was well-tolerated, with the most common adverse effect being insomnia.

A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. Fishbane S, Jamal A, Munera C, et al. *N Engl J Med* 2020; 382(3): 222–32.

This phase 3 double-blind RCT evaluated the efficacy and safety of IV 0.5 mcg/kg difelikefalin in 378 hemodialysis patients with moderate-to-severe pruritus. In the difelikefalin group, 52% of patients had a decrease of at least 3 points in the worst itch

numerical rating score compared with 31% in the placebo group. An improved itch-related quality of life was also noted in the difelikefalin group.

A multicenter, randomized, double-blind, placebo-controlled trial of nalbuphine ER tablets for uremic pruritus. Mathur VS, Kumar J, Crawford PW, et al. *Am J Nephrol* 2017; 46(6): 450–8.

A double-blind RCT of hemodialysis patients with uremic itch. Itch intensity decreased significantly in the 120 mg treatment arm compared with the placebo group.

Drugs on the horizon for chronic pruritus. McEwen MW, Fite EM, Yosipovitch G, et al. *Dermatol Clin* 2018; 36(3): 335–44.

A review of the newly developed therapies targeting the inflammatory and neural pathways implicated in chronic itch, including nalfurafine and CR845/difelikefalin.

Cholestatic Itch

Chronic pruritus may be due to an underlying hepatobiliary disease of intrahepatic (i.e., viral hepatitis B or C, primary biliary cirrhosis [PBC], Alagille syndrome) or extrahepatic (i.e., primary sclerosing cholangitis [PSC] or obstructing tumor) origin. Cholestatic itch typically presents on the palms and soles and is a primary feature of PBC, preceding the diagnosis in the majority of cases. The pathophysiology of cholestatic itch has not been wholly elucidated, but serum levels of lysophosphatidic acid and autotaxin, endogenous opioids, bile salts, and bile acids have been shown to be elevated in these patients.

Despite the correlation of elevated plasma bile acids, levels do not consistently correlate with intensity of pruritus symptoms. Recently, activation of MRGPRX4 in skin nerve cells by bile acids in the skin has been found to be related to cholestatic itch. However, as yet there is no drug developed targeting the MRGPRX4 receptor.

Oral cholestyramine, a non-absorbable anion exchange resin, has been used for years in patients with cholestatic itch at a suggested dosage of 4–16 g/day. However, not all patients show an antipruritic response to cholestyramine and gastrointestinal side effects can limit compliance. The selective serotonin reuptake inhibitor (SSRI) sertraline at a dose of 75–100 mg/day has also demonstrated effectiveness in cholestatic itch. Mirtazapine (15 mg daily) has also been shown to reduce itch in a variety of pruritic conditions and has been proposed as a potential treatment for cholestatic itch. Likely owing to its inducing effects of hepatic metabolism and/or secretions of pruritogens and reduction of autotaxin, rifampicin has been shown to reduce cholestatic itch with suggested dose of 300–600 mg/day. Because of potential hepatotoxicity, liver transaminases must be monitored frequently during rifampicin therapy.

μ-Opioid agonists have long been known to induce pruritus as an adverse effect. Medications that antagonize the μ-opioid receptor such as naloxone (10–20 mcg/kg/hr) and naltrexone (dosage starting at 12.5 mg, increasing to 25–50 mg/day) have been demonstrated effective in RCTs to reduce cholestatic itch. Nalfurafine (oral, 2.5–5 mcg) and butorphanol (intranasal, 1 mg daily) κ-opioid agonists with some μ-opioid antagonist properties have been shown in RCTs and case series, respectively, to effectively reduce itch in cholestasis.

Several inhibitors of ileal bile acid transporter (IBAT), also known as apical sodium-dependent bile transporter, showed antipruritic effect in cholestatic itchy diseases. A recent phase 2 trial with IBAT inhibitor GSK23330672 demonstrated significant

antipruritic effect in patients with intractable itch with PBC with a mean reduction of 57% and a good safety profile.

Intrahepatic cholestasis of pregnancy (ICP) typically presents during the third trimester with generalized pruritus including the palms and soles without a primary rash. ICP resolves shortly after delivery and in some cases induction of labor is recommended to improve fetal outcomes. However, the pruritus can be intense, requiring management of symptoms during the pregnancy. Cholestyramine has been used for treatment of ICP for many years, as it does show efficacy in reducing cholestatic itch. However, its use may interfere with maternal absorption of fat soluble vitamins, notably vitamin K, and adverse gastrointestinal effects are often not tolerated. Ursodeoxycholic acid (UDCA) has been shown to be somewhat effective in reducing pruritus and its use in ICP may improve fetal outcomes.

First-Line Therapies

• Cholestyramine	C
• UDCA (first line for ICP)	A

Pathogenesis and management of pruritus in PBC and PSC. Kremer AE, Namer B, Bolier R, et al. *Dig Dis* 2015; 33 Suppl 2: 164–75.

This article provides a comprehensive review of the pathophysiology of cholestatic pruritus and the proposed management.

Evaluating the effectiveness and safety of ursodeoxycholic acid in treatment of intrahepatic cholestasis of pregnancy: a meta-analysis (a prisma-compliant study). Kong X, Kong Y, Zhang F, et al. *Medicine (Baltimore)* 2016; 95(40): e4949.

This meta-analysis includes 12 RCTs (662 participants) evaluating the efficacy of UDCA vs. control in women with ICP. The analysis concludes that UDCA is safe and effective for the treatment of ICP-related pruritus. In addition, UDCA treatment was associated with improved gestational and fetal outcomes.

Second-Line Therapies

• Sertraline	B
• Mirtazapine	E

Sertraline as a first-line treatment for cholestatic pruritus. Mayo MJ, Handem I, Saldana S, et al. *Hepatology* 2007; 45(3): 666–74.

This is a small study composed of an open label portion and double-blind crossover RCT of 12 participants given sertraline at a dose of 75–100 mg/day for cholestatic pruritus. Pruritus symptoms assessed by VAS were found to improve in both the open label and randomized portions of the study, and there was a significant improvement in pruritus in those treated versus those taking placebo.

Comparison of sertraline with rifampin in the treatment of cholestatic pruritus: a randomized clinical trial. Ataei S, Kord L, Larki A, et al. *Rev Recent Clin Trials* 2019; 14(3): 217–23.

In this single blinded RCT of 36 participants with PBC and PSC, sertraline (100 mg daily) was found to be as equally effective as rifampicin (300 mg daily) in reducing pruritus with fewer adverse effects.

Mirtazapine for reducing nocturnal itch in patients with chronic pruritus: a pilot study. Hundley JL, Yosipovitch G. *J Am Acad Dermatol* 2004; 50(6): 889–91.

This case series describes three patients with intractable chronic itch showing improvement after given mirtazapine 15 mg daily. The article describes

the safety profile of mirtazapine, the proposed mechanisms of the drug's antipruritic properties, and proposed uses of mirtazapine in chronic itch.

Third-Line Therapy

- κ -opioid agonists and μ -opioid antagonists **A**

Effects of naloxone infusions in patients with the pruritus of cholestasis. A double-blind, randomized, controlled trial. Bergasa NV, Alling DW, Talbot TL, et al. *Ann Intern Med* 1995; 123(3): 161–7.

In this double-blind RCT, 29 patients with cholestatic pruritus received four 24-hour intravenous infusions of naloxone (0.2 mcg/kg body weight/min) in 5% dextrose/0.45% NaCl vs. placebo. Pruritus was assessed by VAS every 4 hours and participants were monitored for scratching activity. Pruritus score and scratching activity significantly improved in the treated group in comparison to placebo.

Efficacy and safety of oral naltrexone treatment for pruritus of cholestasis, a crossover, double blind, placebo-controlled study. Terg R, Coronel E, Sorda J, et al. *J Hepatol* 2002; 37(6): 717–22.

This double-blind, crossover RCT included 29 patients with cholestatic pruritus who received either naltrexone (50 mg daily) or placebo for 2 weeks with a 1-week washout period before crossover. Pruritus was assessed by VAS prior to treatment and daily throughout treatment. The mean VAS significantly decreased in the treatment group with 45% of the naltrexone-treated patients reporting a decreased pruritus score of at least 50%. Adverse effects of naltrexone were notable, with symptoms such as dizziness, nausea, vomiting, and headache reported.

Use of butorphanol as treatment for cholestatic itch. Golpanian RS, Yosipovitch G, Levy C. *Dig Dis Sci*. 2021; 66(5): 1693–1699.

This case series details the response to intranasal butorphanol in eight patients with cholestatic pruritus. Five of the eight patients reported significant reductions in severity of itch and the drug was well tolerated by most patients.

Butorphanol for treatment of intractable pruritus. Dawn AG, Yosipovitch G. *J Am Acad Dermatol* 2006; 54(3): 527–31.

In this case series, five patients are presented with intractable pruritus; one with PBC treated with intranasal butorphanol showing rapid improvement of symptoms.

Efficacy of nalfurafine hydrochloride in patients with chronic liver disease with refractory pruritus: a randomized, double-blind trial. Kumada H, Miyakawa H, Muramatsu T, et al. *Hepatol Res* 2017; 47(10): 972–82.

This double-blind RCT included 318 participants given either nalfurafine hydrochloride (2.5 or 5 mcg daily) vs. placebo during an 84-day trial period. Pruritus scores were assessed by VAS and were significantly improved in the treatment group vs. placebo.

Fourth-Line Therapies

- Rifampicin **A**
- IBAT **A**

The efficacy and safety of bile acid binding agents, opioid antagonists, or rifampin in the treatment of cholestasis-associated pruritus. Tandon P, Rowe BH, Vandermeer B, et al. *Am J Gastroenterol*. 2007; 102(7): 1528–36.

This meta-analysis evaluated the available RCTs (n = 12) for various treatments of cholestatic pruritus, including rifampicin. The analysis concluded that rifampin is effective for cholestatic pruritus.

Effect of ileal bile acid transporter inhibitor GSK2330672 on pruritus in primary biliary cholangitis: a double-blind, randomised, placebo-controlled, crossover, phase 2a study. Hegade VS, Kendrick SF, Dobbins RL, et al. *Lancet* 2017; 389(10074): 1114–23.

This double-blind, crossover trial with IBAT demonstrated significant antipruritic effect in 57% of patients with severe itch of PBC vs. 31% in placebo.

Malignancy-Associated Itch

Pruritus is a symptom well reported among those with malignancy, notably lymphoproliferative malignancies such as Hodgkin and non-Hodgkin lymphoma and cutaneous T-cell lymphoma (CTCL). As well as hepatobiliary malignancies, itch may also present as a paraneoplastic sign, prior to or concurrent with diagnosis of a hematologic malignancy or solid tumor. Generalized pruritus with or without primary dermatologic lesions may precede the malignancy diagnosis.

Treatment of pruritus in malignancy is targeted at reducing symptoms while the cancer itself can be treated, as this will ultimately lead to resolution of the pruritus. Antidepressant medications, such as the SSRI paroxetine (20 mg daily), have antipruritic properties that have shown to be effective in malignancy-associated itch and are generally well-tolerated medications. Mirtazapine in doses of 15 mg nightly has been demonstrated in case reports to relieve itch due to malignancy, and in combination therapy with gabapentin has shown effectiveness in CTCL-related itch. The κ -opioid agonist/ μ -opioid antagonist butorphanol at an intranasal dose of 1–4 mg/day has been reported successful in relieving lymphoma-related itch refractory to other treatments. The NK-1 inhibitor aprepitant was first used in patients with malignancy for relief of chemotherapy-related nausea and vomiting and has since been shown to have antipruritic properties. Numerous reported cases demonstrate its antipruritic effect in CTCL as well as lymphomas and solid tumor malignancies. Thalidomide has been shown in case reports to relieve pruritus related to Hodgkin lymphoma and solid tumor malignancy. Thalidomide must be used with caution given its known adverse effects of teratogenicity and peripheral neuropathy.

Hematologic disorders such as polycythemia vera (PV), essential thrombocytosis, and primary myelofibrosis may have pruritus as a predominant symptom. Aquagenic pruritus, characterized as intense pruritus without primary skin lesions following contact with water, is often the presenting symptoms in PV. In the majority of cases, the underlying mechanism of cellular proliferation in PV is an acquired activating mutation in JAK2 tyrosine kinase. The relationship between these disorders and pruritus is thought to be related to proliferation of mast cells and/or basophils. Numerous therapies have shown varying degrees of success in the treatment of PV-related pruritus including the SSRI paroxetine, interferon- α , antihistamines such as cimetidine, and danazol. Phototherapy with psoralen UVA and UVB have also shown to be an effective treatment. A large RCT of the JAK inhibitor ruxolitinib showed itch reduction in PV in addition to the primary outcome measure of improved hematocrit control.

First-Line Therapies

- Paroxetine **A**
- Mirtazapine **E**

Paroxetine in the treatment of severe non-dermatological pruritus: a randomized, controlled trial. Zyllicz Z, Krajnik M, Sorge AA, et al. *J Pain Symptom Manage* 2003; 26(6): 1105–12.

This RCT included 26 patients with chronic pruritus, 17 with malignancy. Patients were randomized to receive treatment with paroxetine (20 mg) versus placebo with crossover after 7 days. Paroxetine significantly reduces pruritus compared to placebo with relief from pruritus seen after an average of 3 days.

Mirtazapine for pruritus. Davis MP, Frandsen JL, Walsh D, et al. *J Pain Symptom Manage* 2003; 25(3): 288–91.

This case report presents four patients with intractable pruritus related to underlying malignancy in which treatment with mirtazapine (dose 15–30 mg daily) provided relief from pruritus.

Second-Line Therapies

- Gabapentin and mirtazapine **E**
- Butorphanol **E**

Mirtazapine and gabapentin for reducing pruritus in cutaneous T-cell lymphoma. Demierre MF, Taverna J. *J Am Acad Dermatol* 2006; 55(3): 543–4.

This published letter describes the rationale of combination therapy of mirtazapine and gabapentin for patients with severe chronic itch related to CTCL.

Butorphanol for treatment of intractable pruritus. Dawn AG, Yosipovitch G. *J Am Acad Dermatol* 2006; 54(3): 527–31.

In this case series, five patients are presented with intractable pruritus, one with non-Hodgkin lymphoma. All were treated with intranasal butorphanol, showing rapid improvement of symptoms.

Third-Line Therapy

- Aprepitant **C**

Aprepitant for the treatment of chronic refractory pruritus. He A, Alhariri JM, Sweren RJ, et al. *Biomed Res Int* 2017; 2017: 4790810.

This article reviews the available literature addressing the use of aprepitant for chronic pruritus in malignant and non-malignant conditions. Mean pruritus score among the studies reduced from 8.1 to 2.7, with relief achieved within hours to up to 2 weeks of therapy.

Fourth-Line Therapy

- Thalidomide **E**

Thalidomide for the control of severe paraneoplastic pruritus associated with Hodgkin's disease. Goncalves F. *Am J Hosp Palliat Care* 2010; 27(7): 486–7.

This case report describes a patient with intractable itch due to Hodgkin lymphoma that was effectively treated with 200 mg nightly thalidomide. The article discusses the clinical uses of thalidomide and proposed mechanism for its antipruritic effects.

Thalidomide therapy for pruritus in the palliative setting—a distinct subset of patients in whom the benefit may outweigh the risk. Lowney AC, McAleer MA, Kelly S, et al. *J Pain Symptom Manage* 2014; 48(2): e3–5.

This case report describes a woman with non-small cell lung cancer with intractable pruritus. She had failed numerous treatments for her pruritus but found complete resolution with treatment with thalidomide nightly 100 mg after 15 days.

Psychogenic Itch

Psychogenic itch is described as an intense impulse to scratch or pick at normal skin. This is a diagnosis of exclusion that can be considered only once a primary dermatologic or systemic etiology of itch has been excluded. Psychogenic itch most commonly presents in individuals with psychiatric conditions and has been associated with obsessive compulsive disorder (OCD), somatic symptom disorder, excoriation disorder, fibromyalgia, and delusional infestation, and has been reported as a symptom of neurodegenerative disorders such as dementia and as an effect of medications activating dopaminergic pathways.

If psychogenic itch is determined to be the etiology, treatment of any underlying psychiatric condition should be initiated. For patients with depression, anxiety, or OCD, antidepressant medications appropriate for those disorders in combination with diagnosis-specific psychotherapy is indicated. Several of the SSRIs, SNRIs, and TCAs have been shown to have antipruritic properties useful in various itch etiologies and may provide relief in psychogenic forms of itch.

In rare cases of delusions of infestation, in which the patient has a fixed, false belief that there is an infestation of the skin by a pathogen, the treatment of choice for many years has been the antipsychotic pimozide (1–10 mg/day). Newer atypical antipsychotics have also been reported to effectively treat this condition and may be preferred if the adverse effects of pimozide, notably extrapyramidal symptoms, are not well-tolerated.

First-Line Therapy

- Antidepressants for underlying mood or anxiety disorders **E**

Use of oral antidepressants in patients with chronic pruritus: a systematic review. Kouwenhoven TA, van de Kerkhof PCM, Kamsteeg M. *J Am Acad Dermatol* 2017; 77(6): 1068–73. e7.

A systematic evaluation of 35 studies on the use of antidepressants (SSRIs, TCAs, mirtazapine) in patients with chronic pruritus of various etiologies, including psychogenic itch effectively treated with paroxetine.

Psychosomatic factors in pruritus. Tey HL, Wallengren J, Yosipovitch G. *Clin Dermatol* 2013; 31(1): 31–40.

A comprehensive review of the etiologies and management options for neuropathic and psychogenic itch.

Second-Line Therapy

- Antipsychotics to treat delusions of infestation **C**

A review of delusions of parasitosis, part 2: treatment options. Bak R, Tumu P, Hui C, et al. *Cutis* 2008; 82(4): 257–64.

This article reviews the condition of delusion of parasitosis and the preferred approach to patients with this condition. The available literature evaluating the medical management is reviewed including the typical and atypical antipsychotics.

Morgellons disease: insights into treatment. Aung-Din D, Sahni DR, Jorizzo JL, et al. *Dermatol Online J* 2018; 24(11).

This article reviews the case reports and case series related to treatment of Morgellons disease. The authors propose the use of antipsychotic medications with close follow-up, given the challenging aspects of the management of this disease.

TREATMENT OF ITCH IN SPECIAL POPULATIONS

Considerations in Itch Treatment in the Elderly

Chronic pruritus is very common in elderly populations, the most common etiology being xerosis, likely related to age-related changes that compromise the epidermal water barrier. Itch in this population may also be due to any number of primary dermatologic conditions, but many cases can also be classified as CPUO. Due to high rates of polypharmacy, physiologic changes with age, and increased prevalence of chronic disease, special considerations must be made in this population. Polypharmacy, defined as use of five or more medications, potentiates the risk for drug-drug interactions. Many itch medications commonly used in the elderly interact with hepatic cytochrome p450 (CYP) metabolism pathways, such as diphenhydramine and SSRIs. Reduced kidney function is common in the elderly and glomerular filtration rate is expected to significantly decline with age even in those without known renal disease. Cetirizine and gabapentin require renal dosing in the elderly or in those with renal disease. Finally, reduced muscle mass and increased body fat may also affect the effective distribution of lipid soluble medications, leading to potential prolongation of drug effects.

Adverse effects should be considered carefully with consideration of reducing initiating doses, as sedation, vertigo, or fatigue as adverse effects may be considered mild in the younger population but may exacerbate already existing limitations in mobility and cognitive function in an elderly person. For example, TCAs are to be avoided in this population due to risk for orthostatic hypotension. Highly anticholinergic agents, such as the first-generation antihistamines and TCAs, are recommended against use in the elderly by the American Geriatric Society (AGS) Beers Criteria. Evidence from a large prospective cohort study also shows that use of medications with strong anticholinergic effects may contribute significantly to Alzheimer disease risk. The second-generation antihistamines are preferred in this age group due to reduced anticholinergic profile. Medications in reduced doses, such as gabapentin, SNRIs, methotrexate, and mycophenolate mofetil are good options for various etiologies of itch in the elderly population.

Management of itch in the elderly: a review. Fourzali KM, Yosipovitch G. *Dermatol Ther (Heidelb)* 2019; 9(4): 639–53.

This article reviews the common etiologies of itch in the elderly and describes the appropriate medications and unique considerations for this age group.

Considerations of Itch Treatment in Pregnancy

Pruritic dermatoses that occur for the first time during pregnancy, such as polymorphic eruption of pregnancy and atopic eruption of pregnancy, may require initiation of treatment. Also, longstanding pruritic conditions, such as AD or psoriasis, may require therapy throughout the prenatal period. Antihistamines have been used during pregnancy for many years and the first-generation medications are supported by a longer history of safety data than those of the second-generation class. Diphenhydramine and chlorpheniramine are considered first choice while loratadine and cetirizine are first and second choices of the second-generation class, respectively. Mild-to-moderate potency topical corticosteroids are appropriate for use if needed for a short period of time. Of the systemic steroids, prednisone is preferred due to its limited placental passage. However, it should not exceed 20 mg daily (7.5 mg daily for prolonged use) due to association with orofacial clefting and unfavorable gestational conditions. Phototherapy is a generally safe treatment option in pregnancy and may be used for a variety of pruritic conditions. Some systemic immunosuppressant medications such as methotrexate have been clearly documented as teratogenic and contraindicated in pregnancy due to demonstrated risks of miscarriage and developmental defects. Evidence for or against the use of medications in pregnancy is often limited, considering that controlled trials in pregnant women pose an ethical challenge. In each case, it is necessary for the clinician to weigh the available evidence of harms of the treatment against the potential harms to the mother and/or fetus if treatment is withheld or discontinued.

Pruritus in pregnancy and its management. Bechtel MA. *Dermatologic Clinics* 2018; 36(3): 259–65.

This review article details the pregnancy-specific dermatoses, diagnostic evaluation of pruritus in pregnancy, and the appropriate management considerations for this population.

Safety of dermatologic medications in pregnancy and lactation: part I. Pregnancy. Murase JE, Heller MM, Butler DC. *J Am Acad Dermatol* 2014; 70(3): 401. e1–14.

This article provides a comprehensive review of dermatologic medications and the available literature that suggests for or against their use in pregnancy.

Pruritus ani

Michal Martinka, Gabriele Weichert



Pruritus ani is characterized by intensely pruritic perianal skin. It is classified into primary (idiopathic) and secondary (induced by an underlying cause). It is common, with incidence ranging from 1% to 5%. Chronic cases are associated with significant discomfort, embarrassment, and sleep disturbance.

MANAGEMENT STRATEGY

Management requires appropriately identifying and treating secondary causes. Categories include inflammatory dermatoses (e.g., atopic dermatitis, contact dermatitis, psoriasis, hidradenitis suppurativa, or lichen sclerosus), infection (e.g., bacterial, viral, fungal, parasitic, or infestations), systemic disease (e.g., diabetes, thyroid disorders, hepatic disorders, and lymphoma/leukemia), neoplasms (e.g., squamous cell carcinoma, melanoma, extramammary Paget disease), local irritants (e.g., fecal contamination, moisture, soaps, diet, topical or systemic medications), and colorectal and anal causes (e.g., hemorrhoids, anal fissures, anal leakage). A complete history, including diet, bowel movements, hygiene practices, and treatments, is prudent, and patients should undergo a total body skin examination to identify possible underlying etiologies. With this approach, most causes of secondary pruritus can be identified and treated. It is the patient in whom none of these factors are identified who suffers from idiopathic pruritus ani.

Overzealous cleansing is not uncommon and may be irritating or sensitizing. Potential topical sensitizers should be stopped. Avoidance of toilet paper after bowel movements can be helpful, as this may be abrasive. Many patients suffer from low-grade fecal incontinence. This is often evident on examination of the underclothes or of the perianal skin.

Therapy is directed at the underlying cause. However, if secondary causes have been ruled out and a diagnosis of primary pruritus ani has been made, empiric treatment is directed toward proper anal hygiene, removal of common irritators and/or sensitizers, and protection of perianal skin. Counsel patients to

avoid scratching, as this can propagate the itch-scratch cycle. Advise patients to cleanse the perianal skin twice a day and after bowel movements using cotton balls or cotton squares (make-up removal pads) moistened with warm water or a liquid cleanser and then dried with a hair dryer on 'cool' setting. Patients with low-grade fecal incontinence should perform this routine several times a day. Some patients have reported success using bidets as they provide a less abrasive means of cleansing the perianal region.

Cleansing has been shown to be as effective as topical steroids. A short (few weeks) course of a low- to mid-potency topical steroid is recommended. Caution must be taken with prolonged high-potency steroid use, as this area is prone to atrophy. Topical tacrolimus, pimecrolimus, or crisaborole may be used in clearance or maintenance treatment. After cleansing, topical zinc paste can limit the degree of irritant dermatitis in patients with fecal incontinence.

A biopsy should be performed if the diagnosis is in doubt or the condition is not responding to treatment. If a patient fails to improve, lower gastrointestinal investigations should be considered to rule out neoplastic disease. Patch testing should be performed in patients who fail to improve. Avoidance of caffeine and increased dietary fiber intake may be helpful. Topical capsaicin can be used for second-line therapy. Finally, intralesional steroid injections to the perianal skin may be considered. Intradermal methylene blue injections are reported to damage dermal nerve endings and provide relief. Injection with phenol in almond oil has been reported to be beneficial.

Specific Investigations

- Bacterial swab
- Fungal microscopy and culture
- Biopsy
- Skin scrapings for scabies
- Patch testing
- Gastrointestinal investigations

Pruritus ani. Ansari P. Clin Colon Rectal Surg 2016; 29: 38–42.

A review of pruritus ani outlining workup, differential diagnosis, and treatment options.

Perianal dermatitis. Agullo-Perez AD, Hervella-Garcés M, Oscoz-Jaime S, et al. Dermatitis 2017; 28: 270–5.

Contact dermatitis in patients with longstanding perianal complaints is frequent. A diagnosis of allergic contact dermatitis was made in 32.3% of patients. Patients with long-lasting (>4 weeks) pruritus ani should be referred for patch testing. Methylchloroisoethiazolinone/methylisothiazolinone was the most common allergen implicated in perianal contact dermatitis.

Abnormal transient internal sphincter relaxation in idiopathic pruritus ani: physiological evidence from ambulatory monitoring. Farouk R, Duthie GS, Pryde A, et al. Br J Surg 1994; 81: 603–6.

Abnormal rectal sphincter tone was demonstrated in patients with pruritus ani. This may be the contributing factor in patients who have occult fecal leakage.

Pruritus ani. Causes and concerns. Daniel GL, Longo WE, Vernava AM. Dis Colon Rectum 1994; 37: 670–4.

In this series of 104 patients, 52% had anorectal disease (including hemorrhoids, anal fissures, genital warts, and fistulas)

and 23% had a colorectal neoplasm found with investigations. In those without neoplasia, there was a direct correlation between increased caffeine intake and severity of irritation. Patients with primary pruritus ani improved with dietary restrictions (not defined), dietary fiber, steroid creams, and drying agents.

First-Line Therapies

• Topical corticosteroids	A
• Topical tacrolimus	A
• Hygiene	B

1% hydrocortisone ointment is an effective treatment of pruritus ani: a pilot randomized control crossover trial. Al-Ghnam R, Short K, Pullen A, et al. *Int J Colorectal Dis* 2007; 22: 1463–7.

In this trial, 19 patients were randomized to 1% hydrocortisone in paraffin twice daily or paraffin base for 2 weeks followed by crossover treatment for 2 weeks. Visual analog score (VAS) showed a 68% reduction with steroid treatment.

Randomized study of topical tacrolimus ointment as possible treatment for resistant idiopathic pruritus ani. Suys E. *J Am Acad Dermatol* 2012; 66: 327–8.

A group of 21 patients were randomized to 0.1% tacrolimus versus petrolatum twice daily for 4 weeks with a further 4-week crossover phase. There was improvement in itch intensity and frequency on tacrolimus, but Dermatology Life Quality Index was not significantly different compared with placebo.

Idiopathic perianal pruritus: washing compared with topical corticosteroids. Oztas MO, Oztas P, Onder M. *Postgrad Med J* 2004; 80: 295–7.

In this study, 28 patients applied topical methylprednisolone cream twice daily for 2 weeks. In a separate group, 32 patients were instructed to cleanse the perianal area twice daily with a liquid cleanser. Effectiveness was similar at 92.3% in the first group and 90.6% in the second group.

Second-Line Therapies

• Topical capsaicin	A
• Topical acrylate barrier	D

Topical capsaicin: a novel and effective treatment for idiopathic intractable pruritus ani: a randomised, placebo controlled, crossover study. Lysy J, Sistiery-Ittah M, Israelit Y, et al. *Gut* 2003; 52: 1323–6.

Capsaicin 0.006% cream was applied three times a day for 1 month. The control treatment was 1% menthol cream. Of 44 patients, 31 experienced partial relief of symptoms ($p < 0.0001$). All patients experienced some degree of perianal burning.

A liquid-forming acrylate cream for the treatment of anal pruritus. Tomi N, Weiser R, Strohal R, et al. *Br J Nurs* 2012; 21: 98–102.

In this study, 28 patients applied an acrylate protection cream (Cavilon Durable Barrier Cream, 3M) daily for 3 weeks. There was an 80% reduction in VAS.

Third-Line Therapies

• Intralesional corticosteroids	C
• Intradermal methylene blue	B
• Subcutaneous phenol injection	B
• Dupilumab	E

The use of intralesional triamcinolone hexacetonide in the treatment of idiopathic pruritus ani. Minvielle L, Hernandez VL. *Dis Colon Rectum* 1969; 12: 340–3.

Nineteen patients were treated weekly for 4 weeks at 5–20 mg/week. Nine of 19 (73.6%) patients had excellent progress, two of 19 reported fair improvement, and three failed to improve. No perianal atrophy was noted at the end of 4 weeks.

Long-term follow-up of intradermal injection of methylene blue for intractable, idiopathic pruritus. Kim JH, Kim DH, Lee YP. *Tech Coloproctol* 2019; 23: 143–9.

Retrospective study of 103 patients treated with intradermal 1% methylene blue and 1% lidocaine. At 6 weeks, 90.6% of patients were symptom free. At 3-year follow-up, only 7.5% of patients had recurred. Some patients required a second injection.

A new concept of the anatomy of the anal sphincter mechanism and the physiology of defecation. XXIII. An injection technique for the treatment of idiopathic pruritus ani. Shafik A. *Int Surg* 1990; 75: 43–6.

In this series, 67 patients were treated with an injection of 5% phenol in almond oil: 62/67 (92.4%) experienced complete relief. Five patients relapsed. Repeat injection led to cure.

Recalcitrant anal and genital pruritus treated with dupilumab. Yang EJ, Murase JE. *Int J of Womens Derm* 2018; 4: 223–6.

A case report describing a patient with asthma and allergic rhinitis presenting with intractable pruritus ani. He was treated with dupilumab and reported improvement at 1- and 12-month follow-up.

Pruritus vulvae

Sydney Rivera, Ruth A. Osborne,
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Pruritus vulvae is the external sensation of itching that results in a need to scratch or rub the vulva. Although pruritus vulvae is a common complaint, the etiopathogenesis remains poorly understood. Primary findings are representative of underlying disease processes and may include macular or papular erythema, dyspigmentation, edema, vesicles, and bullae. Secondary findings include atrophy, lichenification, erosions, fissures, excoriations/scarring, and pigmentary changes; scale is rarely seen due to the inherently moist environment. Vaginal discharge is not necessarily associated and may reflect the normal underlying physiologic state. Pruritus vulvae may be primary (essential), secondary, or multifactorial. Regardless of etiology, longstanding pruritus vulvae may result in lichen simplex chronicus. Primary pruritus vulvae is the condition in which no etiology can be identified and will be the focus of this chapter.

MANAGEMENT STRATEGY

Pruritus vulvae describes a symptom that may be psychologically distressing, socially embarrassing, and detrimental to sexual health and function. Identifying all etiologies is critical to management. Secondary pruritus vulvae may be caused by anatomic alteration, infection/infestation, inflammatory dermatosis, neoplasm, systemic disease, or neurologic dysfunction (Table 207.1). The role of radiculopathies or pudendal nerve entrapment as a cause of vulvar pruritus is increasingly recognized. Furthermore, vulvar pain (vulvodynia) may be difficult to distinguish from vulvar pruritus and is often comorbid.¹ It should be noted that diabetes mellitus, an increasingly common diagnosis worldwide, may contribute to vulvar pruritus through various pathogeneses, including frequent/persistent candidiasis, neuropathic pain, autonomic dysfunction, and primary pruritus. In the absence of any secondary cause of pruritus, the condition is considered primary until proven otherwise.

A thorough history is the first step in understanding all possible etiologies of pruritus vulvae in a given patient. A personal or family history of any inflammatory dermatosis may direct the differential diagnosis. Any history of self-directed treatment should be elicited. In addition, a complete mucocutaneous examination should be performed with attention to primary and secondary findings. This should entail visual and manual inspection of the vulva, vagina, and perianal skin and the complete mucocutaneous integument (i.e., the oral cavity, conjunctivae, and nasal mucosa, as well as a total body skin, scalp, and nails examination). In conducting the genital exam, it is vital to distinguish normal vulvar anatomy (which varies widely) from any pruritus-associated pathology. Special care should be given to distinguish physiologic pigmentation from associated erythema, inflammation, or infiltrative process in vulvar skin, regardless of skin tone. In skin of color, clinical findings can vary from pink to tan to violaceous or hyperpigmented lesions. The clinician should also preform palpation of inguinal lymph nodes and sensory testing for light touch of the vulva and vaginal vestibule. Utilizing current International Society for the Study of Vulvovaginal Disease (ISSVD) terminology to classify dermatologic findings is useful in forming a differential.² A number of specific investigations may further aid in diagnosis.

Specific Investigations

- Saline wet mount with cytologic evaluation of keratinocytes, inflammatory cells
- KOH whiff test
- Wood's lamp or KOH preparation
- Vaginal pH
- Scotch tape test
- Microbial assays
- Laboratory values to identify systemic conditions (i.e., diabetes, liver disease)
- Patch testing
- Vulvoscopy
- Colposcopy
- Nerve conduction studies

Upon identification of any primary or secondary etiologies, appropriate treatment should be instituted. If no etiology is identified (primary pruritus vulvae), then symptomatic relief is the goal of therapy. The tenets of treatment are to interrupt the itch-scratch cycle, restore the skin barrier, and minimize impact on quality of life. The critical first step is to *identify and remove all suspected local irritants and allergens*.³ The patient should be counseled to institute a number of lifestyle modifications (Table 207.2). The patient may resist some measures, particularly the avoidance of fragranced or 'cleansing' products, due to desire for a 'clean' vulva and vagina; they may believe natural secretions and odors are offensive or even the cause of their symptoms. To the contrary, elaborate hygiene regimens contribute to local irritation and contact sensitivity and may confound or be the primary cause of persistent pruritus. Talc in particular is highly irritating, and investigation of its role in ovarian cancer remains inconclusive.⁴ Whenever possible, systemic rather than local preparations should be used in the treatment of pruritus to limit concurrent secondary irritation. However, it has also been reported that *ingested* food and drug metabolites excreted in urine and stool can serve as allergens and/or irritants, contributing to anogenital pruritus.⁵

Maintenance of barrier function facilitates healing and limits irritant contact. The use of *petrolatum-* and *zinc-based ointments*

Table 207.1 Differential diagnosis of pruritus vulvae**Anatomic alterations**

- Fox–Fordyce disease (apocrine duct occlusion)
- Low-estrogen states
 - Prepuberty
 - Postpartum/lactation
 - Peri- and postmenopause

Infections and infestations

- Bacterial
 - Group A β -hemolytic streptococcus
 - Group B β -hemolytic streptococcus
 - *Staphylococcus aureus*
 - *Chlamydia trachomatis*
 - Erythrasma
 - *Gardnerella vaginalis*
 - *Neisseria gonorrhoeae*
 - *Mycobacterium tuberculosis*
- Fungal
 - *Candida albicans*
 - *Candida glabrata* (non-albicans candidiasis)
 - Tinea cruris
- Infestation
 - *Enterobius vermicularis* (pinworm)
 - *Phthirus pubis* (pubic lice)
 - *Sarcoptes scabiei*
 - *Trichomonas vaginalis*
- Viral
 - Herpes simplex virus
 - Human papillomavirus
 - Human immunodeficiency virus
 - Molluscum contagiosum

Inflammatory dermatoses

- Allergic contact dermatitis
- Atopic dermatitis
- Dermatographism
- Desquamative inflammatory vaginitis
- Fixed drug eruption

- Hidradenitis suppurativa
- Irritant contact dermatitis
- Leukoplakia of unknown etiology
- Lichen planus
- Lichen sclerosus
- Lichen simplex chronicus
- Papular acantholytic dyskeratosis (Grover disease)
- Psoriasis
- Seborrheic dermatitis
- Zoon (plasma cell) vulvitis

Neoplasms

- Basal cell carcinoma
- Epidermolytic acanthoma
- Extramammary Paget disease
- Hidradenoma papilliferum
- Langerhans cell histiocytosis
- Lymphoma
- Melanoma
- Squamous cell carcinoma
- Squamous cell carcinoma in situ (Bowen disease, vulvar intraepithelial neoplasia)
- Syringoma

Systemic diseases

- Crohn disease
- Diabetes mellitus
- Hepatic failure
- Hypothyroidism
- Iron-deficiency anemia
- Polycythemia vera
- Renal failure
- Sjögren syndrome

Neurologic

- Fibromyalgia
- Postherpetic neuralgia
- Pudendal nerve entrapment
- Vulvodynia

helps to seal in moisture and protect the affected skin from external chemical and physical insults. Ointments generally contain fewer inactive ingredients, thus limiting potential irritants or allergens. In low-estrogen states, the use of *topical or systemic estrogen* helps restore vaginal and vulvar mucosal barrier function.

Corticosteroids are used to reduce inflammation. Corticosteroid ointment should be used sparingly once or twice a day. Close clinical supervision is necessary to identify and mitigate adverse effects (e.g., striae, folliculitis, atrophy). *Intralesional (injected)* and *systemic corticosteroids* may be effective for recalcitrant pruritus. Non-inflammatory idiopathic disease does not benefit from topical corticosteroids. When topical steroid does not alleviate symptoms, other etiologies must be considered.

Corticosteroids reduce pruritus but are often insufficient to interrupt the itch–scratch cycle. *Antihistamines* such as hydroxyzine or topical doxepin are recommended for night-time therapy. For daytime pruritus, a low-dose *selective serotonin reuptake inhibitor* is advised. *Amitriptyline*, *pregabalin*, or *gabapentin* may be effective in pruritus characterized by pain, burning, or stinging sensations. *Local anesthetics* such as lidocaine 2% jelly may be used to facilitate intercourse or otherwise provide temporary relief.

Numerous investigative treatments for specific genital conditions have shown relief of pruritus and may be indicated off-label. The *systemic immunotherapy* ixekizumab (an interleukin-17A

inhibitor) has been shown to significantly improve itch in patients with genital psoriasis.⁶ Dupilumab (an interleukin-4 receptor α -blocker) was effective in a case of recalcitrant anogenital pruritus in a male.⁷ Innovative therapies, including phototherapy, platelet-rich plasma, and adipose-derived stem cells, have shown promise in specific pruritic conditions (such as lichen sclerosus) and may be considered in the future for primary pruritus vulvae.

Ultimately, management of pruritus vulvae requires that providers display utmost empathy and compassion. Difficulties in diagnosis and treatment can be exhausting and frustrating for affected patients. It is important to assess subjective impact of the condition on the patient's mental health and functional status and refer for supportive therapy as needed. Lifestyle changes and specific therapies should be adopted through shared decision-making.

First-Line Therapies

• Avoidance of irritants	E
• Good hygiene practices	E
• Oral ospemifene	A
• Topical estrogen	E
• Amitriptyline, pregabalin, gabapentin	C

Table 207.2 Lifestyle modifications in the management of pruritus vulvae

Avoid all local products, including soaps, personal hygiene products, moisturizers, and medications not approved by a dermatologist
Bathe with lukewarm (not hot) water
Pat (not rub) the genital area to dry
Minimize pubic grooming (waxing, shaving)
Cool Sitz baths may help symptoms
Avoid occlusive, tight, and/or synthetic clothing items
Launder clothing using a double rinse cycle
Use cotton (or cotton-lined) underwear and washcloths.
Change daily
Menstrual management products must be fragrance-free and changed with appropriate frequency. Silicone menstrual cups or reusable cloth pads may provide less irritation than traditional paper-based products
Avoid wipes and use only the required amount of toilet paper as these items may contribute to local irritation
Wipe gently front-to-back to limit inadvertent introduction of secretions to vagina or vestibule. Urine, stool, sweat, semen, and cervical or vaginal secretions contribute to irritation
Urinary incontinence and contact with stool should be thoroughly addressed with a healthcare provider

Effects of ospemifene on genitourinary health assessed by prospective vulvar-vestibular photography and vaginal/vulvar health indices. Goldstein I, Simon JA, Kaunitz AM, et al. *Menopause* 2019; 26(9): 994–1001.

Pruritus is a significant contributor to postmenopausal morbidity. Ospemifene or deaminohydroxytoremifene is an oral selective estrogen receptor modulator (SERM) FDA-approved for dyspareunia in 2014. A randomized controlled trial of 631 postmenopausal women demonstrated significant improvement of vulvovaginal health with oral ospemifene over placebo, as assessed by visual, objective, and subjective (symptomatic) measures.

Generalized unprovoked vulvodynia; a retrospective study on the efficacy of treatment with amitriptyline, gabapentin or pregabalin. van Beekhuizen HJ, Oost J, van der Meijden WI. *Eur J Gynecol Obstet Reprod Biol* 2018; 220: 118–21.

A Dutch study of 241 women with vulvodynia (of whom 18% had likely vulvar dermatoses and 83% reported symptoms of itching or burning) showed good response to regimens of amitriptyline, gabapentin, and/or pregabalin. Of women with vulvar dermatoses, 43% experienced a relief in symptoms.

Vaginal symptoms in postmenopausal women: self-reported severity, natural history, and risk factors. Huang AJ, Moore EE, Boyko EJ, et al. *Menopause* 2010; 17(1): 121–6.

A longitudinal study of 1017 postmenopausal women found that approximately one-third reported vaginal itching at baseline. In the 77 women who reported itching at baseline and no current or subsequent estrogen use, about half had spontaneous resolution of their itch within the 24-month study period.

Second-Line Therapies

• Topical antihistamine	A
• Subcutaneous triamcinolone	B
• Naltrexone	D

An evidence-based review of the efficacy of topical antihistamines in the relief of pruritus. Eschler DC, Klein PA. *J Drugs Dermatol* 2010; 9(8): 992–7.

Four large, double-blinded, randomized control trials have demonstrated efficacy of topical antihistamines, specifically doxepin, in treating pruritus (note the review was not limited to *vulvar* pruritus). However, topical applications should be considered thoughtfully in patients at risk for increased local vulvar irritation.

Subcutaneous injection of triamcinolone acetonide in the treatment of chronic vulvar pruritus. Kelly RA, Foster DC, Woodruff JD. *Am J Obstet Gynecol* 1993; 169: 568–70.

A series of 45 patients with chronic pruritus vulvae were treated with subcutaneous intralesional injection of triamcinolone acetonide (total 15–20 mg). Thirty-five experienced relief of pruritus for more than 1 month (mean 5.8 months).

Treatment of refractory vulvovaginal pruritus with naltrexone, a specific opiate antagonist. Bottcher B, Wildt L. *Eur J Obstet Gynecol Reprod Biol* 2014; 174: 115–6.

Initial report detailing the rapid and complete response to oral naltrexone 50 mg once daily in five women otherwise healthy with longstanding vulvovaginal pruritus.

Third-Line Therapies

• Topical corticosteroids	A (negative study)
• Alternative therapies (e.g., Chinese medicine, acupuncture, hypnosis)	E

Effectiveness of treating non-specific pruritus vulvae with topical steroids: a randomized controlled trial. Lagro-Janssen AL, Sluis A. *Eur J Gen Pract* 2009; 15: 29–33.

A randomized, double-blind, placebo-controlled trial of 50 women with non-specific vulvar pruritus showed no difference between triamcinolone acetonide 0.1% cream and placebo. Patients with infections and inflammatory dermatoses were excluded.

In contrast to the well-established effectiveness of topical corticosteroids for treating lichen sclerosus-associated pruritus, topical corticosteroids appear to have no benefit in the treatment of non-specific pruritus vulvae. However, these preparations are still reported as first line for idiopathic vulvar pruritus in a number of sources.

SITUATIONAL TREATMENT CONSIDERATIONS

Photodynamic therapy for vulvar lichen sclerosus – a review. Prodromidou A, Chatziioannou E, Daskalakis G, et al. *J Low Genit Tract Dis* 2017; 22(1): 58–65.

A systematic review of 11 studies recruiting 337 women found generally good results in using photodynamic therapy (PDT) to alleviate lesions and associated symptoms (including pruritus) of vulvar lichen sclerosus, with only minor adverse effects. Further research with standardized mechanisms for assessing outcomes is needed.

Fact or fiction? Adipose-derived stem cells and platelet-rich plasma for the treatment of vulvar lichen sclerosus. Eshtiaghi P, Sadownik, LA. *J Low Genit Tract Dis* 2019; 23(1): 65–70.

Seven studies of 98 patients have unanimously reported symptomatic and histologic improvement of lichen sclerosus with adipose-derived stem cells and/or platelet-rich plasma treatment, though study design was not always optimal, necessitating further investigation.

Resolution of chronic vulvar pruritus with replacement of a neuromodulation device. Hill AJ, Paraiso ME. *J Minim Invasive Gynecol* 2015; 889–91.

A case report of a 53-year-old woman with intractable intermittent vulvar itching. The patient was being treated for a neurogenic bladder with sacral nerve stimulation implant. The patient experienced complete resolution of pruritus after device replacement.

SELECT PUBLICATIONS ON ETIOLOGY AND MANAGEMENT

Vulvar diseases: approach to the patient. Mauskar MM, Marathe K, Venkatesen A, et al. *J Am Acad Dermatol* 2020; 82(6): 1277–84.

This review delineates the role of the dermatologist in managing skin disease of the genital region and emphasizes key points in clinical care and patient education.

Vulvar pruritus – causes, diagnosis and therapeutic approach. Woelber L, Prieske K, Mendling W, et al. *Dtsch Arztebl Int* 2020; 117: 126–33.

A review of specific etiologies of pruritus vulvae and respective treatments, with in-depth discussion of candidiasis.

Vulvar pruritus and lichen simplex chronicus. Chibnall R. *Obstet Gynecol Clin North Am* 2017; 44(3): 379–88.

Succinct review with focus on comprehensive treatment through symptomatic management and innovative lifestyle modifications.

Female genital itch. Savas JA, Pichardo RO. *Dermatol Clin* 2018; 36: 225–43.

A review of etiologies and treatments of vulvar itch with detailed information regarding suggested dosing and strength of various treatments.

Anogenital pruritus – an overview. Swamiappan M. *J Clin Diagn Res* 2016; 10: WE01–3.

Excellent review of anogenital pruritus with emphasis on pathophysiology of itch.

Vulvar intraepithelial neoplasia (VIN) diagnostic and therapeutic challenges. Rodolakis A, Diakomanolis E, Vlachos G, et al. *Eur J Gynaecol Oncol* 2003; 24: 317–22.

A retrospective study of 113 women with VIN revealed that pruritus was the most common presenting symptom (60.1%). Diagnosis was made by colposcopy and biopsy.

Dermatotoxicology of specialized epithelia: adapting cutaneous test methods to assess topical effects on the vulva. Farage MA, Maibach HI. In: Wilhelm KP, Zhai H, Maibach HI, eds. *Dermatotoxicology*, 8th edn. Boca Raton, Taylor & Francis Group, 2013; 419–30.

The authors call attention to limitations of patch testing of skin in determining reactivity at the site of the vulva due to anatomic, physiologic, and contact differences in the vulvar mucosa vs. keratinized skin. Patch testing to determine vulvar irritation should be interpreted cautiously.

Similarities between neuropathic pruritus sites and lichen simplex chronicus sites. Cohen AD, Andrews ID, Medvedovsky E, et al. *Isr Med Assoc J* 2014; 16: 88–90.

A large clinical study utilizing nerve conduction studies revealed neuropathy in more than 80% of patients (29 of 36) with anogenital pruritus.

Pruritus vulvae in prepubertal children. Paek SC, Merritt DE, Mallory SB. *J Am Acad Dermatol* 2001; 44: 795–802.

This paper reviews the causes and treatments of pruritus vulvae in 44 prepubertal girls, among whom 75% had non-specific pruritus. Lichen sclerosus, bacterial infections, yeast infection, and pinworm infestation were seen in a minority of patients. Poor hygiene and irritants are major contributors to pruritus vulvae in this population.

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Pseudofolliculitis barbae

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INTRODUCTION

Pseudofolliculitis barbae (PFB) (OMIM 612318) is a chronic, non-infectious inflammatory disorder induced by re-entry of curved hair shafts into the skin following hair removal. After shaving, the sharp tip of curved hair shafts can re-enter the skin a short distance from the follicle after exiting the skin surface (extrafollicular penetration) or by piercing the follicular wall without emerging from the skin surface (transfollicular penetration), resulting in a foreign body inflammatory reaction. It is most prevalent in men of African ancestry (affecting between 45% and 83% of Black men); however, it can be found in all races and genders with a 50-fold increased risk for curly hair. A substitution mutation in the 1A-helical segment of the hair follicle-specific keratin 75 (formerly K6hf) was found to be associated with a sixfold increased risk for PFB. PFB is characterized by inflammatory papules and pustules, and can result in postinflammatory hyperpigmentation, permanent scarring, or even keloid formation.

MANAGEMENT STRATEGY

PFB is a clinical diagnosis, relying on careful inspection and history taking to rule out other diagnoses. Clinicians should obtain pertinent history such as shaving frequency, shaving tools, chronicity, history of keloids, past treatment regimens, and current facial product use. Differential diagnosis includes acne vulgaris, traumatic folliculitis, granulomatous diseases such as sarcoidosis, hidradenitis suppurativa, and bacterial folliculitis. Acne vulgaris can be distinguished from PFB by the presence of comedones as well as lesions in non-hair-bearing areas. Traumatic folliculitis

can be identified by a history of aggressive shaving techniques. Folliculitis is an infectious cause of follicular pustules most commonly caused by *Staphylococcus aureus*.

Specific Investigations

- Punch biopsy if unclear etiology
- Bacterial culture if pustules or abscesses present
- KOH preparation and/or fungal culture if scale present

Complete resolution of PFB is possible if shaving is completely discontinued. Allowing beard hair to grow at least 1 cm in length permits spontaneous release of embedded hairs and resolution of active lesions in 1–2 months. Patients should be informed that symptoms from PFB are likely to be exacerbated over the course of the first week as the curved hairs are initially able to re-enter the skin. For symptomatic control during this time, warm water compresses for 10–15 min three times daily may offer some benefit. The addition of a low-potency topical corticosteroids (e.g., desonide lotion) for approximately 2 weeks can also help to alleviate symptoms. To avoid corticosteroid-induced atrophy and hypopigmentation, it is important to consider a regimen that includes rest periods between treatments if used beyond 2 weeks. In rare instances, a short course of oral steroids can be considered in cases with severe pain, erythema, and inflammation that does not subside with use of warm compresses and topical corticosteroids. If indicated, a 40–60 mg taper of prednisone for 5–10 days can assist with symptomatic control.

Many individuals suffering from PFB may be unable to stop shaving completely due to a variety of reasons, ranging from personal preference for a clean-shaven appearance to occupational requirements. Waivers permitting facial hair growth in PFB patients who have occupational grooming requirements can assist those who would otherwise be forced to shave regularly. Individuals who prefer a clean-shaven appearance should be educated on acceptable shaving techniques. Recommended steps include: (1) prewashing with a hydrating skin cleanser using circular motions with warm water and gentle scrubbing tools to soften the beard and dislodge embedded hair shafts; (2) using a generous amount of shave gel or cream in order to smoothen the glide of the razor; (3) shaving in the direction of hair growth using a clean, sharp razor (e.g., Gillette Skin Guard, a 2-blade razor separated by a skin guard and lubricating strips on the front and back of the razor; Gillette Fusion ProShield, a 5-blade razor with a lubricating strip on the front and back of the cartridge; or Bumpfighter, a single blade razor with a polymer coating and foil guard) while being sure to use light strokes, not pulling the skin taut; (4) using a moisturizing aftershave preparation; and (5) using a low-potency topical corticosteroid for inflamed areas or a topical antimicrobial (e.g., fixed combination benzoyl peroxide-clindamycin gel). Patients should be advised to avoid plucking or tweezing of embedded hairs and depend on gentle hair releasing techniques. As an alternative to manual razor shaving, triple-O electric clippers can be used at a setting that maintains beard hair length at approximately 1 mm, which has been shown to prevent both transfollicular and extrafollicular penetration.

Chemical depilatories, such as barium sulfide and calcium thioglycolate, weaken disulfide bonds in the hair shaft and can be considered as an alternative to shaving. These products are applied every 1–3 days to a moistened beard for 5–15 min and then removed with a blunt edge. However, irritant contact dermatitis is a limitation of chemical depilatories (especially of barium sulfide powder); this can be minimized by recommending cream formulations containing calcium thioglycolate, monitoring

contact time to avoid stinging or burning, and application of emollients immediately postusage.

Topical eflornithine hydrochloride, which inhibits hair growth via irreversible inhibition of ornithine decarboxylase, has also shown to benefit patients with PFB. Topically applied eflornithine hydrochloride cream 13.9% two times daily used in conjunction with laser hair removal has been shown to be more effective than monotherapy with laser alone.

First-Line Therapies

• Cessation of shaving	B
• Optimized shaving technique and moisturizing regimen	B
• Topical benzoyl peroxide 5%–clindamycin 1% gel	B
• Chemical depilatories	B
• Topical retinoids	B

Laser hair removal is an effective long-term therapy for PFB. Given the increased risk for complications in patients with darker complexions, careful selection of a laser device and appropriate settings for a given skin phototype is essential. The long-pulsed 1064 Nd:YAG is considered the safest laser modality for hair removal in Fitzpatrick skin types V and VI owing to its lower incidence of adverse effects. Other laser technologies that have been used in the treatment of PFB in darker skin types include the 800–810-nm diode and the 650 microsecond 1064-nm Nd:YAG laser. The 755 nm Alexandrite laser was found to be superior to intense pulse light in the treatment of PFB in a split face study involving subjects with Fitzpatrick skin phototypes II–IV. Complete resolution requires multiple sessions (typically ranging from 6 to 8 sessions depending on device, settings, and clinical features).

Electrolysis is largely not recommended for patients with PFB due to its limited efficacy and lack of practicability in treating large areas of involvement. Surgical depilation has the potential to cause scarring, including keloids, and is therefore not advised in the opinion of this author (AFA).

Second-Line Therapies

• Laser hair removal	B
• Glycolic acid	B
• Photodynamic therapy	E

Nightly application of topical retinoids (i.e., tazarotene, tretinoin, or adapalene) and other keratolytic agents, such as glycolic acid or monthly chemical peels, can facilitate reductions in follicular penetration via exfoliation. Additional benefits include improvement in the appearance of hyperpigmentation.

A recent case report identified photodynamic therapy as a potential treatment modality for recalcitrant PFB. This novel therapy is the only one of its kind in the literature. More research needs to be done to determine its clinical applicability in patients with PFB.

Pseudofolliculitis barbae: a review of current treatment options. Nussbaum D, Friedman A. *J Drugs Dermatol* 2019; 18(3); 246–50.

Concise and up-to-date review of current treatment modalities.

Folliculitis keloidalis nuchae and pseudofolliculitis barbae: are prevention and effective treatment within reach? Alexis A, Heath C, Halder R. *Dermatol Clin* 2014; 32(2); 183–91.

Expert opinion on management strategy. Simple treatment algorithm.

Lasers and light-based therapies in ethnic skin: treatment options and recommendations for Fitzpatrick skin types V and VI. Alexis A. *Br J Dermatol* 2013; 169(Suppl 3); 91–7.

Expert opinion and concise review on laser therapy in darker skin types.

Comparative evaluation of long pulse Alexandrite laser and intense pulsed light systems for pseudofolliculitis barbae treatment with one year of follow up. Leheta T. *Indian J Dermatol* 2009; 54(4): 364–8.

Randomized, double-blinded, split face, controlled trial comparing the Gentle Lase Alexandrite laser with the Chromolite intense pulsed light system. This study demonstrated that both the intense pulsed light (IPL) and Alexandrite lasers decreased the severity of disease. IPL improved by 50% with 10–12 sessions while Alexandrite improved 90% with seven sessions.

Dermatologic conditions in men of African ancestry. Coley M, Alexis A. *Expert Rev Dermatol* 2009; 4(6): 595–609.

Expert opinion on management of PFB and shaving technique.

Successful treatment of recalcitrant folliculitis barbae and pseudofolliculitis barbae with photodynamic therapy. Diernaes J, Byhum A. *Photodiagnosis Photodyn Ther* 2013; 10(4): 651–3.

Single case report of 58-year-old Caucasian male with 4-year history of recalcitrant PFB. Patient advised on shaving and treated with IPL with limited effect. Methyl aminolevulinate–photodynamic therapy (MAL-PDT) given off label in compassionate use giving 160 mg/g of MAL cream on affected area with 3 hours of occlusion before red light treatment. Patient's skin cleared after two treatments spaced 1 week apart. The patient had not flared for 15 months postprocedure.

Comparative evaluation of men's depilatory composition versus razor in black men. Kindred C, Oresajo C, Yatskayer M, et al. *Cutis* 2011; 88: 98–103.

The authors studied 45 Black men over a period of only 1 week with shaving on Saturday of the whole face and then shaving every 2 days on one side of the face and using one of two patient-mixed and applied depilatory pastes or a depilatory cream to the other side. The depilatories improved tactile and visual roughness and unevenness better than every-other-day shaving, which is not surprising because non-daily shaving promotes the appearance and persistence of PFB.

Pseudofolliculitis Barbae. No 'Pseudoproblem'. Conte M, Lawrence J. *JAMA* 1979; 241(1): 53–4.

The authors studied 96 men, who observed a shaving hiatus, over a 1-month period. During the second month, close shaving with triple 'O' clippers allowed hair growth of about 1 mm. The study showed a net favorable response in 91 of the 96 participants.

Shave frequency and regimen variation effects on the management of pseudofolliculitis barbae. Daniel A, Gustafon C, Zupkosky P, et al. *J Drugs Dermatol* 2013; 12(4): 410–8.

Ninety men were randomized to one of three groups and followed for 12 weeks to study how different daily shaving regimens and products impact the clinical characteristics of PFB. The study participants were evaluated on shaving frequency, product usage, and shaving tool type (3- vs. 5-blade razor). This study showed decreased papule, pustule, and ingrown hair counts for all groups. This study found that shaving

against the grain resulted in fewer papules, which is contrary to current management recommendations. The authors recommend more research in evaluating these secondary measures in order to have a more concrete understanding of the best management strategy.

An unusual Ala12Thr polymorphism in the 1A alpha-helical segment of the companion layer-specific keratin K6hf: evidence for a risk factor in the etiology of the common hair disorder pseudofolliculitis barbae. Winter H, Schissel D, Parry D, et al. *J Invest Dermatol* 2004; 122(3): 652–7.

A large-scale family investigation of both individuals affected and not affected by PFB demonstrate that the Ala12Thr substitution may be responsible for the phenotypic expression of PFB.

Practical applications for medical and aesthetic treatment of skin of color with a new 650-microsecond laser. Burgess C, Chilukuri S, Campbell A, et al. *J Drugs Dermatol* 2019; 18(4): s138–43.

Expert opinion on use of new 650 ms laser in patients with PFB.

Laser treatment of skin of color for medical and aesthetic uses with a new 650-microsecond Nd:YAG 1064 nm laser. Roberts W, Henry M, Burgess C, et al. *J Drugs Dermatol* 2019; 18(4): s135–7.

The authors propose the new 650-ms 1064-nm laser as an advantageous treatment for hair removal and PFB in patients of color. This laser allows patients to remain pain free without the need of cooling techniques owing to the decreased pulse duration. It is also described as a safer treatment option because the collimated beams allow for the operator to change the distance of the device to skin without having to change the fluence.

Pseudofolliculitis barbae: understanding the condition and the role of facial grooming. Gray J, McMichael A. *Int J Cosmet Sci* 2016; 38: 24–7.

Expert treatment and management recommendations for PFB.

Pseudofolliculitis of the beard. Strauss J, Kligman A. *Arch Dermatol Syphilol* 1956; 74: 533–42.

The first modern description of the pathogenesis of this disease and the rationale for allowing beard growth and spontaneous involution.

Pseudofolliculitis barbae. Medical consequences of interracial friction in the US Army. Brauner G, Flandermeyer K. *Cutis* 1979; 23: 61–6.

PFB is a disease affecting primarily Black people who shave. During the Vietnam war era, significant interracial turmoil and animosity arose due to US Army requirements for clean-shaven faces. Lotion depilatories or hair clippers, combined with routine lifting of ingrown hairs, are the most effective treatments, although complete cessation of shaving is required first.

Pseudofolliculitis barbae. 2. Treatment. Brauner G, Flandermeyer K. *Int J Dermatol* 1977; 16: 520–5.

The disease can be cured only by complete cessation of shaving, but it can be adequately controlled in most patients by carefully shaving the hairs neither too close nor too long and by meticulous lifting out of penetrating hairs.

Pseudofolliculitis barbae and related disorders. Halder R. *Dermatol Clin* 1988; 6: 407–12.

This thorough review discusses beards, triple ‘O’ electric clippers, chemical depilatories, safety razors including the

foil-guarded system to reduce the cutting edge, electric razors including the adjustable three-headed rotary razor, manual lifting of hairs, tretinoin lotion, electrolysis, and surgical depilation.

Pseudofolliculitis of the beard and topically applied tretinoin. Kligman A, Mills O. *Arch Dermatol* 1973; 107: 5515–2.

The efficacy of tretinoin 0.05% solution once daily was investigated in 38 Black men with PFB. ‘Good to excellent’ results were reported after 8 weeks among patients with ‘early stage’ PFB.

Twice-daily applications of benzoyl peroxide 5%/clindamycin 1% gel versus vehicle in the treatment of pseudofolliculitis barbae. Cook-Bolden F, Barba A, Halder R, et al. *Cutis* 2004; 73: 18–24.

A total of 77 men with 16–100 combined papules and pustules on the face and neck were randomized to receive twice-daily benzoyl peroxide 5%/clindamycin 1% (BP/C) gel or vehicle for 10 weeks; 77.3% of the participants were Black. At weeks 2, 4, and 6, mean percentage reductions from baseline in combined papule and pustule counts were statistically significantly greater with BP/C gel than with vehicle.

Treatment of pseudofolliculitis barbae with topical glycolic acid: a report of two studies. Perricone N. *Cutis* 1993; 52: 232–5.

Two placebo-controlled trials in 35 adult men showed that glycolic acid lotion was significantly more effective than placebo in treating PFB. There was a reduction of over 60% in lesions on the treated side, which allowed daily shaving with little irritation.

Low-fluence 1064-nm laser hair reduction for pseudofolliculitis barbae in skin types IV, V, and VI. Schulze R, Meehan KJ, Lopez A, et al. *Dermatol Surg* 2009; 35: 98–107.

Twenty-two patients with PFB refractory to conservative therapy received five weekly treatments (unlike the customary every 5 weeks) over the anterior neck using a 1064-nm Nd:YAG laser with a 10-mm spot size set at 12 J/cm² and pulse duration 20 ms. Eleven patients demonstrated 83% improvement.

Topical eflornithine hydrochloride improves the effectiveness of standard laser hair removal for treating pseudofolliculitis barbae: a randomized, double-blinded, placebo-controlled trial. Xia Y, Cho S, Howard R, et al. *J Am Acad Dermatol* 2012; 67: 694–9.

Twenty-seven patients with Fitzpatrick type II–VI skin were enrolled in a split-neck study comparing four monthly treatments with Nd:YAG laser with 10-mm spot and at 25–30 J/cm² with 20- to 30-ms pulse duration with and without twice-daily application of 13.9% eflornithine cream. Shaving was continued. A very significant decrease in countable hairs and papules was evident after only two treatments, and almost no papules were evident at 16 weeks; the eflornithine side was moderately better at each stage.

Modified superlong pulse 810 nm diode laser in the treatment of pseudofolliculitis barbae in skin types V and VI. Smith E, Winstanley D, Ross E. *Dermatol Surg* 2005; 31: 297–301.

Ten of 13 patients with type V or VI skin treated with superlong-pulse 810-nm diode laser at 2-week intervals three times with a mean 29 J/cm² and 438 ms for type V and 26 J/cm² at 450 ms for type VI skin and then followed up to only 3 months showed clinical improvement of PFB papules, which was statistically significant.

Treatment of pseudofolliculitis with a pulsed infrared laser. Kauvar A. *Arch Dermatol* 2000; 136: 1343–6.

Ten women with Fitzpatrick skin types III–V and a history of pseudofolliculitis on the face, axilla, or groin for at least 1 year had three consecutive treatments at 6- to 8-week intervals with an 810-nm diode laser and a chill tip at 30–38 J/cm² and 20-ms pulse duration. After their last visit all showed more than 75% improvement in the pseudofolliculitis and had a 50% reduction in hair growth. No blistering occurred.

Laser-assisted hair removal for darker skin types. Battle E, Hobbs L. *Dermatol Ther* 2004; 17: 177–83.

The authors carefully review the rationale for use of diode, especially long-pulsed diode, and Nd:YAG lasers for highly pigmented patients, as well as testing, dosing, and cooling precautions to improve patient safety.

Treatment of pseudofolliculitis barbae in skin types IV, V, and VI with a long-pulsed neodymium:yttrium aluminum garnet laser. Ross E, Cooke L, Timko A, et al. *J Am Acad Dermatol* 2002; 47: 263–70.

Thirty-seven patients with pseudofolliculitis and Fitzpatrick skin types IV, V, and VI were tested with Nd:YAG laser. There was 33%, 43%, and 40% hair reduction on the thigh for the 50, 80-, and 100-J/cm² fluences, respectively, after 90 days. The highest doses tolerated by the epidermis were 50, 100, and 100 J/cm² for types VI, V, and IV skin, respectively. After testing on the face, mean papule counts after 90 days were 6.95 and 1.0 for the control vs. treatment sites, respectively.

Treatment of pseudofolliculitis barbae using the long-pulse Nd:YAG laser on skin types V and VI. Weaver S, Sagaral E. *Dermatol Surg* 2003; 29: 1187–91.

Twenty subjects with Fitzpatrick type V and VI skin and PFB on the neck or mandible were given two 2-cm × 2-cm treatments with Nd:YAG laser and 10-mm spot size at 40–50 ms and 24–40 J/cm² 3–4 weeks apart, assessed by photographic papule/pustule and hair counts at 1, 2, and 3 months after the final treatment and compared with a neighboring untreated site. The 76–90% reduction in the number of papules/pustules was statistically significant. Hair reduction of 80% at 1 month after testing diminished to 23% by 3 months.

Surgical depilation for the treatment of pseudofolliculitis or local hirsutism of the face: experience in the first 40 patients. Hage J, Bouman F. *Plast Reconstruct Surg* 1991; 88: 446–51.

Forty patients, all but three of whom were Caucasian, were operated on over a 15-year period for local hirsutism, pseudofolliculitis, and beard growth in transgender procedures. Side effects were significant, with wound edge necrosis in 8, seroma or hematoma in 8, and significant subcutaneous scar formation in 15, which was later preventable by postoperative long-term (at least 3 months) pressure bandages.

Pseudoxanthoma elasticum

Roselyn K. Stanger, Mark G. Lebwohl



Pseudoxanthoma elasticum (PXE) is a rare, autosomal recessive disorder causing abnormal fragmentation and calcification of the elastic fibers in the skin, retina, and cardiovascular system. The prevalence of PXE in the population is approximately 1:50,000. The primary lesions are small, asymptomatic, yellow papules on the flexural surfaces of the skin. The papules gradually coalesce into plaques, and the skin begins to appear slightly thickened, inelastic, and leather-like. Ophthalmologic complications include retinal angioid streaks, choroidal neovascularization, and subretinal hemorrhages, with resultant scarring causing central vision loss. Cardiovascular complications include narrowing of the cerebral arteries, intracranial hemorrhage, intermittent leg claudication due to peripheral arterial disease, diminished peripheral pulses, hypertension, and angina pectoris. Gastrointestinal bleeding is reported in about 10% of patients, which may also be due to non-PXE-related factors.

Most patients with PXE are found to harbor mutations in ATP-binding cassette sub-family C member 6 (*ABCC6*) gene on chromosome 16p13.1, which codes for an ATP-dependent transmembrane transporter. Hundreds of mutations have been identified, but approximately one-third are premature termination mutations. Certain mutations might be more commonly found in Caucasians compared with Asian patients. The differential diagnosis is PXE-like papillary

dermal elastolysis (PXE-PDE), also known as white fibrous papulosis of the neck; the clinical history and histopathology can often help confirm the diagnosis of PXE. This distinction is important insofar as PXE can have systemic involvement as noted above.

MANAGEMENT STRATEGY

Establishing the diagnosis of PXE may be difficult during the early stages of the disorder. The initial clinical signs appear most commonly during the early teenage years in flexural skin sites on the neck, axillae, antecubital fossae, and groin as variably sized patches of slightly thickened, leathery-looking skin. The diagnosis is often missed during these early years. Larger patches gradually develop with age. Angioid streaks in the retina usually appear later, beginning in the late teens or early twenties. Frank retinal hemorrhages begin most commonly in the fifth decade, causing central vision loss. Cardiovascular changes are rarely noted in children, although rare cases have been reported.

A heart-healthy lifestyle, including a low-cholesterol diet, aerobic exercises, and avoidance of smoking, should be encouraged. Because of the bleeding diathesis, patients should be advised to avoid aspirin and other blood thinners unless essential, as well as contact sports and other activities that increase the risk of eye trauma. There is some evidence that increased dietary calcium results in more rapid progression of the disease, so patients should be encouraged to avoid calcium supplementation and excessive ingestion of milk products. In contrast, experiments with animal models suggest that diets high in magnesium can inhibit tissue mineralization. An interdisciplinary approach involving dermatologists, retina specialists, and cardiologists is essential. Because this is a rare disease, it is important to provide patients with resources; the following two organizations are good references for patients:

Pseudoxanthoma Elasticum (PXE) International: <https://www.pxe.org>

National Association for Pseudoxanthoma Elasticum (NAPE): <https://www.napeusa.com>

Specific Investigations

- Family history for evidence of similar problems
- Complete skin examination, with special reference to all flexural skin sites and oral mucosa
- General physical examination and routine laboratory tests, including lipid panel, with a focus on risk factors for cardiovascular disease
- A 3- to 4-mm punch biopsy of suspicious lesions and a von Kossa stain to detect calcified elastic fibers to establish a diagnosis
- Retinal examination and photographs for evidence of angioid streaks, neovascularization, and hemorrhages
- Genetic studies on blood may be used to verify the diagnosis of PXE in questionable cases. The tests are expensive and rarely essential to confirm the diagnosis
- Cardiology referral and echocardiogram. There are elastic fibers in cardiac valves, so it should not be surprising that cardiac valvular abnormalities, such as mitral valve prolapse, are common in patients with PXE

First-Line Therapies

- Good nutrition; avoidance of trans fats; dietary calcium intake based on patient age and the current recommended dietary intake **B**
- Regular exercise program, with care to avoid sports with potential for head or eye injury **B**
- Vigorous control of hypertension, abnormal lipid profiles, and other risk factors for cardiovascular disease **C**
- Avoid long-term use of anticoagulants (to minimize the risk of ocular, gastrointestinal, and other sources of bleeding) **C**
- Retinal referral and follow-up on regular basis with a retinal specialist familiar with PXE. If choroidal neovascularization, consider possible treatment with bevacizumab (Avastin) or ranibizumab (Lucentis) **C**
- Cardiology referral: echocardiogram to look for cardiac and valvular abnormalities **C**
- Pregnant women should be closely monitored for hypertension and pre-eclampsia, yet the incidence of gastrointestinal hemorrhage appears to be lower than previously reported **C**

The extent of pseudoxanthoma elasticum skin changes is related to cardiovascular complications and visual loss: a cross-sectional study. Navasolava N, Gnanou M, Douillard M, et al. *Br J Dermatol* 2019; 180: 207–8.

A retrospective review of 125 patients with PXE illustrated that patients with a higher number of affected skin sites had more severe cardiovascular events (including heart attack or stroke) and/or ophthalmological complications (unilateral or bilateral blindness).

Long-term effectiveness of intravitreal bevacizumab for choroidal neovascularization secondary to angioid streaks in pseudoxanthoma elasticum. Finger RP, Charbel IP, Schmitz-Valckenberg S, et al. *Retina* 2011; 31: 1268–78.

Intravitreal bevacizumab improved visual acuity, stabilized leakage from active choroidal neovascularizations, and reduced central retinal thickness. There was improvement of visual acuity in early disease and preservation of function in advanced disease. Initiation of therapy as early as possible is important for preservation of vision.

The most severe ocular complication from PXE is choroidal neovascularization, which can lead to blindness if left untreated.

Ranibizumab for choroidal neovascularization secondary to pseudoxanthoma elasticum: 4-year results from the PIXEL study in France. Mimoun G, Ebran JM, Grenet T, et al. *Graefes Arch Clin Exp Ophthalmol* 2017; 255: 1651–60.

A retrospective chart review of over 70 patients illustrated that ranibizumab, a monoclonal anti-VEGF antibody, provided stable visual acuity over 4 years for patients with choroidal neovascularization. The proportion of eyes affected by retinal hemorrhage also decreased after treatment. Ranibizumab was well tolerated and does not require frequent injections.

Pregnancy and obstetrical outcomes in pseudoxanthoma elasticum. Bercovitch L, Leroux T, Terry S, et al. *Br J Dermatol* 2004; 151: 1011–8.

In this study, 407 women with PXE (a total of 795 pregnancies) answered a detailed questionnaire about their pregnancy and

severity of disease during pregnancy. Gastric bleeding and retinal complications occurred in less than 1%, and 12% of pregnancies were associated with worsening skin outcomes. In conclusion, PXE does not appear to be linked to adverse fetal outcomes or an increased risk of gastric bleeding, and most pregnancies are uncomplicated.

Second-Line Therapies

- Cosmetic surgery for removal of objectionable lesions if desired by patient for cosmetic reasons **B**
- Fractional CO₂ laser **E**
- Injectable collagen **E**

Pseudoxanthoma elasticum treatment with fractional CO₂ laser. Salles AG, Remigio AF, Moraes LB, et al. *Plast Reconstr Surg Glob Open* 2014; 2: e219.

A 32-year-old woman was treated with a fractional CO₂ laser applied to the anterior cervical region (four sessions) and posterior cervical region (five sessions). Significant improvement was noted 1 month after the first session. Two years after the last session, she had improvements in surface irregularities and distensibility.

Pseudoxanthoma elasticum: temporary treatment of chin folds and lines with injectable collagen. Galadari H, Lebwohl MJ. *Am Acad Dermatol* 2003; 49: S265–6.

Two patients with horizontal mental creases received injectable collagen. The first patient received 0.5 mL of collagen (Zyderm II) and showed immediate improvement; however, rhytides and creases recurred 6 months later. The second patient received 1.0 mL of collagen (Zyderm) in two sessions (2 weeks apart), and improvement was noted for at least 6 months. Nine months later, she received 1.0 mL intradermal collagen with effects that lasted for only 1 month. A third injection (1.0 mL Zyplast) provided improvement for 4 weeks.

It is likely that any of the new fillers currently available would work as well as injectable collagen, but the effects do not appear to be long-lasting.

Third-Line Therapies

- Sevelamer hydrochloride 800 mg three times daily **A**
- 800 mg magnesium oxide (MgO) (500 mg elemental Mg) twice daily for one year followed by 1250 mg (750 mg elemental magnesium) twice daily **A**
- Etidronate 20 mg/kg for 2 weeks every 12 weeks for 1 year **A**
- Intravenous sodium thiosulfate **E**

Magnesium supplementation in the treatment of pseudoxanthoma elasticum: a randomized trial. Rose S, On SJ, Fuchs W, et al. *J Am Acad Dermatol* 2019; 81: 263–5.

In this randomized, double-blind, placebo-controlled trial, patients received either 800 mg MgO (500 mg elemental magnesium) twice daily or placebo for one year. In the second year (open label), all patients received 2500 mg MgO (1500 mg elemental magnesium) divided into two daily doses. When considering the secondary end point of a 30% decrease in elastic fiber calcification, 36.3% of patients receiving magnesium were responders compared with 13.6% of patients in the placebo group ($p=0.17$). In addition, after 2 years of treatment with magnesium, 2/8

responders from the first year kept their response level and five patients who had previously been non-responders during the first year became responders.

There are alternative forms of magnesium such as magnesium citrate that have higher bioavailability, yet the form chosen in this study was evaluated in a mouse model of PXE and shown to reduce carotid intima-media thickness.

A randomized controlled trial of oral phosphate binders in the treatment of pseudoxanthoma elasticum. Yoo JY, Blum RR, Singer GK, et al. *J Am Acad Dermatol* 2011; 65: 341–8.

Sevelamer hydrochloride 800 mg three times daily resulted in reduced calcification of elastic fibers on microscopy and improved clinical scores, but the benefit was not significant compared with placebo.

The placebo was discovered to contain magnesium, which may explain the benefit achieved by the placebo group.

Etidronate halts systemic arterial calcification in pseudoxanthoma elasticum. Bartstra JW, de Jong PA, Kranenburg G, et al. *Atherosclerosis* 2020; 292: 37–41.

In this trial, 74 PXE patients received either etidronate 20 mg/kg or placebo for 2 weeks every 12 weeks, for a total of 1 year.

Etidronate halted calcification in the common carotid artery, thoracic aorta, abdominal aorta, iliac arteries, and arteries of the legs. No significant change was observed in the carotid arteries.

In a previous study (TEMP trial), 74 PXE patients with leg arterial calcification were randomized to receive either etidronate or placebo. During 1 year of follow-up, calcification in the femoral arterial wall decreased 4% in the etidronate group and increased 8% in the placebo group (p=0.001).

Severe early-onset manifestations of pseudoxanthoma elasticum resulting from the cumulative effects of several deleterious mutations in the ENPP1, ABCC6 and HBB genes: transient improvement in ectopic calcification with sodium thiosulfate. Omarjee L, Nitschke Y, Verschuere S, et al. *Br J Dermatol* 2019 Oct 24 [Epub ahead of print].

A young boy with severe and rapidly progressive PXE due to mutations in several genes simultaneously (*ABCC6*, *ENPP1*, and *HBB*) was treated with intravenous (IV) sodium thiosulfate 10 g IV/day for 6 months. There was improvement in calcified stenosis of several gastrointestinal arteries. Unfortunately, symptoms relapsed 4 months after the treatment was stopped.

Psoriasis

Mark G. Lebwohl, Peter van de Kerkhof



Plaque psoriasis is a common disorder in which environmental factors contribute to the development of sharply demarcated, erythematous, scaling plaques in genetically predisposed individuals. Because there is an overlap in treatments, guttate psoriasis, and inverse psoriasis, will be discussed under 'Management Strategy' next. Erythrodermic psoriasis and generalized pustular psoriasis (GPP) will be discussed at the end of the chapter; palmoplantar pustulosis is addressed in its own chapter. Patients should be questioned and examined for psoriatic arthritis, and because of recent evidence linking psoriasis to cardiovascular disease, risk factors should be addressed. Involvement of rheumatologists or other specialists may be necessary.

MANAGEMENT STRATEGY

The treatment of psoriasis must take many factors into account, including the extent of involvement, areas of involvement, the patient's lifestyle, and other health problems and medications. For example, if patients are taking medications such as lithium, which are known to exacerbate psoriasis, alternatives should be sought. In patients who have had multiple skin cancers, psoralen UVA (PUVA) and ciclosporin should be avoided as they increase the tendency to develop skin cancers; acitretin, which suppresses the development of skin cancers, should be considered for these individuals.

The body surface area (BSA) affected in patients with psoriasis is important in the selection of therapies. In individuals with less than 5% body surface area involvement, topical therapy is usually started unless the patient has previously failed topical therapy or the psoriasis is debilitating because of the site of involvement. In patients with mild localized plaques, topical corticosteroids can be prescribed, or other topical agents such as calcipotriol (*calcipotriene*), calcitriol, or tazarotene can be tried. Anthralin and coal tar preparations have fallen into disfavor because they are messy and possibly carcinogenic. New topical non-steroids such as roflumilast cream and tapinarof cream are on the horizon. The combination of a superpotent corticosteroid and calcipotriol or tazarotene

is often effective when monotherapy with either of the agents does not work, and new formulations that combine betamethasone dipropionate with calcipotriol and halobetasol propionate with tazarotene are available.

Some areas may be limited in extent but require alternative treatments. For example, involvement of the palms and soles can be debilitating, and these areas are notoriously difficult to treat. Pustular psoriasis of the palms and soles, for example, only occasionally responds to topical therapy. Although the palms and soles involve only a small percentage of the body surface area, treatment with oral medications or injected medications or phototherapy may be warranted. The combination of acitretin 25 mg daily with 'bath-PUVA' – applied by soaking the hands in a water-filled basin to which methoxsalen has been added, followed by ultraviolet A (UVA) irradiation – has been used successfully. The excimer laser can also be effective for palm and sole psoriasis, as can oral methotrexate, acitretin, apremilast, tofacitinib (or other Janus kinase inhibitors), and ciclosporin. Double-blind placebo-controlled trials have demonstrated the efficacy of adalimumab, infliximab, secukinumab, and guselkumab for palm and sole psoriasis, and it is likely that other biologic therapies are effective, though they are not as effective for palms and soles as they are for psoriasis on other parts of the body. Involvement of the scalp is common and requires gels, solutions, sprays, or foams that are not as messy as ointments and creams. Shampoos containing tars, salicylic acid, or corticosteroids are useful adjunctive therapies for the scalp. A new home device that delivers narrowband UVB to the scalp through fiber-optic filaments has recently been introduced. Treatment with intralesional injection of corticosteroids is often effective in patients who are refractory to topical therapies.

The face and intertriginous sites are highly responsive to topical medications but are particularly sensitive to side effects. Topical corticosteroids cause cutaneous atrophy, telangiectasia, and striae. Therefore only milder, safer corticosteroids should be used on the face and intertriginous sites, and alternating with non-corticosteroids may be optimal if psoriasis recurs. The topical immunomodulators tacrolimus 0.1% ointment and pimecrolimus 1% cream are effective and safe for facial and intertriginous psoriasis, but not as effective on thick plaques on the rest of the body. Similarly the non-steroids roflumilast and tapinarof creams are very useful on these sites. Calcipotriol (50 mcg/g) can be irritating on facial or intertriginous psoriasis, but alternative vitamin D analogs such as calcitriol and tacalcitol are less irritating and therefore particularly suited for facial or flexural psoriasis. Tazarotene may be too irritating to use on genital skin, but it can be used on the face. The irritation of tazarotene can also be minimized by using it in a regimen with topical corticosteroids.

With 5%–10% body surface involvement, topical therapy is usually prescribed, but may require the addition of phototherapy or oral medications. In those with more than 10% body surface involvement, topical therapy may be impractical for all lesions but may provide a useful adjunct to phototherapy or systemic therapy.

Sunlight remains an effective therapy. Broadband UVB phototherapy has largely been replaced by narrowband UVB. PUVA is one of the most effective treatments for psoriasis and offers long remissions for many patients. Because of its increased risk of cutaneous malignancy, use of PUVA has diminished.

In patients who have not achieved satisfactory results with these treatments, low-dose oral retinoids can be added. Acitretin in doses of 10–25 mg daily dramatically improves the response to UVB and to PUVA. By keeping the dose at 25 mg or less, the side effects of acitretin can be minimized. For those who are not candidates for UVB phototherapy or PUVA, oral methotrexate

is highly effective in combination with other treatments or as monotherapy. It is associated with hepatic fibrosis in some patients, and regular monitoring of liver function tests in addition to blood counts is necessary. In patients with risk factors for liver disease, safer and more effective biologic therapies are preferable. *Ciclosporin* is also dramatically effective as monotherapy for psoriasis but is associated with nephrotoxicity as well as hypertension and a theoretical risk of malignancy with long-term use. Consequently, current guidelines call for limiting use of ciclosporin to 1 or 2 years. The most recently approved oral medication for psoriasis, apremilast, is another moderately effective option. Tofacitinib, an oral agent approved in the United States for psoriatic arthritis, has also been studied for psoriasis, and a promising tyrosine kinase 2 inhibitor has shown promising results.

In recent years, the ability to create new drugs that target specific parts of the immune system has led to the development of biologic agents for psoriasis. These drugs are not associated with the nephrotoxicity of ciclosporin or the hepatotoxicity and bone marrow toxicity of methotrexate, but the cost of biologics is often prohibitive. Psoriasis experts are divided on the point at which biologics should be considered. Some consider them first-line therapy when the disease is too extensive for topical therapy. Because of their expense, biologics are used by others only after phototherapy or other systemic therapies have been tried.

As newer generations of biologics are introduced and are safer and more effective, more dermatologists are using them early in the management of their patients. Agents that block tumor necrosis factor- α (TNF- α), including *etanercept*, *infliximab*, *adalimumab*, *golimumab*, and *certolizumab*, are effective for patients with psoriasis and psoriatic arthritis. TNF-blocking agents have unique side effects, including the reactivation of latent tuberculosis, exacerbation of multiple sclerosis, and the development of antinuclear antibodies. *Ustekinumab*, a drug that blocks the p40 component of interleukin (IL)-12 and IL-23, is injected subcutaneously in 45-mg and 90-mg doses; dose elevation can be beneficial in overweight patients and refractory patients. The drug can be administered as infrequently as every 3 months. *Ixekizumab* and *secukinumab*, which block IL-17A, and *brodalumab*, which blocks the IL-17 receptor, are fast-acting and more effective therapies that can achieve 100% clearing of psoriasis, but, after a loading period, must be administered every 2–4 weeks. They are also quite effective for psoriatic arthritis. Guselkumab, tildrakizumab, risankizumab, and, in the future, mirikizumab target IL-23 and, following loading doses, are administered as infrequently as every 2–3 months. When all else fails, *combination therapy* using different medications is often effective. Because many of the treatments available are immunosuppressive, side effects of additive immunosuppression must be considered when combining different modalities.

GUTTATE PSORIASIS

Guttate psoriasis is characterized by widespread erythematous, scaling papules. The management of guttate psoriasis is very similar to that of extensive plaque psoriasis. Because streptococcal infection often precedes guttate psoriasis, underlying infection should be sought and treated. Lesions are usually too widespread for topical therapy, so traditionally most patients have been started on *phototherapy with narrowband UVB*. If that is ineffective, *oral retinoids* can be added. Recently short-term administration of biologic therapies has been used successfully to treat guttate psoriasis.

INVERSE PSORIASIS

Patients with inverse psoriasis develop lesions in the axillae, between the buttocks, on the medial aspects of the thighs, and in the umbilicus. These sites are easily treated with *mild topical corticosteroids* but are more susceptible to corticosteroid side effects, such as atrophy and formation of striae. Consequently, non-steroidal treatments can be attempted. *Calcipotriol* (50 mcg/g) can be irritating on intertriginous sites but is nevertheless effective. *Other vitamin D analogs* (*calcitriol*, *tacalcitol*) cause less irritation. *Tazarotene* can be used on the face, but is usually too irritating to use in the axillae or groin. *Tars* and *anthralin* are likewise irritating in intertriginous sites. *Topical tacrolimus ointment* and *pimecrolimus cream*, although not approved for psoriasis, are highly effective for facial and intertriginous psoriasis, but less effective for thick plaques elsewhere on the body. Topical phosphodiesterase inhibitors like roflumilast cream, and topical tapinarof cream, and Janus kinase inhibitors are likely to be introduced for psoriasis, and these may be effective for facial and intertriginous psoriasis without the atrophogenicity of corticosteroids.

Specific Investigations

- Skin biopsy (only if the clinical diagnosis of psoriasis is uncertain)
- Serum electrolytes and calcium for patients with GPP
- ASO or bacterial cultures for patients with guttate psoriasis
- Appropriate drug-related monitoring for patients on systemic therapies including annual TB testing except for acitretin and apremilast

Investigation is not required in the majority of cases. Skin biopsy may be helpful if the diagnosis is in question but is usually not needed.

As discussed later, a range of investigations are required for screening and monitoring when using systemic therapies.

Routine screening for tuberculosis has been advised for patients treated with biologic therapies. Because methotrexate and ciclosporin are also immunosuppressive, testing for tuberculosis and, if positive, chest radiography has been suggested before treatment with these agents. Ciclosporin guidelines call for frequent monitoring of blood pressure and chemistry screening, with particular attention to serum creatinine and magnesium. Methotrexate guidelines call for periodic monitoring of complete blood count (CBC) and platelet counts and chemistry screening with liver function tests. Assays for hepatic fibrosis such as the serum aminoterminal propeptide of type III procollagen or liver biopsies are advised in certain patients. Alternative liver screening is advocated by hepatologists to minimize the need for liver biopsies. Monitoring for viral hepatitis or HIV infection should be considered in populations at risk for those disorders, and many advocate routine hepatitis screening in any patient before biologic therapy, methotrexate, or ciclosporin. Serum cholesterol and triglycerides are particularly important in patients treated with oral acitretin.

From the Medical Board of the National Psoriasis Foundation: monitoring and vaccinations in patients treated with biologics for psoriasis. Lebwohl M, Bagel J, Gelfand JM, et al. *J Am Acad Dermatol* 2008; 58: 94–105.

Apart from history, physical examination, routine chemistry screening, CBC, and platelet counts, testing for tuberculosis is advised for patients treated with all biologics. Liver function tests should be monitored more frequently in patients treated

with infliximab; testing for hepatitis B and C is now advocated before starting biologic therapy. Consider administering vaccinations, particularly with live viruses, prior to initiating biologic therapy.

Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. Elmetts CA, Leonardi CL, Davis DMR, et al. *J Am Acad Dermatol*. 2019; 80: 1073–113.

Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. Menter A, Strober BE, Kaplan DH, et al. *J Am Acad Dermatol* 2019; 80: 1029–72.

Joint American Academy of Dermatology – National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with phototherapy. Elmetts CA, Lim HW, Stoff B, et al. *J Am Acad Dermatol* 2019; 81: 775–804.

Joint American Academy of Dermatology – National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic non-biological therapies. Menter A, Gelfand JM, Connor C, et al. *J Am Acad Dermatol* 2020; S0190-9622(20)30284-X [Epub ahead of print].

Joint American Academy of Dermatology – National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis in pediatric patients. Menter A, Cordero KM, Davis DMR, et al. *J Am Acad Dermatol* 2020; 82: 161–201.

First-Line Therapies

• Coal tar, anthralin	A
• Salicylic acid	C
• Topical corticosteroids	A
• Vitamin D analogs	A
• Tazarotene	A
• Sun exposure	B
• Tacrolimus ointment	A
• Pimecrolimus cream	A

A randomized, double-blind, vehicle-controlled study of a novel liposomal dithranol formulation in psoriasis. Saraswat A, Agarwal R, Katore OP, et al. *J Dermatol Treat* 2007; 18: 40–5.

Twenty patients were enrolled in a bilateral comparison controlled trial of 0.5% dithranol entrapped in phospholipid liposomes on one side of the body compared with the vehicle (10 patients) or a conventional 1.15% dithranol, 1.15% salicylic acid, and 5.3% coal tar preparation (10 patients) applied daily, using a 30-minute short-contact regimen for 6 weeks. Both active preparations resulted in significant improvement in psoriasis, but there was less perilesional erythema and skin staining on the side treated with the liposome preparation than with the conventional cream.

Efficacy of topical 5% liquor carbonis detergens vs. its emollient base in the treatment of psoriasis. Kanzler MH, Gorsulowsky DC. *Br J Dermatol* 1993; 129: 310–4.

Liquor carbonis detergens 5% resulted in more improvement in psoriasis than its vehicle emollient base in a bilateral-paired comparison study.

Tars are available in gels, creams, emollient creams, and ointments and are also available in emulsions that are added to the bath. There is a general belief that more cosmetically elegant preparations are better tolerated by patients but less effective. Crude coal tar is quite effective, but somewhat messy.

The role of salicylic acid in the treatment of psoriasis. Lebowohl M. *Int J Dermatol* 1999; 38: 16–24.

Salicylic acid is a keratolytic agent that removes scale and allows other topical medications to penetrate. There is a marked increase in penetration of topical corticosteroids when combined with 2%–10% salicylic acid. Combinations of salicylic acid and tar or anthralin have also been used successfully, but salicylic acid inactivates calcipotriol. Moreover, salicylic acid blocks UVB and should therefore not be applied before phototherapy.

Evaluation of the efficacy and safety of clobetasol propionate spray in the treatment of plaque-type psoriasis. Jarratt MT, Clark SD, Savin RC, et al. *Cutis* 2006; 78: 348–54.

The efficacy and tolerability of clobetasol propionate foam 0.05% in the treatment of mild to moderate plaque-type psoriasis of nonscalp regions. Gottlieb AB, Ford RO, Spellman MC. *J Cutan Med Surg* 2003; 7: 185–92.

Clobetasol propionate shampoo 0.05%: a new option to treat patients with moderate to severe scalp psoriasis. Jarratt M, Breneman D, Gottlieb AB, et al. *J Drugs Dermatol* 2004; 3: 367–73.

The efficacy of topical corticosteroids for psoriasis has been demonstrated in numerous double-blind, placebo-controlled trials of large numbers of patients. Topical corticosteroids are available in many vehicles, including foams, emollient foams, sprays, shampoos, solutions, lotions, creams, emollient creams, ointments, tapes, and gels.

Superpotent corticosteroids such as clobetasol can be associated with cutaneous and systemic side effects. Clinically significant adrenal suppression is seldom considered, and tests for adrenal function are virtually never performed. Practicing dermatologists are more concerned with the side effects of atrophy, telangiectasia, striae, and tachyphylaxis. For all these reasons, superpotent corticosteroid use should be limited to 2–4 weeks and less than 50 g/week. Superpotent corticosteroids should not be occluded and should not be used on the face or intertriginous sites. If at all possible, they should be avoided in children.

An investigator-masked comparison of the efficacy and safety of twice daily applications of calcitriol 3 µg/g ointment vs. calcipotriol 50 µg/g ointment in subjects with mild to moderate chronic plaque-type psoriasis. Zhu X, Wang B, Zhao G, et al. *J Eur Acad Dermatol Venereol* 2007; 21: 466–72.

In this investigator-blinded study, 250 subjects were treated twice daily for 12 weeks with either calcitriol or calcipotriol ointments. Both agents were comparably effective, but there were more local cutaneous adverse events in patients treated with calcipotriol than in those treated with calcitriol.

Because local irritation occurs in up to 20% of patients treated with calcipotriol on facial or intertriginous skin, calcitriol may be a better therapeutic option for those sites.

Once daily treatment of psoriasis with tacalcitol compared with twice daily treatment with calcipotriol. A double-blind trial. Veien NK, Bjerke JR, Rossmann-Ringdahl I, et al. *Br J Dermatol* 1997; 137: 581–6.

Tacalcitol ointment applied once daily proved to be slightly less effective than calcipotriol ointment twice daily in this 8-week, double-blind study conducted in 287 patients.

Calcipotriol plus betamethasone dipropionate aerosol foam provides superior efficacy vs. gel in patients with psoriasis vulgaris: randomized, controlled PSO-ABLE study. Paul C, Stein Gold L, Cambazard F, et al. *J Eur Acad Dermatol Venereol* 2017; 31: 119–26.

A total of 463 patients were treated with calcipotriol/betamethasone dipropionate foam once daily, calcipotriol/betamethasone dipropionate gel once daily, foam vehicle, or gel vehicle in an investigator-blinded study. Calcipotriol/betamethasone dipropionate foam (Enstilar) at week 4 was superior to calcipotriol/betamethasone dipropionate gel (Taclonex, Daivobet, Dovobet) at week 8.

Calcipotriol is a relatively unstable molecule that is inactivated upon mixing with many other topical agents, so the availability of a stable combination ointment of calcipotriol with a corticosteroid is desirable. Long-term therapy with any product containing a topical corticosteroid should be done with caution to avoid cutaneous atrophy and especially the development of striae. To minimize local cutaneous side effects, avoid strong corticosteroids on the face and intertriginous sites. Use intermittent dosing such as twice-weekly therapy for maintenance of therapeutic effect.

Tazarotene cream in the treatment of psoriasis: two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12 weeks. Weinstein GD, Koo JY, Krueger GG, et al; Tazarotene Cream Clinical Study Group. *J Am Acad Dermatol* 2003; 48: 760–7.

Tazarotene creams 0.1% and 0.05% were compared with vehicle once daily for 12 weeks in this double-blind study. Tazarotene 0.1% was more effective, but also more irritating, than the 0.05% cream, and both were superior in efficacy to vehicle.

Tazarotene creams are slightly less effective, but also less irritating, than tazarotene 0.1% and 0.05% gels.

Tacrolimus ointment is effective for facial and intertriginous psoriasis. Lebwohl M, Freeman AK, Chapman MS, et al.; Tacrolimus Ointment Study Group. *J Am Acad Dermatol* 2004; 51: 723–30.

In this double-blind, placebo-controlled trial, 167 patients were treated for facial and intertriginous psoriasis with tacrolimus 0.1% ointment applied twice daily for 8 weeks. At the end of 8 weeks 65.2% of tacrolimus ointment-treated patients and 31.5% of vehicle-treated patients were clear or almost clear.

Pimecrolimus cream 1% in the treatment of intertriginous psoriasis: a double-blind, randomized study. Gribetz C, Ling M, Lebwohl M, et al. *J Am Acad Dermatol* 2004; 51: 731–8.

In this double-blind study, 57 patients were treated with 1% pimecrolimus cream or placebo. At the end of week 8, 71% of pimecrolimus-treated patients were clear or almost clear, compared with 41% of vehicle-treated patients.

Topical calcineurin inhibitors are valuable alternatives for psoriasis in facial and intertriginous sites, which are particularly susceptible to corticosteroid side effects and easily irritated by calcipotriol or tazarotene.

The percentage of patients achieving PASI 75 after 1 month and remission time after climatotherapy at the Dead Sea. Harari M, Novack L, Barth J, et al. *Int J Dermatol* 2007; 46: 1087–91.

Sixty-four patients were treated with climatotherapy at the Dead Sea, which included bathing in Dead Sea water and gradually increasing sun exposure over 4 weeks. All patients achieved Psoriasis Area and Severity Index (PASI) 50, and 75.9% achieved PASI 75. The median time to recurrence of a lesion of psoriasis was 23.1 weeks, and the median duration of effect, defined as the time to 50% relapse in the PASI improvement, was 33.6 weeks.

The Dead Sea is the lowest point on earth and has the highest concentration of minerals of any body of water on the earth. The mineral haze in the atmosphere, through which sunlight passes, results in a unique spectrum of sunlight that accounts for the exceptional therapeutic responses. Two to four weeks of Dead Sea sun exposure and bathing are required to achieve significant benefit.

Second-Line Therapies

• UVB/narrowband UVB	A
• PUVA	A
• Acitretin	A
• Apremilast	A
• TNF blockers, adalimumab, etanercept, infliximab, certolizumab pegol	A
• Ustekinumab	A
• IL-17 blockers secukinumab, ixekizumab, brodalumab	A
• IL-23 blockers guselkumab, tildrakizumab, risankizumab	A
• Methotrexate	A
• Ciclosporin	A

Components of the Goeckerman regimen. Le Vine MJ, White HA, Parrish JA. *J Invest Dermatol* 1979; 73: 170–3.

The efficacy of UVB phototherapy is improved by the addition of a topical tar preparation or lubricating base; 5% crude coal tar is no more effective than lubricating base when combined with a phototherapy regimen.

The original Goeckerman regimen involved inpatient application of crude coal tar, which was removed before daily UVB phototherapy. Most current phototherapy regimens involve outpatient treatment three times per week with topical application of mineral oil or petrolatum.

Narrowband UV-B produces superior clinical and histopathological resolution of moderate-to-severe psoriasis in patients compared with broadband UV-B. Coven TR, Burack LH, Gilleaudeau R, et al. *Arch Dermatol* 1997; 133: 1514–22.

Twenty-two patients were treated in a bilateral comparison study with narrowband UVB on one side and broadband UVB on the other. The side treated with narrowband UVB cleared more quickly and more completely than the side treated with broadband UVB.

Randomized double-blind trial of the treatment of chronic plaque psoriasis: efficacy of psoralen-UV-A therapy vs. narrowband UV-B therapy. Yones SS, Palmer RA, Garibaldinos TT, et al. *Arch Dermatol* 2006; 142: 836–42.

In this double-blind study 93 patients were treated twice weekly with either narrowband UVB or PUVA until clearance or up to a maximum of 30 sessions. In patients with skin types 1–4, PUVA was significantly more effective than UVB, with 84% of PUVA-treated patients clearing compared with 65% of narrowband UVB-treated patients. PUVA cleared patients after a median of 17

treatments, compared with 28.5 treatments for narrowband UVB. Six months after the last treatment, 68% of patients treated with PUVA remained clear, compared with 35% of patients treated with narrowband UVB.

Although PUVA is more effective than narrowband UVB, it is more difficult to administer and has an increased risk of phototoxicity and carcinogenicity. Baseline and annual eye examinations have been suggested for patients treated with oral PUVA, but initial concerns about the development of cataracts in these patients have not been borne out over time. Baseline serologies for lupus were once recommended before starting patients on PUVA, but are now only obtained in patients who have other signs or symptoms of the disease.

Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Saurat JH, Stingl G, Dubertret L, et al. *Br J Dermatol* 2008; 158: 558–66.

Adalimumab 40 mg every other week after an 80-mg loading dose was compared with methotrexate 7.5 mg orally, increased according to clinical response up to 25 mg per week or placebo for 16 weeks. Of adalimumab-treated patients, 79.6% achieved PASI 75, compared with 35.5% of those patients treated with methotrexate and 18.9% of those treated with placebo. Methotrexate patients suffered the most adverse events leading to study discontinuation, mostly related to hepatic complications.

This was the first placebo-controlled trial of methotrexate for psoriasis. The trial design has been criticized for starting methotrexate at a low dose. Nevertheless, the clear efficacy of adalimumab and the side effects of methotrexate were demonstrated by this study.

A double-blind, placebo-controlled trial of acitretin for the treatment of psoriasis. Olsen EA, Weed WW, Meyer CJ, et al. *J Am Acad Dermatol* 1989; 21: 681–6.

In a double-blind study, 15 patients were treated with a daily acitretin dose of 25 mg or 50 mg or placebo for 8 weeks. All were then treated in an open-label study with either 25 mg or 75 mg of acitretin daily. Improvement in psoriasis was only moderate.

Acitretin plus UVB therapy for psoriasis. Comparisons with placebo plus UVB and acitretin alone. Lowe NJ, Prystowsky JH, Bourget T, et al. *J Am Acad Dermatol* 1991; 24: 591–4.

Photochemotherapy for severe psoriasis without or in combination with acitretin: a randomized, double-blind comparison study. Tanew A, Guggenbichler A, Hönigsmann H, et al. *J Am Acad Dermatol* 1991; 25: 682–4.

This was a double-blind study of 60 patients treated with either PUVA alone or PUVA in combination with acitretin. Ninety-six percent of patients treated with acitretin and PUVA achieved marked or complete clearing, compared with 80% of patients treated with PUVA alone. The cumulative UVA dose used for the acitretin + PUVA group was 42% lower than for the patients treated with PUVA alone.

Acitretin monotherapy has limited benefit for psoriasis, partly because of its limited efficacy and partly because higher dosing results in more mucocutaneous side effects, such as hair loss and cheilitis. In combination with other treatments such as UVB or PUVA, even low doses of acitretin result in dramatically enhanced efficacy. It is also useful in combination or monotherapy for palm and sole psoriasis.

Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. Heydendael VM, Spuls PI, Opmeer BC, et al. *N Engl J Med* 2003; 349: 658–65.

Eighty-eight patients were randomized to treatment with either methotrexate starting at 15 mg and adjusted according to clinical response or ciclosporin starting at 3 mg/kg and adjusted according to clinical response. Psoriasis improved in both groups, with a slightly greater response in the ciclosporin group. Twelve of 44 patients in the methotrexate group had to discontinue treatment because of liver function test abnormalities.

Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). Papp K, Reich K, Leonardi CL, et al. *J Am Acad Dermatol* 2015; 73: 37–49.

Patients were treated with either apremilast 30 mg twice daily or placebo for the first 12 weeks of this study. At week 16, 33.1% of patients achieved PASI 75 compared with 5.3% of placebo-treated patients. *Although these results are modest compared with newer biologic therapies, the advantage of an oral formulation is clear. The safety profile, at least in the short term, appears to be good, with the main adverse events being gastrointestinal symptoms and weight loss.*

Etanercept treatment for children and adolescents with plaque psoriasis. Paller AS, Siegfried EC, Langley RG, et al.; Etanercept Pediatric Psoriasis Study Group. *N Engl J Med* 2008; 358: 241–51.

In this double-blinded trial, 211 patients age 4–17 years received weekly injections of placebo or 0.8 mg/kg of etanercept; 57% of etanercept-treated children achieved PASI 75, compared with 11% of those treated with placebo.

In adults etanercept can be administered in doses of 50 mg twice weekly. In the United States, after 3 months the dosage is lowered to 50 mg administered subcutaneously once weekly, but in other countries the twice-weekly dosing can continue. As in adults, the pediatric dose of 0.8 mg/kg is effective in children with psoriasis and psoriatic arthritis. Ustekinumab and adalimumab are also effective in children and teenagers.

Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. Menter A, Tyring SK, Gordon K, et al. *J Am Acad Dermatol* 2008; 58: 106–15.

In this 1212 patient, double-blind, placebo-controlled trial of adalimumab 40 mg every other week for 15 weeks, 71% of adalimumab-treated patients achieved PASI 75, compared with 7% of placebo-treated patients.

Even higher response rates were achieved in patients treated with adalimumab 40 mg subcutaneously every week. A loading dose of 80 mg of adalimumab results in much faster clinical responses.

Successful treatment of moderate to severe plaque psoriasis with the PEGylated Fab' certolizumab pegol: results of a phase II randomised, placebo-controlled trial with a re-treatment extension. Reich K, Ortonne JP, Gottlieb AB, et al. *Br J Dermatol* 2012; 167: 180–90.

After a loading dose of certolizumab pegol 400 mg, subjects were treated with subcutaneous injections of 200 mg, 400 mg, or placebo every other week; 75%, 83%, and 7% of subjects achieved PASI 75, respectively.

Certolizumab is one of the most effective TNF blockers for psoriasis and does not cross the placenta, making it ideal for women of childbearing potential.

A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. Menter A, Feldman SR, Weinstein GD, et al. *J Am Acad Dermatol* 2007; 56: 31. e1–15.

In this double-blind study, 835 patients with moderate-to-severe psoriasis were treated with either infliximab 3 mg/kg or 5 mg/kg or placebo at weeks 0, 2, and 6. PASI 75 was achieved by 75.5% of patients in the 5 mg/kg group, compared with 70.3% in the 3 mg/kg group. At week 14, infliximab-treated patients were rerandomized to continuous or intermittent maintenance regimens. Greater improvements in psoriasis occurred with continuous rather than intermittent treatment and with the 5 mg/kg dose.

Continuous infliximab therapy may suppress the development of human antichimeric antibodies, which have been associated with more infusion reactions and reduced responsiveness to the drug.

Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Papp KA, Langley RG, Lebwohl M, et al. *Lancet* 2008; 371: 1675–84.

In this double-blind study, 1230 patients were treated with ustekinumab 45 mg or 90 mg or placebo. The drug was administered subcutaneously at weeks 0 and 4 and every 12 weeks thereafter. Of those treated with 45 mg, 66.7% achieved PASI 75 compared with 75.7% of those treated with 90 mg and 3.7% of those treated with placebo. At week 28, partial responders (i.e., those who achieved PASI 50 but not PASI 75) were rerandomized to increase dosing to every 8 weeks or to continue every 12 weeks. Of those who increased to 90 mg of ustekinumab every 8 weeks, 68.8% achieved PASI 75 by week 52, compared with only 33.3% of those who continued dosing every 12 weeks.

Ustekinumab is highly effective for psoriasis, and safety data up to 8 years are promising with regard to infection, malignancy, and cardiovascular disease. Because of the duration of its effect, ustekinumab can be administered as infrequently as every 12 weeks, although many patients need injections every 8 weeks to maintain clearing.

Secukinumab in plaque psoriasis – results of two phase 3 trials. Langley RG, Elewski BE, Lebwohl M, et al. *N Engl J Med* 2014; 371: 326–38.

Subcutaneous secukinumab 300 mg, 150 mg, or placebo was administered once weekly for 5 weeks and then every 4 weeks and compared with placebo or etanercept 50 mg twice weekly in this double-blind study. Up to 81.6% of patients achieved PASI 75 with the 300-mg dose of secukinumab and up to 71.6% with the 150-mg dose, which were superior to etanercept and to placebo.

Secukinumab 300 mg (two 150-mg subcutaneous injections) is the preferred dose and results in rapid and sustained clearing of psoriasis. Significant numbers of patients achieved PASI 90 and even PASI 100. The only side effect clearly linked to the drug was an increase in monilial infections.

Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Griffiths CE, Reich K, Lebwohl M, et al. *Lancet* 2015; 386: 541–51.

Subcutaneous 160 mg of ixekizumab followed by 80 mg every 2 weeks or every 4 weeks was compared with etanercept 50 mg every 2 weeks or placebo in this double-blind, double-dummy study. PASI 75 was achieved by up to 89.7% of patients treated with ixekizumab every 2 weeks and up to 77.5% in those treated every 4 weeks. Both regimens were superior to etanercept and to placebo.

After a loading dose of 160 mg (two 80-mg subcutaneous injections), 80 mg of ixekizumab every 2 weeks is the approved dose for up to 12 weeks. Thereafter, 80 mg every 4 weeks is approved for maintenance, although every-2-week maintenance is being studied. Rapid, sustained clearing of psoriasis can be expected, and significant numbers of patients achieve PASI 90 and PASI 100. Monilial infections can occur.

Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. Lebwohl M, Strober B, Menter A, et al. *N Engl J Med* 2015; 373: 1318–28.

Psoriasis patients were treated with brodalumab (210 mg or 140 mg every 2 weeks), ustekinumab (45 mg for patients with a body weight ≤100 kg and 90 mg for patients >100 kg at weeks 0 and 4), or placebo for the first 12 weeks of these double-blind trials. Up to 86% of patients achieved PASI 75 and up to 44% achieved PASI 100 with the 210-mg dose of brodalumab, which was superior in several outcomes to 140-mg brodalumab, ustekinumab, and placebo.

A low frequency of monilial infections occurred in brodalumab-treated subjects in these early trials. In later phases of this study, and in other studies, there were a small number of suicides, which may not be related to the drug but which did not occur with other treatments blocking IL-17. As a result, in the United States brodalumab requires a risk minimization program directed at minimizing suicides.

Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. Reich K, Armstrong AW, Langley RG, et al. *Lancet*. 2019; 394(10201): 831–9.

Of patients treated with guselkumab for 48 weeks, 84% achieved PASI 90 compared to 70% of secukinumab-treated patients.

Guselkumab is highly effective and requires injection every 8 weeks after treatment at weeks 0 and 4. It is, however, slower than secukinumab, which showed superiority in efficacy for the first 12 weeks of this study.

Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. Reich K, Papp KA, Blauvelt A, et al. *Lancet* 2017; 390(10091): 276–88.

Tildrakizumab in doses of 100 mg or 200 mg was administered subcutaneously at weeks 0 and 4 and every 12 weeks thereafter. At week 12, 66% of patients in the 200 mg group and 61% of patients in the 100 mg group achieved PASI 75, which was superior to etanercept-treated patients (48% achieving PASI 75) and placebo.

Tildrakizumab is available in 100 mg doses in the United States, and up to 200 mg doses elsewhere. This pivotal trial looked at week 12 for its primary end point even though efficacy continues to climb for at least 7 months with up to 86% of patients achieving PASI 75, and up to 59% achieving PASI 90. Patients achieve long remissions when the drug is discontinued.

Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. Gordon KB, Strober B, Lebwohl M, et al. *Lancet* 2018; 392(10148): 650–61.

Risankizumab 150 mg administered subcutaneously at weeks 0 and 4 and every 12 weeks thereafter resulted in PASI 90 in 75% of patients in both trials at week 16. Improvement was maintained through 52 weeks of continued treatment. With such impressive responses and safety and injections every 2–3 months, the threshold for starting patients on IL-23 blockers is limited only by the cost of the drugs and the hesitation of patients to try any injected medications.

Third-Line Therapies

• Combination therapy	A
• Topical 5-fluorouracil	C
• Sulfasalazine (sulfasalazine)	A
• Mycophenolate mofetil	B
• Hydroxycarbamide (hydroxyurea)	B
• Azathioprine	C
• FK-506	A
• Fumaric acid esters	B
• Antibiotics	C
• Colchicine	C
• Laser (excimer, pulsed dye)	C
• Cryotherapy	C
• Grenz rays	B
• Leflunomide	A
• Golimumab	A
• BMS-986165	A
• Tofacitinib	A
• Mirikizumab	A
• Bimekizumab	A
• Topical phosphodiesterase inhibitors	A
• Topical Janus kinase inhibitors	A
• Tapinarof cream	A

Combination treatments for psoriasis: a systematic review and meta-analysis. Bailey EE, Ference EH, Alikhan A, et al. Arch Dermatol 2012; 148: 511–22.

The side effects of psoriasis treatments can be minimized and efficacy enhanced by combining low doses of different therapies. Rotational therapy refers to a method in which patients cleared with one psoriasis therapy are subsequently treated with different therapies to minimize the cumulative toxicity of any given treatment. Thus the hepatotoxicity of cumulative doses of methotrexate, the nephrotoxicity of ciclosporin, and the carcinogenicity of PUVA can be minimized.

Commonly used combinations involve retinoids and UVB and retinoids and PUVA. UVB and PUVA have been used in combination with one another as well as with methotrexate. Retinoids are among the safest systemic agents for psoriasis and have been combined with methotrexate and ciclosporin, although liver function tests should be watched carefully when methotrexate and acitretin are used together. The combination of methotrexate and ciclosporin is a dramatically effective therapy, as is the combination of ciclosporin and hydroxycarbamide. Methotrexate has also been used with hydroxycarbamide, but blood counts must be watched very carefully.

Although this conference predated the introduction of biologic therapies for psoriasis, all of the currently approved biologics have been administered with methotrexate, acitretin, ciclosporin, and phototherapy. Because methotrexate and ciclosporin are immunosuppressive, they should be used cautiously with biologics and for as short a period of combination as possible. An exception may be

the combination of methotrexate with infliximab, as concomitant methotrexate has been shown to reduce the development of antichimeric antibodies, and methotrexate also significantly improves the response to adalimumab.

Clinical efficacy of a 308 nm excimer laser for treatment of psoriasis vulgaris. He YL, Zhang XY, Dong J, et al. Photodermatol Photoimmunol Photomed 2007; 23: 238–41.

In this open-label study 40 patients were treated twice weekly for up to 15 treatments. PASI scores improved by approximately 90%.

The excimer laser is a useful therapy for localized plaques of psoriasis. Its main side effect is local cutaneous burning. There are more limited data on the use of pulsed-dye laser (PDL) (595 nm) and intense pulsed light with a 550-nm filter for nail psoriasis and for localized plaques.

Targeted UVB phototherapy for psoriasis: a preliminary study. Lapidoth M, Adatto M, David M. Clin Exp Dermatol 2007; 32: 642–5.

This high-intensity targeted UVB lamp (290–320 nm; Be Clear) resulted in significant improvement in localized plaques without treating normal surrounding skin.

Efficacy of the pulsed dye laser in the treatment of localized recalcitrant plaque psoriasis: a comparative study. Erceg A, Bovenschen HJ, van de Kerkhof PC, et al. Br J Dermatol 2006; 155: 110–4.

PDL was compared with the combination calcipotriol/betamethasone dipropionate ointment in an open-label, bilateral comparison study. Twelve weeks after treatment there was 62% improvement in psoriasis severity scores on the PDL-treated side, compared with 19% reduction on the combination calcipotriol/betamethasone dipropionate side.

Weekly pulse dosing schedule of fluorouracil: a new topical therapy for psoriasis. Pearlman DL, Youngberg B, Engelhard C. J Am Acad Dermatol 1986; 15: 1247–52.

Fourteen patients were treated with topical 5-fluorouracil with occlusion 2–3 days per week for a mean of 15.7 weeks. Eleven patients achieved 90% clearing of treated lesions, compared with 6% for placebo.

Because of concern about absorption, topical 5-fluorouracil should only be used on isolated plaques. Irritation is the main side effect.

Sulfasalazine improves psoriasis. A double-blind analysis. Gupta AK, Ellis CN, Siegel MT, et al. Arch Dermatol 1990; 126: 487–93.

Fifty patients participated in this double-blind, placebo-controlled trial. Marked improvement was reported in 41% of the sulfasalazine-treated patients and moderate improvement in another 41%. Over one-quarter of the sulfasalazine-treated patients discontinued the study because of side effects of rash or nausea.

Mycophenolate mofetil (CellCept) for psoriasis: a two-center, prospective, open-label clinical trial. Zhou Y, Rosenthal D, Dutz J, et al. J Cutan Med Surg 2003; 7: 193–7.

Twenty-three patients were treated in an open-label study of mycophenolate mofetil 2–3 g daily for 12 weeks. At the end of 12 weeks PASI scores improved by 47%. Only 22% of patients did not have a significant response. Five patients developed nausea, and one developed transient leukopenia.

Mycophenolate mofetil is highly effective in a subset of psoriasis patients. Gastrointestinal side effects can be limited by administering the drug in four divided daily doses instead of the twice-daily dosing recommended in the package insert. An enteric-coated form is also helpful in reducing nausea.

Hydroxyurea in the management of therapy resistant psoriasis. Layton AM, Sheehan-Dare RA, Goodfield MJ, et al. *Br J Dermatol* 1989; 121: 647–53.

Eighty-five patients with psoriasis were treated with long-term hydroxycarbamide in doses of 0.5–1.5 g daily. Remissions occurred in 61%. Reversible bone marrow suppression occurred in 35% of patients. Four patients developed cutaneous side effects.

Azathioprine in psoriasis. Greaves MW, Dawber R. *Br Med J* 1970; 2: 237–8.

Azathioprine can be effective monotherapy for psoriasis, but its use is limited by bone marrow toxicity.

As with 6-thioguanine and hydroxycarbamide, the therapeutically effective dose of azathioprine is close to doses that are toxic to the bone marrow. With all three of these drugs, frequent blood counts are essential.

Systemic tacrolimus (FK 506) is effective for the treatment of psoriasis in a double-blind, placebo-controlled study. European FK 506 Multicentre Psoriasis Study Group. *Arch Dermatol* 1996; 132: 419–23.

Fifty patients with psoriasis were treated for 9 weeks in this double-blind, placebo-controlled study. Starting doses were 0.05 mg/kg daily and could be increased up to 0.15 mg/kg daily. Tacrolimus-treated patients had significantly greater improvements in PASI scores than those receiving placebo. Diarrhea, paresthesias, and insomnia were the most commonly reported side effects.

Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study: German Multicentre Study. Mrowietz U, Christophers E, Altmeyer P. *Br J Dermatol* 1998; 138: 456–60.

Of 101 patients who started this prospective study, 70 completed 4 months of treatment. There was an 80% reduction in PASI scores. Side effects consisted of lymphocytopenia, gastrointestinal complaints, and flushing.

Although not noted in this study, nephrotoxicity has been a recognized side effect of fumaric acid therapy.

Use of rifampin with penicillin and erythromycin in the treatment of psoriasis. Preliminary report. Rosenberg EW, Noah PW, Zanolli MD, et al. *J Am Acad Dermatol* 1986; 14: 761–4.

All nine patients with streptococcal-associated psoriasis responded to a 5-day course of rifampin (rifampicin) combined with 10 to 14 days of oral penicillin or erythromycin.

The use of oral antibiotics has been championed by Rosenberg and colleagues. Although supported by sound theories and numerous anecdotes, the use of antibiotics for psoriasis has not been supported by controlled clinical trials. Other infections have been linked to psoriasis flares, and other agents that have been used include oral nystatin and oral fluconazole; even tonsillectomy has been advocated.

Therapeutic trials with oral colchicine in psoriasis. Wahba A, Cohen H. *Acta Dermatol Venereol* 1980; 60: 515–20.

Twenty-two patients were treated in an open trial of colchicine 0.02 mg/kg daily for 2–4 months. Of the nine patients with thin papules and plaques, eight noted marked improvement or clearing, but there was little improvement in patients with thick plaques.

Cryotherapy for psoriasis. Nouri K, Chartier TK, Eaglstein WH T, et al. *Arch Dermatol* 1997; 133: 1608–9.

Target plaques of psoriasis were treated with cryotherapy, resulting in improvement. Local reactions, including pain and vesiculation, were the only side effects other than discoloration.

As with lasers, cryotherapy is only practical for isolated, localized plaques. Despite the Koebner phenomenon, psoriasis does not commonly occur in frozen plaques, but scarring or discoloration can occur.

Psoriasis of the scalp treated with Grenz rays or topical corticosteroid combined with Grenz rays. A comparative randomized trial. Lindelof B, Johannesson A. *Br J Dermatol* 1988; 119: 241–4.

Forty patients were treated with either Grenz rays or Grenz rays plus topical corticosteroids for scalp psoriasis. Grenz rays were administered at a dosage of 4 Gy at weekly intervals for six treatments; 84% of the Grenz ray-treated patients and 72% of the Grenz ray plus corticosteroid group healed. The addition of topical corticosteroids offered little benefit.

The association between X-ray therapy and squamous cell carcinomas, particularly in patients subsequently treated with PUVA, has led to less use of this valuable modality.

Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. Kaltwasser JP, Nash P, Gladman D, et al.; Treatment of Psoriatic Arthritis Study Group. *Arthritis Rheum* 2004; 50: 1939–50.

In this double-blind, placebo-controlled trial, 199 patients with psoriasis and psoriatic arthritis were treated.

Leflunomide proved to be effective for psoriatic arthritis but only modestly effective for psoriasis.

Golimumab, a human TNF-alpha antibody, administered every 4 weeks as a subcutaneous injection in psoriatic arthritis: clinical efficacy, radiographic, and safety findings through 1 year of the randomized, placebo-controlled, GO-REVEAL study. Kavanaugh A, van der Heijde D, McInnes I, et al. *Arthritis Rheum* 2012; 64: 2504–17.

Golimumab 50 mg or 100 mg administered subcutaneously every 4 weeks resulted in significant improvement in symptoms of psoriatic arthritis. Prevention of X-ray progression of disease was documented.

Although golimumab is approved for psoriatic arthritis, this TNF antagonist also benefits skin lesions of psoriasis.

Phase 2 trial of selective tyrosine kinase 2 inhibition in psoriasis. Papp K, Gordon K, Diamant T, et al. *N Engl J Med* 2018; 379: 1313–21.

In this placebo-controlled, dose-ranging trial, there was a dose-related increase in the percentage of patients achieving PASI 75. Of those treated with once daily oral BMS-986165, 75% achieved PASI 75. *Unlike other Janus kinase inhibitors tested for psoriasis, the safety profile of BMS-986165 in its phase 2 studies do not raise any warnings.*

Efficacy and safety of mirikizumab (LY3074828) in the treatment of moderate-to-severe plaque psoriasis: results from a randomized phase II study. Reich K, Rich P, Maari C, et al. *Br J Dermatol*. 2019; 181: 88–95.

In this blinded, dose-ranging study, subjects received injections of placebo or mirikizumab 30 mg, 100 mg, or 300 mg at weeks 0 and 8. There were dose-related response rates in PASI 90 at week 16 with 67% of the 300 mg group reaching that end point.

Like other anti-IL-23 antibodies, responses are likely to take longer, but infrequent injections may be required.

Bimekizumab in patients with active psoriatic arthritis: results from a 48-week, randomised, double-blind, placebo-controlled, dose-ranging phase 2b trial. Ritchlin CT, Kavanaugh A, Merola JF, et al. *Lancet* 2020; 395(10222): 427–40.

Subjects were treated with either placebo or four doses of bimekizumab administered subcutaneously every 4 weeks for 12 weeks. The primary end point, 50% improvement in American College of Rheumatology scores at week 12, was achieved by significantly more subjects in the bimekizumab arms, with particularly high response rates in those receiving 160 mg or more.

Blocking both IL-17A and IL-17F appears to be an effective approach for psoriatic arthritis. Bimekizumab-treated patients achieve not only the greatest improvements seen in psoriatic arthritis with any of the biologic therapies, but also achieve striking improvements in psoriasis.

A randomized phase 2a efficacy and safety trial of the topical Janus kinase inhibitor tofacitinib in the treatment of chronic plaque psoriasis. Ports WC, Khan S, Lan S, et al. *Br J Dermatol* 2013; 169: 137–45.

Topical tofacitinib 2% applied twice daily for 4 weeks was effective in one but not both vehicles tested.

Topical Janus kinase (JAK) inhibitors are under investigation for atopic dermatitis, vitiligo, and alopecia areata and will likely be available for those indications in the future. Once on the market, psoriasis is an obvious therapeutic target.

Phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of plaque psoriasis. Robbins K, Bissonnette R, Maeda-Chubachi T, et al. *J Am Acad Dermatol* 2019; 80(3): 714–21.

In this dose-ranging study, there was a dose-related achievement of clear or almost clear skin peaking at 65% of those treated with 1% tapinarof cream applied twice daily.

Tapinarof, a novel non-steroid with impressive efficacy, should be available soon for the treatment of psoriasis and atopic dermatitis.

ERYTHRODERMIC PSORIASIS

Erythrodermic psoriasis (EP) is characterized by marked erythema and scaling affecting the entire cutaneous surface. All the protective functions of the skin are lost, including protection against infection, temperature control, and prevention of fluid loss. Loss of nutrients through the skin leads to anemia and electrolyte imbalance. The most common precipitating cause of EP is the withdrawal of systemic corticosteroids; this should be avoided in patients with psoriasis. Excessive use of topical superpotent corticosteroids, phototherapy burns, and infections have also been implicated as causes of EP.

Patients may require hospitalization with bed rest, emollients, and application of *mild topical corticosteroids*. Because sepsis and shock are complications of EP, monitoring of temperature, blood pressure, urine output, and weight may be important, depending

on the severity of the condition. In males and in females not of childbearing potential, *oral retinoids* are among the safest treatments for EP, but are not as reliably effective as *biologics*, *ciclosporin*, or *methotrexate*. *Acitretin* can be started in doses of 25 mg daily and can be increased to 50 mg or higher. *Ciclosporin* in doses of 4–5 mg/kg daily results in rapid improvement. *Oral methotrexate* starting at 15 mg per week and gradually increasing up to 30 mg/week is effective within a few weeks. Because methotrexate is slower than IL-17 blockers, it is used less often for severe EP. Once erythema has cleared with topical or systemic agents, patients can occasionally be switched to phototherapy or PUVA or to other long-term therapies, including the biologics. Many of the available biologic agents, including *infliximab*, *adalimumab*, *etanercept*, *ustekinumab*, *ixekizumab*, *secukinumab*, *brodalumab*, and *IL-23 blockers like guselkumab* have been used to treat EP. *Infliximab* and *IL-17 blockers* are the fastest. When these agents either do not work or cannot be used, many of the third-line therapies listed for psoriasis are effective. For example, there are anecdotal reports of *mycophenolate mofetil*, *azathioprine*, and *hydroxyurea* working for EP. Combination therapy such as the *combination of methotrexate and ciclosporin* in low doses, or the combination of *methotrexate and infliximab*, can also be effective. There are also anecdotal reports of *carbamazepine* clearing EP.

First-Line Therapies

• Emollients	D
• Topical corticosteroids	D

Second-Line Therapies

• Ciclosporin	B
• Anti-IL-17 antibodies	D
• TNF blockers	D
• Ustekinumab	D
• Anti-IL-23 antibodies	E
• Retinoids	D
• Methotrexate	D

Third-Line Therapies

• Combination therapy	D
• Mycophenolate mofetil	E
• Hydroxycarbamide (hydroxyurea)	E
• Azathioprine	E
• Carbamazepine	E

Treatment of erythrodermic psoriasis: from the medical board of the National Psoriasis Foundation. Rosenbach M, Hsu S, Korman NJ, et al. *J Am Acad Dermatol* 2010; 62: 655–62.

Ciclosporin and infliximab are listed as the fastest agents for this condition, which often requires a rapid response. *New data also shows rapid efficacy of the anti-IL-17 antibodies, brodalumab, ixekizumab, and secukinumab.*

Use of short-course class 1 topical glucocorticoid under occlusion for the rapid control of erythrodermic psoriasis. Arbiser JL, Grossman K, Kaye E, et al. *Arch Dermatol* 1994; 130: 704–6.

EP will respond rapidly to oral corticosteroids or to superpotent corticosteroids with occlusion, but withdrawal of these agents often results in a more severe flare. Consequently, these treatments are avoided in patients with EP.

Management of erythrodermic psoriasis with low-dose cyclosporine. Studio Italiano Muticentrico nella Psoriasi (SIMPSON). *Dermatology* 1993; 187: 30–7.

Thirty-three patients with EP were treated with ciclosporin, starting with up to 5 mg/kg daily; 67% achieved complete remission in a median of 2–4 months, and another 27% noted substantial improvement.

Efficacy and safety of ixekizumab treatment for Japanese patients with moderate to severe plaque psoriasis, erythrodermic psoriasis and generalized pustular psoriasis: results from a 52-week, open-label, phase 3 study (UNCOVER-J). Saeki H, Nakagawa H, Nakajo K, et al. *J Dermatol.* 2017; 44(4): 355–62.

Six of eight EP patients and three of five generalized pustular psoriasis (GPP) patients achieved clear or almost clear skin at week 52. *Secukinumab and brodalumab, which work by similar mechanisms, will be effective for EP as well.*

Efficacy and safety of biologics in erythrodermic psoriasis: a multicentre, retrospective study. Viguier M, Pagés C, Aubin E, et al. *Br J Dermatol* 2012; 167: 417–23.

Twelve to 14 weeks after treatment, 75% reduction in BSA or PASI was achieved by 48% of patients treated with infliximab, 50% of those treated with adalimumab, and 40% of those treated with etanercept. *Certolizumab pegol is another highly effective TNF blocker. Of anti-TNF-α agents used for EP, in our experience infliximab is the fastest and most effective despite the data reported here.*

Erythrodermic psoriasis treated with ustekinumab: an Italian multicenter retrospective analysis. Pescitelli L, Dini V, Gisondi P, et al. *J Dermatol Sci* 2015; 78: 149–51.

Ustekinumab in approved doses (90 mg for patients ≥100 kg; 45 mg <100 kg subcutaneously at w.0, 4, and 16) was administered to 22 patients with EP. At week 4, 50% had achieved PASI 50; at week 16, two-thirds had achieved PASI 75; and at week 28, 86.3% had achieved PASI 75 and 68.2% had achieved PASI 90.

A case of erythrodermic psoriasis successfully treated with guselkumab. Megna M, Ruggiero A, Camela E, et al. *Dermatol Ther* 2020 Jan 30; e13238.

PASI 100 was achieved after 20 weeks. *Anti-IL-23 antibodies can be very helpful in the long-term management of EP, but their slow onset of efficacy limit their use for patients with severe disease.*

The treatment of psoriasis with etretinate and acitretin: a follow-up of actual use. Magis NL, Blummel JJ, Kerkhof PC, et al. *Eur J Dermatol* 2000; 10: 517–21.

In a retrospective review of 94 patients treated with retinoids, there were no serious side effects after 10 years of follow-up. The efficacy of retinoids for GPP and EP was stressed.

The efficacy of methotrexate in psoriasis – a review of 40 cases. Collins P, Rogers S. *Clin Exp Dermatol* 1992; 17: 257–60.

At the time of this publication, prior to the use of biologic therapies, methotrexate was considered the treatment of choice for EP and GPP.

Accidental success with carbamazepine for psoriatic erythroderma. Smith KJ, Skelton HG. *N Engl J Med* 1996; 335: 1999–2000.

A patient with HIV infection and EP was inadvertently treated with carbamazepine instead of etretinate. The patient's erythroderma cleared.

Carbamazepine in doses of 200–400mg daily has been reported to clear EP in some, but not all, patients. When all else fails we have seen this work.

GENERALIZED PUSTULAR PSORIASIS

Management of GPP begins with the *removal of precipitating causes*. Lithium, antimalarials, diltiazem, propranolol, and irritating topical therapy with tar have all been implicated, but the most common cause is the withdrawal of systemic corticosteroids. As in EP, all protective functions of the skin are compromised, and patients are susceptible to infection, fluid loss, electrolyte imbalance, loss of nutrients through the skin, and loss of temperature control. Supportive care and treatment of infection are mandatory. *Oral acitretin* results in rapid improvement. In women of childbearing potential *isotretinoin* may be preferred because the period of teratogenicity of this drug is shorter than that of acitretin. *Ciclosporin, infliximab, adalimumab, IL-17 blockers, IL-23 blockers, and methotrexate* are also highly effective for this life-threatening condition. TNF blockers have been used to treat GPP, but caution should be exercised as there have been rare cases of GPP caused by their use. *Hydroxycarbamide (hydroxyurea), 6-thioguanine, mycophenolate mofetil, azathioprine, dapsone, and colchicine* have also been used in isolated patients. Because a rapid response is desirable for patients who are seriously ill, IL-17 blockers are among our fastest therapies and should be considered. *Anti-IL-36 antibodies* have been very effective and very fast in early clinical trials.

First-Line Therapies

• Topical corticosteroids	D
• Retinoids	B
• Ciclosporin	D
• Anti-IL-17 antibodies	C
• TNF blockers	C
• Ustekinumab	E
• Methotrexate	B

Second-Line Therapies

• Anti-IL-23 antibodies	E
• 6-Thioguanine	E
• Hydroxycarbamide (hydroxyurea)	E
• Mycophenolate mofetil	E
• Azathioprine	E

Third-Line Therapy

• Colchicine	E

Isotretinoin vs. etretinate therapy in generalized pustular and chronic psoriasis. Moy RL, Kingston TP, Lowe NJ. *Arch Dermatol* 1985; 121: 1297–301.

Although isotretinoin was less effective than etretinate for plaque psoriasis, 10 of 11 patients with GPP responded.

Many consider acitretin or isotretinoin to be the treatment of choice for patients with GPP. Apart from the shorter period of teratogenicity of isotretinoin, it also causes less hair loss than acitretin.

Generalized pustular psoriasis (von Zumbusch) responding to cyclosporine A. Meinardi MM, Westerhof W, Bos JD. Br J Dermatol 1987; 116: 269–70.

This is one of numerous case reports documenting the dramatic response of GPP to ciclosporin.

Ciclosporin in doses of 4–5 mg/kg daily is usually effective in the treatment of GPP.

Efficacy and safety of secukinumab in patients with generalized pustular psoriasis: a 52-week analysis from phase III open-label multicenter Japanese study. Imafuku S, Honma M, Okubo Y, et al. J Dermatol 2016; 43: 1011–7.

Secukinumab 150 mg was administered subcutaneously weekly for 5 weeks followed by 150 mg every 4 weeks in 12 patients with GPP. Two patients increased their dosage to 300 mg. Treatment success at week 16 was achieved by 10 of 12 patients. *The rapid efficacy of anti-IL-17 antibodies makes them ideal for the treatment of GPP. Brodalumab and ixekizumab are also rapidly effective.*

Adalimumab treatment in Japanese patients with generalized pustular psoriasis: results of an open-label phase 3 study. Morita A, Yamazaki F, Matsuyama T, et al. J Dermatol 2018; 45: 1371–80.

In an open-label 52-week study, adalimumab starting with 80 mg subcutaneously followed by 40 mg every other week resulted in seven of 10 patients achieving clinical responses at week 16, including three patients who had escalated dosing to 80 mg every other week. At week 52, five patients achieved clinical response. *TNF blockers including etanercept, adalimumab, certolizumab pegol, and infliximab have been used successfully to treat GPP. Because this condition is often severe, speed of response is important. Infliximab is the most rapidly effective, followed by both adalimumab and certolizumab. Etanercept is the subcutaneous formulation that has been used longest and therefore has many case reports of its use in GPP.*

Psoriasis and palmoplantar pustulosis associated with tumor necrosis factor- α inhibitors: the Mayo Clinic experience, 1998 to 2010. Shmidt E, Wetter DA, Ferguson SB, et al. J Am Acad Dermatol 2012; 67(5): e179–85.

Fifty-six patients with Crohn disease or rheumatoid arthritis developed psoriasis following treatment with TNF blockers. Palmoplantar pustulosis occurred in 25 and GPP in seven. *Numerous reports of psoriasis, and specifically pustular psoriasis, developing after treatment with TNF- α blockers have emerged. Nevertheless, these agents can be highly useful for the treatment of GPP.*

Ustekinumab: effective in a patient with severe recalcitrant generalized pustular psoriasis. Daudén E, Santiago-et-Sánchez-Mateos D, Sotomayor-López E, et al. Br J Dermatol 2010; 163: 1346–7.

There have been paradoxical cases of pustular psoriasis induced by ustekinumab.

Guselkumab, a human interleukin-23 monoclonal antibody in Japanese patients with generalized pustular psoriasis and erythrodermic psoriasis: efficacy and safety analyses of a 52-week, phase 3, multicenter, open-label study. Sano S, Kubo H, Morishima H, et al. J Dermatol 2018; 45(5): 529–39.

Subcutaneous guselkumab 50 mg was administered to 10 patients with GPP and 11 patients with EP at weeks 0 and 4 and every 8 weeks thereafter. At week 16, at least minimal improvement was achieved by 77.8% (7/9) of GPP patients and 90.9% (10/11) of EP patients.

Systemic corticosteroids and folic acid antagonists in the treatment of generalized pustular psoriasis. Evaluation and prognosis based on the study of 104 cases. Ryan TJ, Baker H. Br J Dermatol 1969; 81: 134–45.

Despite the short-term benefit of systemic corticosteroids for GPP, once the dose is reduced, rebound flares occur. In this study a significant proportion of patients treated with systemic corticosteroids died.

Methotrexate remains a highly effective modality for the treatment of GPP. Doses beginning at 15 mg per week (after an initial test dose) are used.

Colchicine in generalized pustular psoriasis: clinical response and antibody-dependent cytotoxicity by monocytes and neutrophils. Zachariae H, Kragballe K, Herlin T. Arch Dermatol Res 1982; 274: 327–33.

Three of four patients with GPP cleared within 2 weeks of starting oral colchicine.

Colchicine 0.6 mg twice daily can be effective for GPP. The dose can be increased by one pill daily, but side effects of diarrhea frequently intervene.

Psychogenic excoriation

Vidhatha Reddy, Quinn Thibodeaux, John Y.M. Koo



Psychogenic excoriation is a psychodermatologic condition in which patients participate in destructive scratching and picking of normal skin or skin with minor surface irregularities. These behaviors may cause self-inflicted ulcers, abscesses, or scars that can ultimately become disfiguring and significantly impair quality of life. This condition, which predominantly affects women, is also known as skin-picking disorder or excoriation disorder. In the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), excoriation disorder is characterized as one of the obsessive-compulsive and related disorders. Although sometimes referred to as neurotic excoriation, the authors do not prefer this term because the underlying psychopathology may not be neurosis and can range from depression to obsessive-compulsive disease to even psychosis. The etiology of psychogenic excoriation in any particular patient cannot be identified without a thorough evaluation of his or her mental status. Additionally, treatment requires a multidisciplinary approach and must be individually tailored in each case. The authors recommend the following approach to treating psychogenic excoriation:

1. First, evaluate beyond the skin to clearly ascertain the nature of the underlying psychopathology. Psychogenic excoriation may be associated with underlying depression, anxiety, obsessive-compulsive disorder, psychosis, or borderline personality disorder. The condition may also be precipitated by emotional stress.
2. Second, before diagnosing a patient with psychogenic excoriation, it is important to rule out other psychodermatologic disorders. For example, dermatitis artefacta is often associated with damage done with sharp objects or other elaborate means rather than fingernails alone, including lit cigarette butts or feces injected into the skin. It is also characterized by secrecy regarding the etiology of lesions, oddly indifferent affect despite severe skin damage, and demanding or manipulative personality.
3. Finally, the appropriate treatment strategy for psychogenic excoriation should be determined based on the nature of the underlying psychopathology.

MANAGEMENT STRATEGY

Although psychogenic excoriation is primarily a psychiatric disorder, patients usually present first to a dermatologist rather than seeking assistance from a psychiatric professional. In general, concurrent psychotherapy and psychopharmacological treatment is recommended.

If depression or anxiety is the underlying psychopathology, antidepressants and anxiolytics are considered first-line treatment. Selective serotonin reuptake inhibitors (SSRIs) have been shown to be effective in patients with psychogenic excoriation. The author JK has also found success using the tricyclic antidepressant doxepin. Although there are no clinical trials demonstrating its efficacy in this condition, doxepin is often useful due to its combined antidepressant and antihistaminic/antipruritic activity, which may be critical in disrupting the itch-scratch cycle. Doxepin is typically started at 10 mg nightly, with a gradual increase in dose of 10 mg every 2–4 weeks. A dose of 100 mg every evening is the usual effective antidepressant dose and may be particularly effective if the underlying psychopathology is major depression. For anxiety, lower doses typically suffice. If the patient requires higher dosages, a maximum of 300 mg daily may be used per US Food and Drug Administration (FDA) guidelines following careful titration, provided there are no side effects. Because doxepin can prolong the QT interval, a screening electrocardiogram (ECG) is recommended for patients over age 55 or any patient with a past history of cardiac dysrhythmia. Sedation, syncope, seizures, weight gain, and orthostatic hypotension are other potential side effects. Of note, SSRIs have better safety profiles than doxepin, as they are less associated with sedation and cardiac conduction abnormalities. However, SSRIs do not provide the same antipruritic/antihistaminergic as doxepin, and some, such as fluoxetine, may increase anxiety in patients at initiation of therapy.

A recent randomized, placebo-controlled, double-blinded trial of the glutamatergic agent *N*-acetylcysteine (NAC) dosed at 1200–3000 mg/day found significant improvement in skin picking when compared with placebo. Other tricyclic antidepressants, such as clomipramine and amitriptyline, and various benzodiazepines are third-line therapies that should only be considered if the patient does not respond to more conventional treatments or cannot tolerate the side effects.

For treatment of underlying psychosis, antipsychotics can be effective. For example, pimozide and risperidone may have a role in rare cases in which patients present with psychogenic excoriations due to false ideations. These include trichophobia, a delusion in which patients believe that they must dig out something from the skin that surrounds hair roots in order for their hair to grow normally.

When borderline personality is the underlying psychopathology, psychotherapy is recommended. Psychotherapy and cognitive behavioral techniques, including habit-reversal therapy, aversion therapy, and acceptance and commitment therapy, have been reported to be effective for this disorder.

Other treatment options may further enhance systemic pharmacologic treatments and psychotherapy. Treating associated infection and pruritus with antibiotics and antihistamines (oral or topical), respectively, may provide additional benefit. Narrowband ultraviolet (NB-UVB) phototherapy may also be helpful for pruritus.

Specific Investigation

- Close follow-up with a primary care physician or psychiatrist is recommended because of the high incidence of comorbid psychiatric conditions

Skin-picking disorder: a guide to diagnosis and management. Jafferany M, Patel A. *CNS Drugs* 2019; 33: 337–46.

A helpful overview of excoriation disorder management, including various types of cognitive behavioral therapy techniques and pharmacological options.

Excoriation (skin-picking) disorder: a systematic review of treatment options. Lochner C, Roos A, Stein DJ. *Neuropsychiatr Dis Treat* 2017; 13: 1867–72.

A useful guide that summarizes the latest studies evaluating treatment options for psychogenic excoriation.

Systematic review of pharmacological and behavioral treatments for skin picking disorder. Schumer MC, Bartley CA, Bloch MH. *J Clin Psychopharmacol* 2016; 36(2): 147–52.

Systematic review and meta-analysis including 11 studies that demonstrate superior efficacy of behavioral treatments, including habit-reversal therapy and cognitive behavioral therapy, when compared to both pharmacotherapy and placebo.

The reconstructive challenges and approach to patients with excoriation disorder. Galdyn IA, Chidester J, Martin MC. *J Craniofac Sur* 2015; 26: 824–5.

Treating patients with psychogenic excoriation requires a multidisciplinary approach. Before any surgical repair or treatment can be rendered, the patient must be stabilized from a psychiatric standpoint.

The psychiatric profile of patients with psychogenic excoriations. Mutasim DF, Adams BB. *J Am Acad Dermatol* 2009; 61: 611–3.

In a study of 50 patients with psychogenic excoriations compared with controls, the most significantly associated psychiatric comorbidities are depression and bipolar disorder.

Characteristics of 34 adults with psychogenic excoriation. Arnold LM, McElroy SL, Mutasim DF, et al. *J Clin Psychiatry* 1998; 59: 509–15.

Patients with psychogenic excoriations have a high prevalence of concurrent psychiatric illnesses such as mood disorders (68%), anxiety disorders (41%), somatoform disorders (21%), substance abuse (12%), and eating disorders (12%).

Dermatology and conditions related to obsessive-compulsive disorder. Stein DJ, Hollander E. *J Am Acad Dermatol* 1992; 26: 237–42.

Patients with psychogenic excoriations often have obsessive-compulsive symptoms and may therefore respond to specific therapies aimed at this type of disorder.

First-Line Therapies

• Fluoxetine	A
• N-Acetylcysteine	A
• Sertraline	B
• Cognitive behavioral therapy (including habit-reversal therapy)	B
• Doxepin	E

A double-blind trial of fluoxetine in pathologic skin picking. Simeon D, Stein DJ, Gross S, et al. *J Clin Psychiatry* 1997; 58: 341–7.

Fluoxetine was started at 20 mg daily and increased by 20 mg/week up to a maximum of 80 mg daily. Improvements in the treatment arm were statistically significant (based on an intent-to-treat analysis) at 6 weeks, with an average dose of 55 mg daily.

Fluoxetine in pathologic skin-picking: open-label and double-blind results. Bloch MR, Elliott M, Thompson H, et al. *Psychosomatics* 2001; 42: 314–9.

In the open-label phase of this study, 53% of participants responded to fluoxetine (maximum dose 60 mg/day).

N-Acetylcysteine in the treatment of excoriation disorder: a randomized clinical trial. Grant JE, Chamberlain SR, Redden SA, et al. *JAMA Psychiatry* 2016; 73(5): 490–6.

A randomized, placebo-controlled trial in 66 patients with excoriation disorder that compared N-acetylcysteine (NAC) to placebo. Treatment with NAC resulted in significant reductions in skin-picking symptoms in 46.9% of subjects (compared with 19.0% in the placebo group) and was well-tolerated.

Sertraline in the treatment of neurotic excoriations and related disorders. Kalivas J, Kalivas L, Gilman D, et al. *Arch Dermatol* 1996; 132: 589–90.

Sertraline was started at 25–50 mg daily and titrated upward to 100–200 mg daily as necessary, with improvements seen in 19 of 28 patients (68%) at an average of 4 weeks.

The effects of brief cognitive-behaviour therapy for pathological skin picking: a randomized comparison to wait-list control. Schuck K, Keijsers GP, Rinck M. *Behav Res Ther* 2011; 49(1): 11–7.

Four-week randomized controlled trial of 34 subjects who received either four sessions of cognitive behavioral therapy or a waiting list. At 2 months' follow-up, skin-picking severity, psychosocial impact of skin picking, and dysfunctional cognitions related to skin picking were significantly reduced in the treatment group.

Habit reversal as a treatment for chronic skin picking: a pilot investigation. Teng EJ, Woods DW, Twohig MP. *Behav Modif* 2006; 30(4): 411–22.

Subjects (n=19) with excoriation disorder were randomized to habit-reversal therapy vs. waiting list, with treated patients demonstrating a decrease in skin-picking at posttreatment and 3 months' follow-up compared with waiting-list patients.

Acne excoriée: a case report of treatment using habit reversal. Kent A, Drummond LM. *Clin Exp Dermatol* 1989; 14: 163–4.

This is a case report on the success of habit reversal, a cognitive behavioral technique, for psychogenic excoriations.

The behavioral treatment of neurodermatitis through habit reversal. Rosenbaum MS, Ayllon J. *Behav Res Ther* 1981; 19: 313–8.

This article reports a response to habit-reversal therapy for neurodermatitis in three patients.

Psychopharmacology for dermatologic patients. Koo J, Gambla C. *Dermatol Clin* 1996; 14: 509–24.

Describes in further detail the use of doxepin in psychogenic excoriations.

Improvement of chronic neurotic excoriations with oral doxepin therapy. Harris BA, Sherertz EF, Flowers FP. *Int J Dermatol* 1987; 26: 541–3.

Case report of two patients who responded to doxepin 30 mg and 75 mg daily.

Second-Line Therapies

• Escitalopram	C
• Fluvoxamine	C
• Psychotherapy	D
• Paroxetine	E

Open-label escitalopram treatment for pathological skin picking. Keuthen NJ, Jameson M, Loh R, et al. *Int Clin Psychopharmacol* 2007; 22(5): 268–74.

In this open-label trial ($n=29$) of escitalopram dosed up to 30 mg/day, 44.7% of subjects were full responders and 27.6% were partial responders in decreasing pathologic skin picking after 18 weeks.

Use of escitalopram in psychogenic excoriation. Pukadan D, Antony J, Mohandas E, et al. *Aust NZ J Psychiatry* 2008; 42: 435–6.

Escitalopram was administered at 10 mg/day to two patients: a 63-year-old woman with a 1-month history of diffuse pruritus and excessive excoriation, as well as major depressive disorder; and a 24-year-old man with a 10-year history of repeated nail biting and features of major depressive disorder. In both patients, scratching abated within 2 weeks.

An open clinical trial of fluvoxamine treatment of psychogenic excoriation. Arnold LM, Mutasim DF, Dwight MM, et al. *J Clin Psychopharmacol* 1999; 19: 15–8.

Fluvoxamine was started at 25–50 mg daily and increased by up to 50 mg/week to a maximum of 300 mg daily for 12 weeks. Although all 14 participants demonstrated significant improvement in six of eight self-reported scales, the seven subjects who completed the study (50%) had improvement in only two of eight self-reported scales.

Psychotherapeutic strategy and neurotic excoriations. Fruensgaard K. *Int J Dermatol* 1991; 30: 198–203.

This article reports a positive impact of goal-directed psychotherapy in 22 patients followed over a period of approximately 5 years for psychogenic excoriations.

Paroxetine in a case of psychogenic pruritus and neurotic excoriations. Biondi M, Arcangeli T, Petrucci RM. *Psychosom* 2000; 69: 165–6.

This is one case report demonstrating success with the SSRI paroxetine, which was thought to work secondary to its anticomulsive activity.

Third-Line Therapies

• Narrowband ultraviolet light	C
• Olanzapine	D
• Venlafaxine	E
• Clomipramine	E
• Amitriptyline	E
• Pimozide	E
• Aripiprazole	E
• Naltrexone	E
• Benzodiazepines	E
• Hypnosis	E

Narrow-band ultraviolet B as a potential alternative treatment for resistant psychogenic excoriation: an open-label study. Ozden MG, Aydin F, Senturk N, et al. *Photodermatol Photoimmunol Photomed* 2010; 26: 162–4.

Prospective study assessing the effectiveness of phototherapy for psychogenic excoriation. Of the seven patients who completed the study and received NB-UVB, 50% or more reduction in clinical improvement scale scores was found in 71.4% (five of seven) of patients. The only side effects were xerosis and moderate erythema.

Efficacy of olanzapine in the treatment of psychogenic excoriation. Blanch J, Grimalt F, Massana G, et al. *Br J Dermatol* 2004; 151: 714–6.

This article describes a series of six patients with psychogenic excoriation who improved dramatically after treatment with olanzapine 2.5–10 mg daily.

Aripiprazole augmentation of venlafaxine in the treatment of psychogenic excoriation. Carter WG 3rd, Shillcutt SD. *J Clin Psychiatry* 2006; 67: 1311.

Case report that discusses the success of aripiprazole and venlafaxine in a 50-year-old woman with psychogenic excoriation, major depressive disorder, and generalized anxiety disorder who had been unresponsive to a serotonin–norepinephrine reuptake inhibitor alone.

Neurotic excoriations: a review and some new perspectives. Gupta MA, Gupta AK, Haberman HF. *Compr Psychiatry* 1986; 27: 381–6.

A case report of successful treatment using clomipramine 50 mg every evening for 6 months.

Neurotic excoriations: a personality evaluation. Fisher BK, Pearce KI. *Cutis* 1974; 14: 251–4.

Successful treatment with amitriptyline 50–75 mg daily was reported.

Clinical experience with pimozide: emphasis on its use in postherpetic neuralgia. Duke EE. *J Am Acad Dermatol* 1983; 8: 845–50.

This case report primarily demonstrates the efficacy of pimozide (2 mg two or three times daily) in the treatment of postherpetic neuralgia (eight patients) and psychogenic excoriations (two patients).

The treatment of psychogenic excoriation and obsessive compulsive disorder using aripiprazole and fluoxetine. Curtis AR, Richards RW. *Ann Clin Psychiatry* 2007; 19: 199–200.

Case report on the success of aripiprazole, a second-generation antipsychotic, and fluoxetine in an 18-year-old woman with psychogenic excoriations and obsessive-compulsive disorder.

Naltrexone for neurotic excoriations. Smith KC, Pittelkow MR. *J Am Acad Dermatol* 1989; 20: 860–1.

This article discusses the reported efficacy of naltrexone for psychogenic excoriation.

Pyoderma gangrenosum

Sheevam Shah, Stanislav N. Tolkachjov



Pyoderma gangrenosum (PG) is a neutrophilic dermatosis presenting as pustules enlarging and ulcerating with violaceous, necrotic, and undermined borders healing with cribriform scarring. Multiple subtypes exist involving any skin location. PG has several associations (Table 212.1) that should be considered in the workup.

MANAGEMENT STRATEGY

Goals of PG treatment include pain control, superinfection prevention, and facilitating healing. Pain is managed with oral acetaminophen, non-steroidal antiinflammatory drugs, opioids, gabapentin, pregabalin, and nortriptyline. Medical and surgical management should be combined with maintaining a moist wound environment with foam or hydrocolloid dressings. Consider conservative debridement, keeping in mind the risk of pathergy.

No treatment is consistently effective for PG. Conservative therapy with wound care and *topical corticosteroids or calcineurin*

Table 212.1 Systemic associations of PG

Associated conditions (most to least common)

Hematologic disease (leukemia, lymphoma, myelodysplasia, myelofibrosis, monoclonal gammopathy of undetermined significance, polycythemia vera, IgA gammopathy)
IBD (ulcerative colitis, Crohn disease)
Other inflammatory diseases and syndromes (rheumatoid arthritis; Sjögren syndrome; systemic lupus erythematosus; granulomatosis with polyangiitis; pyogenic arthritis, hidradenitis suppurativa [PASH]; pyogenic arthritis, pyoderma gangrenosum, acne [PAPA])
Solid organ malignancy
Infectious (hepatitis B/C, human immunodeficiency virus)
Hidradenitis suppurativa
Pregnancy
Leukocyte adherence deficiency
Endocrine disorders (i.e., metabolic syndrome)

inhibitors are reasonable first-line options for small areas of slowly progressive PG. However, if PG is rapidly progressive, systemic therapies like *systemic corticosteroids (sCS)* or *ciclosporin* should be initiated early.

sCS are often first-line therapies in conjunction with topical care. Response to sCS is also a diagnostic feature of PG. If PG is associated with a systemic disorder, treating the underlying disorder may improve PG. Suggested investigations for working up PG are listed in Specific Investigations. When active inflammation is evident, therapy should be continued; however, if inflammation subsides, immunomodulatory therapy is discontinued while wound care continues. This is often called 'Gulliver Sign' (Landis ET, Taheri A, Jorizzo JL. Gulliver's sign: a recognizable transition from inflammatory to healing stages of pyoderma gangrenosum. *J Dermatolog Treat.* 2015;26(2):171–172).

Specific Investigations

- Hematology (complete blood count with differential and peripheral blood smear)
- Serum protein electrophoresis with immunofixation
- Rheumatoid factor, antinuclear antibody, extractable nuclear antigen, and other potential connective tissue disease markers
- Antineutrophil cytoplasmic antibodies and proteinase 3/myeloperoxidase
- Gastrointestinal workup for inflammatory bowel disease
- Age- or risk-appropriate cancer screenings including potential imaging
- Infectious (including hepatitis panel, HIV) and immunodeficiency workup
- Consider genetic testing in a pediatric patient with severe PG or PG with hidradenitis suppurativa, severe acne (acne conglobata), pyogenic arthritis, or other signs of an autoinflammatory syndrome
- Consider drug-induced PG including medications and illicit drugs such as cocaine
- Consider pregnancy testing in a female of childbearing potential

First-Line Therapies

• Topical tacrolimus	C
• Topical corticosteroids	C
• Oral dapsone	D
• Intralesional corticosteroids	D
• Tetracycline class antibiotics	D
• Nicotine	D
• Topical pimecrolimus	E
• Sodium cromoglycate	D
• Sulfasalazine	D
• Targeted antibiotic therapy	E

Efficacy of topical calcineurin inhibitors in pyoderma gangrenosum. Abdul-Fattah B, Al-Murieh M, Huang CZ. *Dermatol Ther* 2018; 31(5): e12697.

Pyoderma gangrenosum successfully treated with topical tacrolimus. Napolitano M, Megna M, Patrì A, et al. *G Ital Dermatol Venereol* 2019; 154(3): 361–3.

Case report of female with refractory Crohn disease and parastomal PG with PG responding to topical tacrolimus 0.1% ointment BID.

Caution: a case of systemic absorption and acute nephrotoxicity has been reported in a patient who applied 60 g of tacrolimus ointment (i.e., presumably 60 g of 0.1% ointment) daily to PG.

Pyoderma gangrenosum: a rare cause of cutaneous ulceration and one easily misdiagnosed. Abdelrahman W, Walsh MY, Hoey SE, et al. Case Rep Pediatr 2016; 2016: 5971706.

Dramatic improvement of pediatric PG with clobetasol ointment within 24 hours.

Beclomethasone inhaler used to treat pyoderma gangrenosum. Chriba M, Skellett AM, Levell NJ. Clin Exp Dermatol 2010; 35: 337–8.

A case of peristomal PG healed over 4 weeks using beclomethasone dipropionate 200 mcg, four puffs daily.

Efficacy of systemic dapsone treatment for pyoderma gangrenosum: a retrospective review. Din RS, Tsiaras WG, Li DG, et al. J Drugs Dermatol 2018; 17(10): 1058–60.

The authors reviewed 27 patients with PG treated with dapsone with the most common peak dosage at 50 mg or 100 mg daily. The average time to initial treatment response was 5.3 weeks. The average duration of treatment was 14.3 months.

Low cost and familiarity of dermatologists with dapsone probably contribute to its popularity. Dapsone is often used in combination with other modalities, especially sCS.

Pediatric pyoderma gangrenosum: a retrospective review of clinical features, etiologic associations, and treatment. Schoch JJ, Tolkachjov SN, Cappel JA, et al. Pediatr Dermatol 2017; 34(1): 39–45.

Retrospective review of 13 children with PG. Sulfasalazine or related 5-aminosalicylate drugs were used in 46% of patients, four of whom had complete response (CR) while two had a partial response.

Triamcinolone and pyoderma gangrenosum. Gardner LW, Acker DW. Arch Dermatol 1972; 106: 599–600.

A case of multifocal PG responded to intralesional triamcinolone acetonide 10 mg/mL. Doses ranging from 40 mg to 200 mg were injected at any one time.

The successful use of minocycline in pyoderma gangrenosum – a report of seven cases and review of the literature. Berth-Jones J, Tan SV, Graham-Brown RAC, et al. J Dermatol Treat 1989; 1: 23–5.

Seven cases improved on minocycline dosed at 100 mg BID or 200 mg BID.

Doxycycline and dapsone in chronic pyoderma gangrenosum: revisiting the old therapies. Garg S, Arora D, Singh K, et al. Clin Dermatol Rev 2018; 2: 41–2.

Case report of PG treated with dapsone 100 mg daily and doxycycline 100 mg BID with complete healing.

Successful treatment of pyoderma gangrenosum with topical 0.5% nicotine cream. Patel GK, Rhodes JR, Evans B, et al. J Dermatol Treat 2004; 15: 122–5.

Two cases responded to nicotine in Cetomacrogol cream.

Successful treatment of severe pyoderma gangrenosum with pimecrolimus cream 1%. Bellini V, Simonetti S, Lisi P. J Eur Acad Dermatol Venereol 2008; 22: 113–5.

A patient demonstrated clearance of PG within 8 weeks of using pimecrolimus cream BID.

The treatment of pyoderma gangrenosum with sodium cromoglycate. De Cock KM, Thorne MG. Br J Dermatol 1980; 102: 231–3.

Two cases responded to sodium cromoglycate aqueous solution (2% weight/volume Rynacrom nasal spray).

Safe treatment. Solutions have been applied to lesions in concentrations from 1% to 4%. The solution can be sprayed onto the ulcer or applied on gauze or under occlusion with a hydrocolloid dressing. This drug may act by inhibiting neutrophil migration or cytotoxicity.

Remission of refractory pyoderma gangrenosum, severe acne, and hidradenitis suppurativa (PASH) syndrome using targeted antibiotic therapy in 4 patients. Join-Lambert O, Duchatelet S, Delage M, et al. J Am Acad Dermatol 2015; 73(5 Suppl 1): S66–9.

Four cases of PASH treated with intravenous ceftriaxone and oral metronidazole or intravenous ertapenem for 3–6 weeks, followed by oral therapy combining 2–3 antibiotics (rifampin, moxifloxacin, metronidazole, amoxicillin, and/or linezolid) given in 4–6-week cycles.

Second-Line Therapies*

- Ciclosporin B
- Systemic corticosteroids B

*If severe or rapidly progressing, can consider these as first-line therapies.

Comparison of the two most commonly used treatments for pyoderma gangrenosum: results of the STOP GAP randomized controlled trial. Ormerod AD, Thomas KS, Craig FE, et al. BMJ 2015; 350: h2956.

In this study with 112 randomized patients, prednisolone 0.75 mg/kg/day was compared with ciclosporin 4 mg/kg/day to a maximum dose of 75 and 400 mg/day, respectively. The treatments did not differ across a range of objective and patient-reported outcomes. At 6 months, 47% of ulcers healed in each group. Infections were more common serious adverse events in the group receiving prednisolone.

Third-Line Therapies

- Infliximab A
- Other TNF- α antagonists C
- Alkylating agents (cyclophosphamide, chlorambucil) D
- Plasmapheresis (plasma exchange) E
- Leukocytapheresis D
- Intravenous immunoglobulin (IVIG) C
- Intralesional ciclosporin E
- Tacrolimus (FK506) D
- Azathioprine or mercaptopurine D
- Colchicine D
- Thalidomide D
- Potassium iodide E
- Topical nitrogen mustard (mechlorethamine) E
- Mycophenolate mofetil D
- GM-CSF (also reported to cause PG) E
- Methotrexate E

• Topical platelet-derived growth factor	E
• Platelet-rich plasma	E
• Platelet-rich fibrin	E
• Recombinant human epidermal growth factor	E
• Clofazimine	D
• Hyperbaric oxygen	D
• Isotretinoin	E
• Anakinra	D
• Ustekinumab	E
• Imiquimod	E
• Visilizumab	E
• Topical phenytoin	D
• Surgical debridement, closure, graft, or flap	E
• Cladribine	E
• Human amnion/chorion membrane	E
• Canakinumab	E
• Becaplermin	E
• Tocilizumab	E
• Ledipasvir/sofosbuvir	E
• Topical timolol	E
• Er:YAG laser	E
• Bortezomib	E
• 5-Aminosalicylic acid	E
• Apremilast	E
• Medical cannabis	E
• Etoposide	E
• Decitabine	E
• Janus kinase (JAK) inhibitors (ruxolitinib, tofacitinib)	D
• Cryopreserved human placental membrane grafts	E
• Topical dapsone	E
• Keratin gel	E
• Vacuum seal + oxygen loaded fluid	E
• Tildrakizumab	E
• Activated protein C (APC)	E

Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. Brooklyn TN, Dunnill MG, Shetty A, et al. Gut 2006; 55: 505–9.

Improvement of pyoderma gangrenosum and psoriasis associated with Crohn's disease with anti-tumor necrosis factor alpha monoclonal antibody. Tan MH, Gordon M, Lebwohl O, et al. Arch Dermatol 2001; 137: 930–3.

Numerous case reports further established response to infliximab.

Treatment of pyoderma gangrenosum with etanercept. McGowan JW 4th, Johnson CA, Lynn A. J Drugs Dermatol 2004; 3: 441–4.

The first of several cases reported to respond to etanercept 25–50 mg twice weekly.

Adalimumab for treatment of pyoderma gangrenosum. Pomerantz RG, Husni ME, Mody E, et al. Br J Dermatol 2007; 157: 1274–5.

Improvement occurred in a case that failed etanercept.

Conventional dosing regimens: 40–80 mg every 2 weeks with and without an initial loading dose of 80 mg.

Pyoderma gangrenosum successfully treated with golimumab: case report and review of the literature. Diotallevi F, Campanati A, Radi G, et al. Dermatol Ther 2019; 32(4): e12928.

Case of ulcerative rectocolitis and PG treated with golimumab, improving both.

Pyoderma gangrenosum. Response to cyclophosphamide therapy. Newell LM, Malkinson FD. Arch Dermatol 1983; 119: 495–7.

A refractory case of PG responded to cyclophosphamide 150 mg daily.

Intravenous cyclophosphamide pulses in the treatment of pyoderma gangrenosum associated with rheumatoid arthritis. Report of 2 cases and review of the literature. Zonana-Nacach A, Jimenez-Balderas FJ, Martinez-Osuna P, et al. J Rheumatol 1994; 21: 1352–6.

Two patients improved on pulsed intravenous cyclophosphamide at doses of 500 mg/m² combined with oral corticosteroid. In both cases, CR was subsequently maintained using oral cyclophosphamide 100 mg daily.

Chlorambucil is an effective corticosteroid-sparing agent for recalcitrant pyoderma gangrenosum. Burruss JB, Farmer ER, Callen JP. J Am Acad Dermatol 1996; 35: 720–4.

Chlorambucil, 2–4 mg daily, was successfully used in six cases, both alone and in combination with sCS.

Pyoderma gangrenosum – response to topical nitrogen mustard. Tsele E, Yu RCH, Chu AC. Clin Exp Dermatol 1992; 17: 437–40.

The application of nitrogen mustard 20 mg/100 mL in aqueous solution on gauze swabs proved helpful in a treatment-resistant case associated with immunoglobulin A (IgA) paraproteinemia.

Leukocytapheresis treatment for pyoderma gangrenosum. Fujimoto E, Fujimoto N, Kuroda K, et al. Br J Dermatol 2004; 151: 1090–2.

Efficacy of granulocyte and monocyte adsorption apheresis for three cases of refractory pyoderma gangrenosum. Seishima M, Mizutani Y, Shibuya Y, et al. Ther Apher Dial 2007; 11: 177–82.

Three patients improved after weekly treatments for 10 or 11 weeks.

Intravenous immunoglobulin as adjunct therapy for refractory pyoderma gangrenosum: systematic review of cases and case series. Song H, Lahood N, Mostaghimi A. Br J Dermatol 2018; 178(2): 363–8.

Case series of 49 patients with PG treated with IVIG with CR or partial response (PR) noted in 43 and CR in 26.

Clearing of pyoderma gangrenosum by intralesional cyclosporin A. Mrowietz U, Christophers E. Br J Dermatol 1991; 125: 498–9.

PG on shoulder improved after two intralesional injections in 1 week of 35 mg ciclosporin into the active edges and beneath the lesion.

Successful therapy of refractory pyoderma gangrenosum and periorbital phlegmona with tacrolimus (FK506) in ulcerative colitis. Baumgart DC, Wiedenmann B, Dignass AU. Inflamm Bowel Dis 2004; 10: 421–4.

Two cases associated with UC responded to tacrolimus 0.1 mg/kg/day.

Crohn's disease with cutaneous involvement. Parks AG, Morson BC, Pegum JS. *Proc R Soc Med* 1965; 58: 241.

Mercaptopurine was used at the dose of 75 mg/day with prednisone 20 mg/day.

Treatment of pyoderma gangrenosum with colchicine. Paolini O, Hebuterne X, Flory P, et al. *Lancet* 1995; 345: 1057–8.

Colchicine at 1 mg daily was effective and well tolerated in PG associated with Crohn colitis.

Pyoderma gangrenosum with severe pharyngeal involvement. Buckley C, Bayoumi AHM, Sarkany I. *J R Soc Med* 1990; 83: 590–1.

A refractory case responded to thalidomide 100 mg daily.

Pyoderma gangrenosum associated with Behçet's syndrome – response to thalidomide. Munro CS, Cox NH. *Clin Exp Dermatol* 1988; 13: 408–10.

PG refractory to prednisolone and dapsone responded within 48 hours to thalidomide 400 mg daily.

Successful treatment of pyoderma gangrenosum with potassium iodide. Akihiko A, Yohei M, Yayoi T, et al. *Acta Derm Venereol* 2006; 86: 84–5.

Mycophenolate mofetil in pyoderma gangrenosum. Lee MR, Cooper AJ. *J Dermatol Treat* 2004; 15: 303–7.

Mycophenolate mofetil 1 to 2.5 g daily was used in combination with prednisolone in three cases and as monotherapy (with 500 mg BID) in one.

Pyoderma gangrenosum successfully treated with perilesional GM-CSF. Shpiro D, Gilat D, Fisher-Feld L, et al. *Br J Dermatol* 1998; 138: 368–9.

In this case the GM-CSF was injected perilesionally at weekly doses of 400 mg for 4 weeks.

Treatment of pyoderma gangrenosum with methotrexate. Teitel AD. *Cutis* 1996; 57: 326–8.

PG unresponsive to prednisone 60 mg daily improved within 2 weeks of adding methotrexate 15 mg weekly.

Intralesional methotrexate as an adjuvant treatment for pyoderma gangrenosum: a case report. Del Puerto C, Navarrete-Dechent CP, Carrasco-Zuber JE, et al. *Indian J Dermatol Venereol Leprol* 2017; 83(2): 277.

Refractory pyoderma gangrenosum treated with platelet-rich plasma. Alvarez-Lopez MA, Burón-Alvarez I, Villegas-Fernández C. *J Eur Acad Dermatol Venereol* 2016; 30(8): 1423–4.

Case of refractory PG responding to platelet-rich plasma embedded in a calcium alginate dressing once weekly for 6 weeks.

Management of facial pyoderma gangrenosum using platelet-rich fibrin: a technical report. Fortunato L, Barone S, Benardino F, et al. *Oral Maxillofac Surg* 2018; 76(7): 1460–3.

Case of PG treated with oral corticosteroids and topical solid and liquid platelet-rich fibrin with CR within a few weeks.

Recombinant human epidermal growth factor enhances wound healing of pyoderma gangrenosum in a patient with ulcerative colitis. Kim TY, Han DS, Eun CS, et al. *Inflamm Bowel Dis* 2008; 14: 725–7.

Clofazimine. A new agent for treatment of pyoderma gangrenosum. Michaelsson G, Molin L, Ohman S, et al. *Arch Dermatol* 1976; 112: 344–9.

Pyoderma gangrenosum treated with hyperbaric oxygen therapy. Wasserteil V, Bruce S, Sessoms SL, et al. *Int J Dermatol* 1992; 31: 594–6.

Superficial pyoderma gangrenosum responding to treatment with isotretinoin. Proudfoot LE, Singh S, Staughton RC. *Br J Dermatol* 2008; 159: 1377–8.

Successful treatment of pyoderma gangrenosum with anakinra in a patient with Wiskott–Aldrich syndrome. Mercuri SR, Paolino G, De flammis E, et al. *Dermatol Ther* 2018; 31(2): e12582.

Interleukin 23 expression in pyoderma gangrenosum and targeted therapy with ustekinumab. Guenova E, Teske A, Fehrenbacher B, et al. *Arch Dermatol* 2011; 147: 1203–5.

Penile pyoderma gangrenosum successfully treated with topical imiquimod. Rathod SP, Padhiar BB, Karia UK, et al. *Indian J Sex Transm Dis* 2011; 32: 114–7.

Monoclonal gammopathy of undetermined significance related pyoderma gangrenosum successfully treated with autologous peripheral blood stem cell transplantation. Chang CM, Hwang WL, Hsieh ZY, et al. *Ann Hematol* 2010; 89: 823–4.

Pyoderma gangrenosum treated successfully with visilizumab in patients with ulcerative colitis. Lorincz M, Kleszky M, Szalóki T Jr, et al. *Orv Hetil* 2010; 151: 144–7.

Two percent topical phenytoin sodium solution in treating pyoderma gangrenosum: a cohort study. Fonseka HE, Ekanayake SM, Dissanayake M. *Int Wound J* 2010; 7: 519–23.

Split skin grafts in the treatment of pyoderma gangrenosum: a report of four cases. Cliff S. *Dermatol Surg* 1999; 25: 299–302.

It is important to completely halt inflammatory/active PG before considering surgical treatment.

Free flap coverage of pyoderma gangrenosum leg ulcers. Clasen DA, Thomson C. *J Cutan Med Surg* 2002; 6: 327–31.

Extensive abdominal wall and genital pyoderma gangrenosum: combination therapy in unusual presentations. Shahmoradi Z, Mokhtari F, Pourazizi M, et al. *J Cutan Aesthet Surg* 2014; 7: 238–40.

Surgical debridement and suture closure of the lesions was successful in combination with sCS therapy.

Bullous pyoderma gangrenosum associated with hairy cell leukemia and its complete response to cladribine therapy. Jain A, Lad D, Prakash G, et al. *Indian J Hematol Blood Transfus* 2017; 33(2): 273–5.

Dehydrated human amnion/chorion membrane as adjunctive therapy in the multidisciplinary treatment of pyoderma gangrenosum: a case report. Snyder RJ, Ead J, Glick B, et al. *Ostomy Wound Manage* 2015; 61(9): 40–9.

Canakinumab in adults with steroid-refractory pyoderma gangrenosum. Kolios AG, Maul J-T, Meier B, et al. *Br J Dermatol* 2015; 173(5): 1216–23.

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Use of Becaplermin for nondiabetic ulcers: pyoderma gangrenosum and calciphylaxis. Twu O, Mednik S, Scumpia P, et al. *Dermatol Ther* 2016; 29(2): 104–8.

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Recalcitrant pyoderma gangrenosum treated with parenteral iron sucrose therapy. Buhalog B, Eastman K, McDonald R. *JAAD Case Rep* 2015; 1(2): 54–5.

The article's authors suggest that iron sucrose itself has an inhibitory effect on the functioning of hyperactive neutrophils.

Use of tocilizumab in a patient with pyoderma gangrenosum and rheumatoid arthritis. Lee WS, Choi YJ, Yoo WHJ. *Eur Acad Dermatol Venereol* 2017; 31(2): e75–7.

Successful treatment of pyoderma gangrenosum with cryoglobulinemia and hepatitis C. Pourmorteza M, Tawadros F, Bader G, et al. *Am J Case Rep* 2016; 17: 434–8.

Hepatitis C treated with ledipasvir/sofosbuvir induced near CR of PG.

Topical timolol for the treatment of pyoderma gangrenosum. Moreira C, Lopes S, Cruz MJ, et al. *BMJ Case Rep* 2017; 2017: bcr2016218589.

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Er:YAG laser ablation: an adjuvant treatment for medically resistant pyoderma gangrenosum. Çalışkan E. *Dermatol Surg* 2017; 43(11): 1405–7.

Refractory PG treated with ciclosporin and three sessions of Er:YAG laser at 2-week intervals.

Dramatic resolution of disseminated pyoderma gangrenosum associated with monoclonal gammopathy after therapy with bortezomib and dexamethasone. Velasco-Tamariz V, Carreño-Tarragona G, Tous-Romero F, et al. *Int Wound J* 2017; 14(6): 1382–4.

Therapeutic efficacy of the combination therapy of corticosteroids and 5-aminosalicylic acid for treatment of pyoderma gangrenosum with ulcerative colitis. Chen W, Xiang L, Li L. *Indian J Dermatol* 2020; 65(1): 38–41.

Although listed as a third-line treatment option, the article's authors encourage use of 5-ASA as a first-line treatment for UC-associated PG.

Novel use of apremilast for adjunctive treatment of recalcitrant pyoderma gangrenosum. Laird ME, Tong LX, Lo Sicco KI, et al. *JAAD Case Rep* 2017; 3(3): 228–9.

Apremilast 30 mg twice daily was added to recalcitrant vegetative PG with CR of one lesion and PR of another.

Topical medical cannabis: a new treatment for wound pain – three cases of pyoderma gangrenosum. Maida V, Corban J. *J Pain Symptom Manage* 2017; 54(5): 732–6.

Three patients with PG treated with topical medical cannabis resulted in clinically significant analgesia and decreased opioid use. Healing was not discussed.

Successful use of etoposide for pyoderma gangrenosum associated with myelodysplastic syndrome and trisomy 8: cytokine profiles during treatment. Fujiwara D, Hamada T, Yamasaki O, et al. *Eur J Dermatol* 2017; 27(5): 525–7.

Severe pyoderma gangrenosum caused by myelodysplastic syndrome successfully treated with decitabine administered by a noncytotoxic regimen. Saleh MFM, Sauntharajah Y. *Clin Case Rep* 2017; 5(12): 2025–7.

Portable negative-pressure wound therapy for pyoderma gangrenosum: report of two cases. Yamaguchi Y, Yanagi T, Sato K, et al. *J Dermatol* 2018; 45(4): 483–6.

Combination of negative pressure wound therapy and systemic steroid therapy in postsurgical pyoderma gangrenosum after reduction mammoplasty; a case of proven efficacy and safety. Tanini S, Calugi G, Russo GL. *Dermatol Reports* 2017; 9(2): 7209.

Clinically inactive pyoderma gangrenosum successfully treated with negative pressure therapy and punch grafting. Grado Sanz R, Conde-Montero E, Pérez Jerónimo L, et al. *Int Wound J* 2020; 17(2): 516–8.

Managing ulcers associated with pyoderma gangrenosum with a urinary bladder matrix and negative-pressure wound therapy. Dillingham CS, Jorizzo J. *Adv Skin Wound Care* 2019; 32(2): 70–6.

Successful therapy for pyoderma gangrenosum with a Janus kinase 2 inhibitor. Nasifoglu S, Heinrich B, Welzel J. *Br J Dermatol* 2018; 179(2): 504–5.

Refractory PG treated with ruxolitinib demonstrated CR.

Effects of vedolizumab therapy on extraintestinal manifestations in inflammatory bowel disease. Fleisher M, Marsal J, Lee SD, et al. *Dig Dis Sci* 2018; 63(4): 825–33.

Eight patients with inflammatory bowel disease (IBD) with two patients having PG. Both were treated with vedolizumab with resolution.

Application of viable cryopreserved human placental membrane grafts in the treatment of wounds of diverse etiologies: a case series. Anselmo DS, McGuire JB, Love E, et al. *Wounds* 2018; 30(3): 57–61.

Improvement of ulcerations in treatment-resistant chronic scarring in a patient with pyoderma gangrenosum after improving vascular insufficiency, gently removing necrotic debris, and decreasing wound fluid. Nahm WJ, Mota JA, Rojas S, et al. *Am J Case Rep* 2018; 19: 844–8.

A patient with vascular insufficiency and PG treated with topical clobetasol with no improvement until addition of cadexomer iodine, pentoxifylline, and compression stockings.

Evaluating the efficacy of topical dapsone treatment for pyoderma gangrenosum: a retrospective case series. Li DG, Din RS, Tsiaras WG, et al. *J Cutan Med Surg* 2018; 22(6): 650–1.

Twenty-one patients with PG treated with 5% topical dapsone over 4 weeks with PR noted in 18 and CR in three.

The authors ultimately recommend topical dapsone as an adjunctive therapy.

Keratin gel as an adjuvant in the treatment of recalcitrant pyoderma gangrenosum ulcers: a case report. Paulsen E, Bygum A. *Acta Derm Venereol* 2019; 99(2): 234–5.

Case of lower extremity PG failing treatment with sCS, ciclosporin, and methotrexate. Topical keratin gel was added with CR of PG after 6 months.

Two cases of maggot debridement therapy in pyoderma gangrenosum. Din RS, Tsiaras WG, Mostaghimi A. *JAAD Case Rep* 2018; 4(10): 1027–9.

Two cases of refractory PG treated with maggot debridement therapy leading to lesional improvement.

One case of pyoderma gangrenosum in the lower limbs in Tibetan Plateau treated with vacuum sealing drainage combined with irrigation of oxygen loaded fluid. Yang SS, Jiang SG, Tudeng DCC, et al. *Zhonghua Shao Shang Za Zhi* 2019; 35(1): 69–71.

Successful treatment of pyoderma gangrenosum with concomitant tofacitinib and infliximab. Gregory MH, Ciorba MA, Deepak P, et al. *Inflamm Bowel Dis* 2019; 25(7): e87–8.

Infliximab-refractory PG treated with addition of tofacitinib 10 mg BID with almost CR at 3 weeks.

Tofacitinib for the treatment of pyoderma gangrenosum. Kochar B, Herfarth N, Mamie C, et al. *Clin Gastroenterol Hepatol* 2019; 17(5): 991–3.

Three patients with refractory PG treated with tofacitinib 5 mg twice daily. Two healed completely within 12 weeks while the third improved after 1 month.

Tildrakizumab for treatment of refractory pyoderma gangrenosum of the penis and polymyalgia rheumatica: killing two birds with one stone. John JM, Sinclair RD. *Australas J Dermatol* 2020; 61(2): 170–171.

Refractory PG in a 69-year-old man failing topical clobetasol and ciclosporin. Tildrakizumab was added at 100 mg subcutaneously on weeks 0 and 4, and then a 12-weekly schedule. At week 32, the ulceration had healed completely.

Use of dermal injection of activated protein C for treatment of large chronic wounds secondary to pyoderma gangrenosum. Kapila S, Reid I, Dixit S, et al. *Clin Exp Dermatol* 2014; 39(7): 785–90.

Two PG patients were refractory to prednisone; 400 mcg of APC was injected dermally into the edges of the wound weekly for 6 weeks. After 12 weeks, both patients had significant reductions in wound size.

Pyogenic granuloma

Danielle M. DeHoratius



Pyogenic granuloma (PG), also known as a *lobular capillary hemangioma*, is a common benign vascular growth. It often develops rapidly into a solitary erythematous papule or polyp. PGs can be friable and hemorrhagic and frequently ulcerate. They most commonly occur in children and young adults. The etiology is unclear, although reactive neovascularization is suspected because of their occurrence at sites of previous trauma. They have also been reported as a cutaneous adverse effect of various medications. There is no gender or racial predominance. PGs are more common in pregnancy. The most common locations are the head and neck region (including the oral mucosa, especially in pregnant women, known as *granuloma gravidarum*) and digits. Rarely, an amelanotic melanoma can be mistaken as a PG, so histology is preferred for isolated lesions where this might be possible, for example, non-pigmented skin of the digit in a darkly pigmented patient. Occasionally, PGs have been found in subcutaneous or intravascular locations. The term PG is a misnomer – there is no infectious or granulomatous component to these lesions.

MANAGEMENT STRATEGY

Histologic confirmation is beneficial, as other disorders may clinically mimic PGs, examples being amelanotic melanoma, Kaposi sarcoma, and bacillary angiomatosis. Dermoscopy of these lesions can be useful but should not substitute for histology. The most sensitive and specific pattern is a reddish homogeneous area, white collarette, and white rail lines.

Although they can eventually resolve spontaneously, treatment is usually required. Because this is a benign growth, it is important to consider the cosmetic outcome of the therapeutic intervention. PGs are most commonly treated by destruction using *shave excision with electrocautery* to the base, *curettage with electrodesiccation*, or *cryotherapy*. There is a possibility of recurrence and/or the development of satellite lesions, but these options are less invasive than excision and do not result in significant scarring.

Complete *excision* requiring sutures may lower the recurrence rate and reduce the possibility of bleeding; however, a linear scar will be present. Hemostasis can be obtained by electrocautery, silver nitrate, or argon laser photocoagulation.

Vascular *lasers* also destroy these lesions, although multiple treatments are usually required, and there is no histologic confirmation. *Pulsed dye laser* has proved to be more successful with smaller lesions. For larger lesions the *Nd:YAG laser* has been efficacious. *Sclerotherapy* destroys these vascular lesions and has been reported to have a very high cure rate in experienced hands. Various application schedules of *imiquimod* 5% have resolved PGs, presumably due to its antiangiogenic properties. *Photodynamic therapy* has been shown to be effective with very few adverse events.

More recently, topical β -blockers have been reported useful in treating PGs while maintaining ease of application, cosmetic considerations, and reducing adverse events. Additional investigation is necessary to assess its efficacy. It is an important option in younger children as well as delicate cosmetic locations.

Specific Investigation

- Histology

First-Line Therapies

• Simple shave excision/curettage with electrocautery of the base	A
• Full-thickness skin excision	A
• Cryotherapy	A
• Topical β -blockers	C
• Silver nitrate cautery	D

Pyogenic granuloma in children. Pagliai KA, Cohen BA. *Pediatric Dermatology* 2004; 21: 10–3.

A retrospective study of 128 children, including follow-up phone interviews of 76. Of these, 72.3% underwent a shave excision with electrocautery. The second most common treatment was laser therapy (16.9%). Fifty-five percent of the children in the first group reported a subtle scar, and 33% of the CO₂ laser group and 44% of the pulsed dye laser group reported a similar scar. The mean age was 5.9 years old (4 months to 17 years). A eutectic mixture of lidocaine and prilocaine was used topically for 1–2 hours prior to the laser treatments. Intradermal lidocaine was added when the CO₂ laser was used. All patients were pleased with the cosmetic result.

Comparison of cryotherapy and curettage for the treatment of pyogenic granuloma: a randomized trial. Ghodsi SZ, Razieli M, Taheri A, et al. *Br J Dermatol* 2006; 154: 671–5.

In total, 89 patients were treated with either liquid nitrogen cryotherapy or curettage followed by electrodesiccation. Of the 86 patients who completed the study, all had complete resolution of the lesions after one to three sessions (mean 1.42) in the cryotherapy group and after one to two sessions (mean 1.03) in the curettage group. No scar or residual pigmentation was reported in 57% of the cryotherapy group or in 69% of the curettage group. The authors concluded that curettage should be a first-line therapy as fewer treatment sessions were necessary and cosmesis was better.

Pyogenic granuloma – the quest for optimum treatment audit of treatment of 408 cases. Giblin AV, Clover AJ, Athanassopoulos A, et al. *Plast Reconstruct Aesthet Surg* 2007; 60: 1030–5.

A retrospective study of 408 cases analyzed between 1994 and 2004. The excision and direct closure group had the fewest recurrences.

Cryotherapy in the treatment of pyogenic granuloma. Mirshams M, Daneshpazhoo M, Mirshekari A, et al. *J Eur Acad Dermatol Venereol* 2006; 20: 788–90.

A prospective study of 135 patients treated with liquid nitrogen cryotherapy using a cotton-tipped applicator. Patients required anywhere from one to four treatments (mean 1.58). All patients had complete resolution, with 96.2% occurring after three treatments. Minor scars were reported in 11.8%, and 5.1% had hypopigmentation.

These authors report that cryotherapy should be considered first-line therapy as it is an easy and inexpensive technique; however, the main limitation is a lack of histologic confirmation.

Treatment of pediatric pyogenic granulomas using β -adrenergic receptor antagonists. Lee LW, Goff KL, Lam JM, et al. *Pediatric Dermatol* 2014; 31: 203–7.

A series of seven cases of cutaneous and mucosal PGs successfully treated with oral or topical β -blockers. Three of the seven had failed previous modalities. In most of the cases, topical timolol was applied three times daily and either a complete or partial response was achieved. A partial response was achieved as early as 6 weeks and complete resolution took anywhere from 2 to 6 months.

An excellent option when destruction procedures either failed or are not desirable.

Topical 1% propranolol ointment with occlusion in treatment of pyogenic granulomas: an open-label study in 22 children. Neri I, Baraldi C, Balestri R, et al. *Pediatric Dermatol* 2018; 35: 117–20.

An open-label, prospective study of 22 children treated with topical propranolol 1% ointment under occlusion. Propranolol ointment was found to cause complete regression in 59% in a mean of 66 days (range 14–150 days), 18% initially improved and then remained stable, and 22% did not respond. No side effects were noted.

These authors report that topical propranolol ointment 1% should be considered first-line therapy as it is relatively easy and can be used to minimize complications with other destructive modalities such as surgery.

Is timolol an effective treatment for pyogenic granuloma? Gupta D, Singh N, Thappa DM. *Int J Dermatol* 2016; 55: 592–5.

A series of 10 patients with PG who received 0.5% timolol maleate ophthalmic solution applied four times per day, two drops per dose. Half of the patients had a complete response (anywhere from 3–24 days), two had a partial response, and three had no response.

The efficacy of silver nitrate cauterization for pyogenic granuloma of the hand. Quitkin HM, Rosenwasser MP, Strauch RJ. *J Hand Surg Am* 2003; 28: 435–8.

Thirteen lesions were treated with simple removal and cautery of the base using silver nitrate; 85% of the lesions resolved with an average of 1.6 treatments. The average time to complete healing was 3.5 weeks.

Second-Line Therapies

• Pulsed dye	B
• CO ₂ laser	B
• Nd:YAG laser	B

Treatment of pyogenic granuloma in children with the flashlamp-pumped pulsed dye laser. Tay YK, Weston WL, Morelli JG. *Pediatrics* 1997; 99: 368–70.

Twenty-two children with solitary lesions were treated with a vascular-specific (585 nm), pulsed (450 ms) dye laser using a 5-mm spot size with energy of 6–7 J/cm² without anesthesia. This treatment was successful in 91%, and all healed without scarring. Fifteen patients required from two to six treatments at 2-week intervals, and seven required three or more. The two patients who did not respond had larger lesions (0.5–1 cm). No recurrences were reported during the follow-up period (6 months to 3 years). The limitation was the depth of penetration of 1 mm.

This can be a useful modality in children, as no anesthesia is required and there is minimal scarring. The drawback is that no tissue is obtained for histology.

The combined continuous-wave/pulsed carbon dioxide laser for treatment of pyogenic granuloma. Raulin C, Greve B, Hammes S. *Arch Dermatol* 2002; 138: 33–7.

In this study, 100 patients were treated. The laser was first used in the continuous mode (power 15 W) and then in the pulsed mode (pulse length 0.6–0.9 ms; energy fluence 500 mJ/pulse). Follow-up was 6 weeks and 6 months, and 98 of 100 patients had complete resolution after one treatment. In 88 patients there were no visible scars, and 10 had only slight textural changes. No erythema or pigmentary changes were observed.

Pyogenic granulomas: treatment with the 1064-nm long-pulsed neodymium-doped yttrium aluminum garnet laser in 20 patients. Hammes S, Kaiser K, Pohl L, et al. *Dermatol Surg* 2012; 38: 918–23.

Twenty patients required one to four treatment sessions (settings used: fluences 60–180 J/cm², spot size of 7 mm, and a pulse duration of 40 ms). Nineteen had recurrence-free healing (follow-up duration 6–22 months) with good cosmetic results. This can be a satisfactory laser modality, especially when the diameter of the lesion is larger.

Third-Line Therapies

• Ligation	E
• Imiquimod 5%	C
• Sclerotherapy	D
• Photodynamic therapy	D
• Intralesional corticosteroids	E
• Intralesional bleomycin	E
• Topical phenol	E

Surgical pearl: ligation of the base of a pyogenic granuloma – an atraumatic, simple, and cost-effective procedure. Holbe HC, Frosch PJ, Herbst RA. *J Am Acad Dermatol* 2003; 49: 509–10.

A pedunculated PG was ligated using an absorbable suture tightly tied at the base. Over a few days the lesion became necrotic and fell off.

This was atraumatic and required no anesthesia, but there was no histologic confirmation.

Pyogenic granuloma in ten children treated with topical imiquimod. Tritton SM, Smith A, Wong LC, et al. *Pediatr Dermatol* 2009; 26: 269–72.

Children with a mean age of 2.5 years were instructed to apply imiquimod 5% once a day, twice a day, or three times per week, depending on the clinical response. All lesions were located on the face (3–6 mm), and local erythema was unanimously observed. Three had no residual disease, whereas five had either small hypopigmented or erythematous lesions, which were continuing to improve at the completion of the study. No systemic side effects were reported.

The authors suggest a trial of three times per week initially, increasing to daily if tolerated, for up to 2 months. Treatment should be discontinued 1 week after complete disappearance of the lesion. This appears to be a reasonable alternative to surgical excision.

Treatment of pyogenic granuloma by sodium tetradecyl sulfate sclerotherapy. Moon SE, Hwang EJ, Cho KH. *Arch Dermatol* 2005; 141: 644–6.

Fifteen PGs were injected with 0.5% sodium tetradecyl sulfate until blanching appeared. Follow-up was every 1–2 weeks, and at 6 weeks 80% showed complete resolution. In two patients a small shallow vascular area remained, which responded to the CO₂ laser.

The authors felt that this treatment can be an alternative to excision because of its simplicity and lack of scarring; however, multiple treatments may be necessary to achieve resolution. There is no tissue for histologic sampling.

Photodynamic therapy with 5-aminolevulinic acid intralesional injection for pyogenic granuloma. Lee DJ, Kim EH, Jang YH, et al. *Arch Dermatol* 2012; 148: 126–8.

A total of 14 lesions were injected (26-gauge needle) with 0.3 mL/cm³ of 5-aminolevulinic acid, 20% solution, followed by occlusion with polyurethane film. The lesions were illuminated with red light (600–720 nm, light dose 100 J/cm², and fluence 100 mW/cm²). Eleven patients showed a marked response and

had no recurrence at 1-year follow-up. One patient showed moderate response (lesion was on the lip), and two did not respond (lesions large >1 cm). Only three patients complained of perilesional swelling.

The authors felt that this treatment can be an alternative to standard therapy, especially in patients with small lesions who refuse surgery.

Pyogenic granuloma that responded to local injection of steroid. Niiyama S, Amoh Y, Katsuoka K. *J Plast Reconstr Aesthet Surg* 2009; 62: 153–4.

Two lesions were injected with triamcinolone acetonide 2 mg weekly for a total of seven or eight times. The lesions became smaller and were subsequently excised.

This can be used when the lesion is in an unfavorable location for simple excision.

Complete resolution of recurrent giant pyogenic granuloma on the palm of the hand following single dose of intralesional bleomycin injection. Daya M. *J Plast Reconstr Aesthet Surg* 2010; 63: e331–3.

A 63-year-old woman presented with a recurrent giant PG (5 cm × 6 cm) after previous surgical excision and intralesional steroids. The lesion was injected with a total of 8 mL of 0.5 mg/mL of bleomycin given under general anesthesia with tourniquet control. The lesion regressed after 2 months and did not recur with only mild hypersensitivity within the scar.

Topical phenol as a conservative treatment for periungual pyogenic granuloma. Losa Iglesias ME, Becerro de Bengoa Vallejo R. *Dermatol Surg* 2010; 36: 675–8.

A report of 18 patients treated with a 98% phenol solution, three applications of 1 min each consecutively with the entire tumor and a small surrounding area turning white. The areas were then treated with 10% silver sulfadiazine and 10% povidone iodine and wrapped in sterile gauze. At 14 weeks all lesions had resolved with no scarring or adverse events.

This approach is simple to perform, fairly inexpensive, and relatively pain free; however, recurrence is possible, and treatment may necessitate frequent office visits.

Radiation dermatitis

Joseph R. Stoll, Alina Markova



Radiation dermatitis (RD) is a common complication of cutaneous radiation exposure, most frequently from treatment of malignancies or interventional radiologic procedures. Acute radiation dermatitis (ARD) typically occurs within 2–3 weeks of radiation exposure and is caused by damage to the appendageal structures and basal keratinocytes. The damage gradually builds over the treatment course and peaks at 1–2 weeks after completion of radiation therapy (RT). ARD manifests as erythema, edema, epilation, dry or wet desquamation, and blistering (see figure). Pain and pruritus often accompany these changes. The most widely used tools for assessment are the National Cancer Institute's Common Terminology Criteria for Adverse Events and the Radiation Therapy Oncology Group, which both grade ARD from 1 to 4. Chronic RD is defined as skin changes persisting 90 days after radiation exposure, and these changes result from radiation-induced dermal and vascular damage leading to atrophy, dyspigmentation, telangiectasia, fibrosis, ulceration, and necrosis. Radiation recall is a dermatitis developing at sites of prior radiation exposure, usually induced by chemotherapeutic drugs such as the anthracycline doxorubicin, taxanes (docetaxel >paclitaxel), and antimetabolites (gemcitabine >capecitabine).

MANAGEMENT STRATEGY

Despite advances in radiation technology aimed at reducing side effects, skin toxicity is still common. The goals of treatment consist of maintaining skin integrity, minimizing patient discomfort, and preventing trauma and infection. Patients should gently wash the skin with *mild soap and water*. *Topical corticosteroids* treat dry desquamation (painless peeling of the skin) and moist desquamation (painful, full-thickness loss of the epidermis), control pruritus, and reduce inflammation. Addition of *silver nylon dressings* or *topical silver sulfadiazine* may provide prophylaxis against infection and expedite healing. Thin or moderately applied topical agents have minimal influence on skin radiation dose;

however, patients should avoid applying very thick amounts of a topical agent just before RT as this may increase the surface dose. Patients should also avoid friction from tight fitting clothing. Of note, topical corticosteroids have demonstrated the highest prophylactic and therapeutic efficacy for ARD when compared with other topical agents.

Chronic RD is treated symptomatically. Topical emollients or corticosteroids can be employed as needed. Skin necrosis or ulceration must be monitored for signs of infection and managed with appropriate wound dressings. For reduction of skin fibrosis, oral supplementation with *pentoxifylline* and *vitamin E* as well as *physical massage* are recommended. Telangiectasias can be treated with *pulsed-dye laser*.

Specific Investigations

- History of previous radiation exposure and chemotherapeutic drugs
- Evaluation of affected skin for development of malignancy and late effects

Post radiation skin tumors: basal cell carcinomas, squamous cell carcinomas and angiosarcomas. A review of this late effect of radiotherapy. Cuperus E, Leguit R, Albrechts M, et al. *Eur J Dermatol* 2013; 23: 749–57.

Basal cell carcinomas are the most common malignancies to develop in sites of radiation exposure. Patients with breast cancer treated with radiotherapy are also at risk for angiosarcomas.

First-Line Therapies

Acute radiation dermatitis

• Topical corticosteroids	A
• Washing with soap and water	B
• Silver nylon dressing	B
• Topical silver sulfadiazine	B

Chronic radiation dermatitis

• Pentoxifylline	B
• Vitamin E	B
• Pulsed-dye laser (PDL)	C

Management of acute radiation dermatitis: a review of the literature and proposal for treatment algorithm. Rosenthal A, Israilevich R, Moy R. *J Am Acad Dermatol* 2019; 81: 558–67.

This article reviews the clinical efficacy and level of evidence of topical agents used in the management of ARD. Daily washing of skin within the radiation field with mild soap and water during RT to reduce pruritus and severity is supported by randomized controlled trials (RCTs). RCTs also support the application of a mid-potency topical corticosteroid, twice a day from the first day of RT through 2 weeks following completion of RT, to reduce rates of wet desquamation. Evidence shows that silver nylon dressings used daily and for 2 weeks after completion of RT reduce pruritus, pain, and burning.

A randomized trial of mometasone furoate 0.1% to reduce high-grade acute radiation dermatitis in breast cancer patients receiving postmastectomy radiation. Ho AY, Olm-Shipman M, Zhang Z, et al. *Int J Radiat Oncol Biol Phys* 2018; 101: 325–33.

Mometasone furoate (MF) 0.1% cream was compared to Eucerin Original (E) cream in this double-blind randomized trial of 124 breast cancer patients receiving postmastectomy radiation (PMRT). The creams were applied twice daily from day 1 of PMRT for 2 weeks. The rate of moist desquamation was significantly reduced in the MF arm compared to the E arm. The MF arm had a lower incidence of maximum-grade ARD and longer time to development of grade 3 ARD.

The impact of skin washing with water and soap during breast irradiation: a randomized study. Roy I, Fortin A, Laroche M. *Radiother Oncol* 2001; 58: 333–9.

Ninety-nine patients treated for breast cancer were prospectively randomized prior to receiving radiotherapy to the breast into two groups: no washing (49) and washing with soap and water (50). Moist desquamation was seen in 33% of non-washing patients, but only 14% of washing patients. The median scores of pain, itching, and burning of the treated skin were higher in the non-washing group, although this was not statistically significant.

Silver clear nylon dressing is effective in preventing radiation-induced dermatitis in patients with lower gastrointestinal cancer: results from a phase III study. Niazi TM, Vuong T, Azoulay L, et al. *Int J Radiat Oncol Biol Phys* 2012; 84: e305–10.

Rectal or anal cancer patients undergoing RT were randomized to either use a silver clear nylon dressing (SCND) applied on day 1 of RT and worn continuously until 2 weeks after treatment completion or standard skin care comprising silver sulfadiazine (SSD) cream applied at the time of skin dermatitis with photographs scored by blinded observers. On the last day of RT, the mean dermatitis scores were significantly lower in the SCND-treated group compared with the SSD group.

Topical silver sulfadiazine for the prevention of acute dermatitis during irradiation for breast cancer. Hemati S, Asnaashari O, Sarvzadeh M, et al. *Support Care Cancer* 2012; 20: 1613–8.

Topical SSD 1% cream was applied three times a day for 3 consecutive days after weekly radiation treatment for 5 weeks and 1 week thereafter in women receiving RT for breast cancer. Patients using SSD cream developed significantly less severe dermatitis as scored by a blinded observer compared with a control group treated with general skin care alone.

Striking regression of chronic radiotherapy damage in a clinical trial of combined pentoxifylline and tocopherol. Delanian S, Balla-Mekias S, Lefaix JL. *J Clin Oncol* 1999; 17: 3283–90.

Patients with radiation-induced fibrosis (RIF) for a mean period of 8.5 ± 6.5 years were treated with a combination of oral pentoxifylline 800 mg/day and vitamin E 1000 IU/day for at least 6 months and had reduced mean RIF surface area, and significantly improved Subjective Objective Medical Management and Analytic (SOMA) injury evaluation scores at 3, 6, and 12 months.

Intense pulsed light vs. long-pulsed dye laser treatment of telangiectasia after radiotherapy for breast cancer: a randomized split-lesion trial of two different treatments. Nymann P, Hedelund L, Haedersdal M. *Brit J Dermatol* 2009; 160: 1237–41.

Thirteen patients with Fitzpatrick skin types II–III received a series of three treatments at 6-week intervals with long-pulsed dye (LPDL) (V-beam Perfecta, 595 nm) and intense pulsed light (Ellipse Flex). LPDL was superior in telangiectasia clearance, pain scores, and patient satisfaction.

Second-Line Therapies

Acute radiation dermatitis

- Film dressing B
- Oral zinc supplement A

Chronic radiation dermatitis

- Physical massage B

Prophylactic use of Mepitel Film prevents radiation-induced moist desquamation in an intra-patient randomised controlled clinical trial of 78 breast cancer patients. Herst PM, Bennett NC, Sutherland AE, et al. *Radiother and Oncol* 2014; 110: 137–43.

In patients receiving RT for breast cancer, lateral and medial halves of the skin areas to be irradiated were randomized to Mepitel Film or aqueous cream. Mepitel Film completely prevented moist desquamation and reduced skin reaction severity by 92% compared with aqueous cream (Modified Radiation-Induced Skin Assessment Scale).

Effect of film dressing on acute radiation dermatitis secondary to proton beam therapy. Arimura T, Ogino T, Yoshiura T, et al. *Int J Radiat Oncol Biol Phys* 2016; 95: 472–6.

In this trial of 271 patients undergoing proton beam therapy for prostate cancer, patients self-randomized to using a continuously applied AIRWALL film dressing (FD) with no medical ingredients or to standard treatment. Patients using the FD showed a significantly decreased grade 2 RD. Side effects of FD use included itching sensation, redness, and folliculitis.

Zinc supplementation to improve mucositis and dermatitis in patients after radiotherapy for head-and-neck cancers: a double-blind, randomized study. Lin LC, Que J, Lin LK, et al. *Int J Radiat Oncol Biol Phys* 2006; 65: 745–50.

This double-blind, placebo-controlled RCT of patients with head-and-neck cancers receiving RT treated with an oral zinc supplement (Pro-Z 25 mg), three tablets per day for approximately 2 months during RT, had a delayed grade 2 dermatitis, decreased development of grade 3 dermatitis, and overall milder dermatitis than those taking the placebo.

A randomized, prospective study using the LPGs technique in treating radiation-induced skin fibrosis: clinical and profilometric analysis. Bourgeois JE, Gourgou S, Kramar A, et al. *Skin Res Technol* 2008; 14: 71–6.

Twenty women treated for breast cancer were randomized to mechanical massage (LPG technique) or medical supervision. The LPG group had decreased erythema, pain, pruritus, and subjective feeling of induration of the skin compared to the control group.

Third-Line Therapies

Acute radiation dermatitis

- Topical calendula B
- Topical statin A
- Topical beta-sitosterol B
- Topical GM-CSF B

Phase III randomized trial of Calendula officinalis compared with trolamine for the prevention of acute dermatitis

during irradiation for breast cancer. Pommier P, Gomez F, Sunyach MP, et al. *J Clin Oncol* 2004; 22: 1447–53.

At the onset of radiotherapy, 254 women applied calendula or trolamine ointment at least twice per day. Incidence of grade 2–3 acute skin toxicity and mean maximal pain scores were significantly less in the calendula-treated group. Trolamine ointment was considered easier to apply.

Topical atorvastatin 1% for prevention of skin toxicity in patients receiving radiation therapy for breast cancer: a randomized, double-blind, placebo-controlled trial. Ghasemi A, Ghashghai Z, Akbari J, et al. *Eur J Clin Pharmacol* 2019; 75: 171–8.

This randomized, placebo-controlled, double-blind study of 70 breast cancer patients who received twice daily topical atorvastatin (ATV) 1% versus placebo found that administration of ATV gel during radiotherapy significantly reduced radiation-induced breast swelling, itching, and pain in breast cancer patients. However, unlike the itching and pain scores, radiation-related dermatitis was not significantly improved with ATV.

Randomized, prospective, open-label phase III trial comparing β -sitosterol (Mebo®) ointment with trolamine (Biafine®) cream for the management of acute skin reaction during radiation therapy for breast cancer. Geara FB, Eid TA, Youssef BY, et al. *Int J Radiat Oncol Biol Phys* 2018; 102: e610.

In this randomized, open-label study of 161 breast cancer patients treated with RT, no differences in incidence or severity of RD were observed between the β -sitosterol and trolamine group. However, the incidences of severe pruritus and local skin pain were both significantly reduced in the β -sitosterol group.

Topical granulocyte-macrophage colony-stimulating factor for radiation dermatitis of the vulva. Kouvaris JR, Kouloulis VE, Plataniotis GA, et al. *Br J Dermatol* 2001; 144: 646–7.

In this study of 61 patients treated for vulvar carcinoma, patients who received topical corticosteroids with GM-CSF-saturated gauze demonstrated significantly reduced severity and duration of ARD compared with historical controls treated with topical corticosteroids alone.

Raynaud disease and phenomenon

Nidhi Shah, Ruth Ann Vleugels



Raynaud phenomenon (RP) is characterized by intermittent peripheral vasoconstriction leading to pallor, cyanosis, and reactive vasodilatation of the arterioles of the fingers and toes. It is caused by vasospasm in response to cold, emotion, hormones, and certain vasospastic drugs. Primary Raynaud disease is a milder, idiopathic form, whereas secondary RP coexists with autoimmune connective tissue disorders, such as systemic lupus erythematosus and systemic sclerosis (SSc), among others, or other conditions that reduce blood flow, such as localized structural abnormalities. The pathogenesis and pathophysiology vary between the primary (idiopathic) and the secondary forms but are still not fully understood.

Primary Raynaud disease is often mild and may not require treatment; the vasospasm is entirely reversible. However, secondary Raynaud disease often involves fixed blood vessel damage in addition to vasospasm; therefore, the ischemia can be more severe. Complications include digital ulcers and gangrene, which can lead to osteomyelitis and even amputation.

MANAGEMENT STRATEGY

Treatment is often non-pharmacologic, including avoiding cold (especially sudden drops in temperature) and smoking cessation. Counseling should emphasize keeping the core temperature warm (additional layers, hats, etc.) in addition to wearing thick socks and gloves/mittens, in order to prevent vasoconstriction in the periphery. The use of *warming devices* such as hand or toe warmers can be

beneficial. Avoidance of triggers should be stressed (e.g., caffeine, smoking, use of vibratory equipment). Drugs that may exacerbate the condition include β -blockers, amphetamine/dextroamphetamine, bleomycin, cisplatin, ergot preparations, interferon, methysergide, oral contraceptives, reboxetine, tegaserod, and vinblastine.

Pharmacologic therapy is warranted when: 1) the patient's symptoms impact their quality of life to a substantial degree; and 2) the patient is developing changes, including digital ulcers, loss of digital pulp, etc.

Calcium channel antagonists, such as *nifedipine*, are considered first-line treatment. The side effect profile includes hypotension, vasodilatation, peripheral edema, and headaches. A common dosing strategy is to initiate nifedipine at 30 mg extended release QHS and increase the dose as needed. Other treatments that have been studied in randomized controlled trials include *phosphodiesterase-5 inhibitors* (PDE-5) (e.g., *sildenafil*, 25–50 mg up to four times a day) and *nitrates* (topical or oral), *angiotensin II inhibitors*, and *selective serotonin reuptake inhibitors* (*fluoxetine* 20–60 mg daily). PDE-5 inhibitors are effective in patients who respond poorly to calcium channel antagonists as an alternative or adjunct. They are used frequently in patients with severe SSc- or other CTD-related RP. For refractory Raynaud disease or its complications, *botulinum toxin* or *prostacyclin* agonists may be used. Endothelin receptor blockade with *bosentan* (62.5 mg twice a day) has been demonstrated to reduce the number of new digital ulcers in patients with systemic sclerosis. However, it does not affect the healing period and has no effect on the number and severity of attacks of RP in those without ulcers.

Specific Investigations

- Nailfold capillaroscopy
- Careful physical examination and review of systems for potentially associated connective tissue diseases, other conditions, and structural abnormalities; systemic workup and autoantibody testing based on these findings

Careful history taking and clinical examination followed by investigation to detect potential underlying disease are essential.

A study comparing videocapillaroscopy and dermoscopy in the assessment of nailfold capillaries in patients with systemic sclerosis spectrum disorders. Hughes M, Moore T, O'Leary N, et al. *Rheumatology* (Oxford) 2015; 54(8): 1435–42.

In this study, rheumatologists graded nailfold capillary images from dermoscopy and nailfold videocapillaroscopy (NVC) in 32 subjects. Dermoscopy is a comparable technique to NVC in grading nailfold capillary images; however, NVC graded images approximately half a point more severely than dermoscopy due to its higher magnification properties.

First-Line Therapies

• Calcium channel blockers (nifedipine)	A
• Phosphodiesterase-5 inhibitors (sildenafil)	A
• Behavioral modification	N/A

Calcium channel blockers for primary Raynaud's phenomenon. Ennis H, Hughes M, Anderson ME, et al. *Cochrane Database Syst Rev* 2016; 25: CD002069.

This represents a meta-analysis of seven randomized trials with 296 patients evaluating the effects of nifedipine and nicardipine

in the treatment of primary RP only. A decrease in the frequency of attacks was reported for patients on a calcium channel blocker. Doses of nifedipine used included 10–20 mg three times daily and 30–60 mg sustained-release daily. Nicardipine doses ranged between 20 mg and 30 mg thrice daily and 50 mg long-acting preparation twice daily.

Head-to-head comparison of udenafil vs. amlodipine in the treatment of secondary Raynaud's phenomenon: a double-blind, randomized, cross-over study. Lee EY, Park JK, Lee W, et al. *Rheumatology* 2014; 53: 658–64.

Twenty-nine patients with secondary RP associated with connective tissue diseases received udenafil 100 mg daily (a phosphodiesterase-5 inhibitor) or amlodipine 10 mg daily for 4 weeks. Both decreased the rate of RP attacks with comparable efficacy.

Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomised trials. Herrick AL, van den Hoogen F, Gabrielli A. *Ann Rheum Dis* 2013; 72: 1696.

Six randomized controlled trials were included: one with sildenafil (50 mg twice daily), one with modified-release sildenafil (200 mg once daily), three with tadalafil (20 mg on alternate days when used as add-on therapy), and 20 mg once daily. One study looked at vardenafil 10 mg twice daily. A meta-analysis showed PDE-5 inhibitors significantly decreased frequency and duration of RP attacks compared with placebo in secondary RP.

Nifedipine cream versus sildenafil cream for patients with secondary Raynaud phenomenon: a randomized, double-blind, controlled pilot study. Wortsman X, Del Barrio-Díaz P, Meza-Romero R, et al. *J Am Acad Dermatol* 2018; 78(1): 189–90.

In this double-blind study, 10 patients with secondary RP were randomly assigned to receive treatment with 5 g of 10% nifedipine on one hand and 5 g of 5% sildenafil cream on the other hand. Topical sildenafil significantly increased blood flow by 9.2 mm/sec ($p < 0.0083$), whereas no significant change in blood flow was observed with topical nifedipine.

Combination therapy with bosentan and sildenafil improves Raynaud's phenomenon and fosters the recovery of microvascular involvement in systemic sclerosis. Bellando-Randone S, Lepri G, Bruni C, et al. *Clin Rheumatol* 2016; 35(1): 127–32.

In this retrospective study, 123 patients were evaluated based on their treatments: bosentan, sildenafil, bosentan + sildenafil. Patients treated with both bosentan and sildenafil demonstrated a significantly greater improvement in Raynaud Condition Score and reversal of NVC.

Second-Line Therapies

• Botulinum toxin	B
• Alpha-1-adrenergic receptor antagonist (prazosin/doxazosin)	B
• Selective serotonin reuptake inhibitors (fluoxetine)	B
• Angiotensin II receptor type I antagonist (losartan)	B
• Prostacyclin analogs (iloprost)	A
• Topical and oral nitrates	A

Optimisation of botulinum toxin type A treatment for the management of Raynaud's phenomenon using a dorsal approach: a prospective case series. Dhaliwal K, Griffin MF, Salinas S, et al. *Clin Rheumatol* 2019; 38(12): 3669–76.

In this prospective case series, 40 patients were injected with 100 units of botulinum toxin type A (BTX-A) in both hands through a dorsal approach; 80% of the patients reported improvement in swelling, color changes, and reduction in pain at 6 weeks. Additionally, 80% of the patients with improved symptoms also reported reduction in the frequency and severity of RP attacks as well as improved cold sensitivity. Significant improvements in the Disabilities of the Arm, Shoulder, and Hand (DASH) score ($p = 0.001$), Kapandji (thumb opposition test) score ($p = 0.001$), and hand strength ($p < 0.05$) were also observed. At 12 weeks, improvement in symptoms and hand strength as well as reduction in the DASH and Kapandji scores were still observed but to a lesser degree than 6 weeks.

A 28-day prospective, randomized, double-blind, placebo controlled clinical trial of botulinum toxin type A for Raynaud's phenomenon. Webb KN, Berry NN, Bueno RA, et al. *Plast Reconstr Surg* 2014; 133: 13.

A group of 35 patients were treated with either placebo or botulinum toxin type A (BTX-A) 100U into the palm around involved digital neuromuscular bundles. Of placebo patients, 10% reported pain relief compared with 62% of BTX-A-treated patients ($p = 0.0288$). Average pain relief duration was 127 days, and 60% of patients with digital ulcers healed after BTX-A injection.

Double-blind, placebo-controlled study of prazosin in Raynaud's phenomenon. Wollersheim H, Thien T, Fennis J, et al. *Clin Pharmacol Ther* 1986; 40: 219–25.

In this study, prazosin 1 mg three times daily was compared with placebo and showed a moderate subjective improvement with a reduction in daily number and duration of attacks.

Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. Coleiro B, Marshall SE, Denton CP, et al. *Rheumatology* 2001; 40: 1038–43.

This crossover study compared fluoxetine, a selective serotonin reuptake inhibitor (20 mg/day), with nifedipine (40 mg/day) as treatment for primary or secondary RP. While attack frequency and severity reduction occurred with both nifedipine and fluoxetine, the effect was only statistically significant with fluoxetine. Females and patients with primary RP reported the greatest response to fluoxetine. Response to thermographic cold challenge was only observed for patients receiving fluoxetine and not with nifedipine. The results confirmed the tolerability of fluoxetine and suggested that it would be effective as a treatment for RP.

Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel group, controlled trial. Dziadzio M, Denton CP, Smith R, et al. *Arthritis Rheum* 1999; 42: 2646–55.

Treatment with losartan (50 mg daily) was shown to reduce the severity and frequency of attacks in primary and secondary RP at 12 weeks.

Long-term treatment of scleroderma-related digital ulcers with iloprost: a cohort study. Colaci M, Lumetti F, Giuggioli D, et al. *Clin Exp Rheumatol* 2017; 35(4): S179–83.

In this study, 50 patients with SSs received monthly infusions of 0.8–1 ng/kg/min iloprost for 10 ± 4.2 years. Of the patients who had digital ulcers at baseline, 71% recovered after treatment. Of the 19 of 50 patients without digital ulcers at baseline, only one developed digital ulcers at the end of the 10-year follow-up.

Effects of long-term cyclic iloprost therapy in systemic sclerosis with Raynaud's phenomenon: a randomized controlled study. Scorza R, Caronni M, Mascagni B, et al. Clin Exp Rheumatol 2001; 19: 503.

A 12-month prospective, randomized, parallel-group, blind-observer trial to compare the effects of intravenously infused iloprost (2 ng/kg/min on 5 consecutive days over a period of 8 hours/day and subsequently for 8 hours on 1 day every 6 weeks) with those of conventional vasodilating therapy with nifedipine (40 mg/day orally) in 46 patients with SSc and RP. Both iloprost and nifedipine were able to significantly reduce RP symptoms, with no differences between treatments.

Although multiple studies have demonstrated benefit with iloprost, other reports have demonstrated no substantial benefit from beraprost (another oral prostacyclin analog) and oral iloprost.

A systematic review and meta-analysis of the effects of topical nitrates in the treatment of primary and secondary Raynaud's phenomenon. Curtiss P, Schwager Z, Cobos G, et al. J Am Acad Dermatol 2018; 78(6): 1110–18. e3. doi:10.1016/j.jaad.2018.01.043.

Seven placebo-controlled trials comprising 346 patients were included in this systematic review. The meta-analysis reported a moderate-to-large treatment effect of nitroglycerin use in RP compared to placebo. Further, subgroup analysis found the treatment effect to be larger in secondary RP than in primary RP.

A multi-center, blinded, randomized, placebo-controlled, laboratory-based study of MQX-503, a novel topical gel formulation of nitroglycerine, in patients with Raynaud phenomenon. Hummers LK, Dugowson CE, Dechow FJ, et al. Ann Rheum Dis 2013; 72: 62–7.

In this multicenter, double-blind, randomized, placebo-controlled, crossover study, 37 subjects were treated with 0.5% or 1.25% nitroglycerin or placebo gel. There was significant improvement in skin blood flow with nitroglycerin compared with placebo.

Third-Line Therapies

• Prostaglandin E ₁ (alprostadil)	B
• Endothelin receptor antagonist (bosentan)	B
• Cilostazol	
• Pentoxifylline	B
• Glyceryl trinitrate patch	A
• Hexopal	A
• Dipyridamole and low-dose acetylsalicylic acid	B
• Calcitonin gene-related peptide	C
• L-Arginine	D
• Triiodothyronine	C
• <i>Helicobacter pylori</i> treatment	B
• Sympathectomy	C
• Low-level laser therapy	C
• Acupuncture	C
• Evening primrose oil supplementation	C
• Fish oil supplementation	B
• Statins	A
• Low-molecular-weight heparin	B

Efficacy evaluation of prostaglandin E1 against placebo in patients with progressive systemic sclerosis and significant Raynaud's phenomenon. Bartolone S, Trifilatti A, De Nuzzo G, et al. Minerva Cardioangiol 1999; 47: 137–43.

Alprostadil infusions at 60 mcg in 250 mL for 6 days reduced the frequency and severity of attacks in patients with secondary RP.

Efficacy of cilostazol for the treatment of Raynaud's phenomenon in systemic sclerosis patients. Negrini S, Spanò F, Penza E, et al. Clin Exp Med 2016; 16(3): 407–12.

In this open-label study, 13 patients received 100 mg cilostazol twice a day for 12 months. The duration and frequency of RP attacks significantly reduced after cilostazol initiation. Additionally, the visual analog scale and brachial artery diameters significantly increased after treatment.

Functional vascular disorders: treatment with pentoxifylline. Neirotti M, Longo FF, Molaschi M, et al. Angiology 1987; 38(8): 575–80.

A cohort of 11 females with RP were treated with 400 mg pentoxifylline TID for 2 months. Following treatment, 7 out of 11 patients demonstrated improvement in peripheral blood flow, decrease of attacks, and decreased pain and color change under normal conditions and under exposure to cold. Laboratory changes were significant for increase in antithrombin III levels and decrease in plasma fibrinogen; thromboelastogram was unchanged.

Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind placebo-controlled trial. Matucci-Cerinic M, Denton CP, Furst DE, et al. Ann Rheum Dis 2011; 70: 32–8.

This double-blind, placebo-controlled, multicenter trial randomized 188 patients with SSc with at least one active digital ulcer (DU) to bosentan 62.5 mg twice daily for 4 weeks and 125 mg twice daily thereafter for 20 weeks or placebo. Bosentan was found to reduce the occurrence of new DUs compared with placebo in patients with SSc, but had no effect on DU healing.

Sustained-release transdermal glyceryl trinitrate patches as a treatment for primary and secondary Raynaud's phenomenon. Teh LS, Manning J, Moore T, et al. Br J Rheumatol 1995; 34: 636–41.

In this randomized, double-blind, placebo-controlled, crossover study, patients with primary Raynaud disease and patients with RP secondary to SSc ($n=21$) were included. Glyceryl trinitrate patches (0.2 mg/h) were found to be effective in reducing the number and severity of Raynaud attacks in both groups of patients.

A double-blind randomized placebo-controlled trial of Hexopal in primary Raynaud's disease. Sunderland GT, Belch JJ, Sturrock RD, et al. Clin Rheumatol 1988; 7: 46–9.

Hexopal (hexanicotinate inositol) (2–4 g daily) is safe and effective in reducing the vasospasm of primary Raynaud disease during the winter months.

A double-blind controlled trial of low dose acetylsalicylic acid and dipyridamole in the treatment of Raynaud's phenomenon. Van der Meer J, Wouda AA, Kallenberg CG, et al. Vasa 1987; 18: 71–5.

In this placebo-controlled, double-blind study, 25 patients with RP were treated with three regimens separated by a 3-week washout period. The three regimens included: (1) acetylsalicylic acid 80 mg once daily and dipyridamole 75 mg four times a day (ASA/DIP); (2) acetylsalicylic acid 80 mg once daily and placebo-dipyridamole one coated tablet four times a day (ASA/plac./DIP); (3) placebo-acetylsalicylic acid one tablet once daily and placebo-dipyridamole one coated tablet four times daily (plac. ASA/plac. DIP). There was no significant change in RP

severity between the three treatment regimens. Treatment with ASA or DIP did not significantly impact digital blood flow during cooling or warming.

Calcitonin gene-related peptide in treatment of severe peripheral vascular insufficiency in Raynaud's phenomenon. Bunker CB, Reavley C, O'Shaughnessy DJ, et al. *Lancet* 1993; 342: 80–3.

Calcitonin gene-related peptide, a potent vasodilator, given intravenously (0.6 mcg/min for 3 hours a day for 5 days) resulted in an increase in blood flow, ulcer healing, and effective vascular dilation in patients with severe RP.

Oral L-arginine can reverse digital necrosis in Raynaud's phenomenon. Rembold CM, Ayers CR. *Mol Cell Biochem* 2003; 244: 139–41.

The authors demonstrate a beneficial response to oral L-arginine therapy (up to 8 g daily), which reversed digital necrosis and improved the symptoms of severe RP. This evidence suggests that a defect in nitric oxide synthesis or metabolism is associated with RP and demonstrates the potential effectiveness of L-arginine therapy.

Triiodothyronine treatment for Raynaud's phenomenon: a controlled trial. Dessin PH, Morrison RC, Lamparelli RD, et al. *J Rheumatol* 1990; 17: 1025–8.

In this trial, T₃ 80 mcg/day increased finger skin temperature and reduced recovery times after cold exposure. Treatment was recommended for patients with severe RP and digital ulcers.

***Helicobacter pylori* eradication ameliorates primary Raynaud's phenomenon.** Gasbarrini A, Massari I, Serrichio M, et al. *Dig Dis Sci* 1998; 43: 1641–5.

Of 46 RP patients, 36 were infected with *H. pylori*. After treatment to eradicate *H. pylori*, RP disappeared in 17% of patients; 72% of the remaining patients noticed a reduction in frequency and duration of their vasospastic attacks.

Effects of endoscopic thoracic sympathectomy on Raynaud's disease. Karapolat S, Turkyilmaz A, Tekinbas C. *J Laparoendosc Adv Surg Tech* 2018; 28(6): 726–9. doi:10.1089/lap.2017.0634.

In this retrospective review of nine patients with RP who underwent endoscopic thoracic sympathectomy, all reported improvement in symptoms at 1 month; however, at 6 months 66.6% reported recurrence of symptoms and at 1 year 89% of the patients reported no sustained improvement from the sympathectomy.

The use of digital artery sympathectomy as a salvage procedure for severe ischemia of Raynaud's disease and phenomenon. McCall TE, Petersen DPM, Wong LB. *J Hand Surg [Am]* 1999; 24: 173–7.

In six of seven patients, the use of digital artery sympathectomy was effective; the patients' digital ulcers healed and amputation was avoided.

The influence of Multiwave Locked System (MLS) laser therapy on clinical features, microcirculatory abnormalities and selected modulators of angiogenesis in patients with Raynaud's phenomenon. Kuryliszyn-Moskal A, Kita J, Dakowicz A, et al. *Clin Rheumatol* 2015; 34(3): 489–96.

In this study, 78 patients with RP were administered Multiwave Locked System (MLS) laser therapy for 3 weeks. After 3 weeks of therapy, patients reported reduced RP attack frequency and severity. Additionally, reduction in angiopoietin 2 (Ang-2) levels were found in patients with both primary and secondary RP.

Double-blind, randomised, placebo controlled low laser therapy study in patients with primary Raynaud's phenomenon. Hirschl M, Katzenschlager R, Ammer K, et al. *Vasa* 2002; 31: 91–4.

This study examined 15 patients with primary RP and demonstrated that low-level laser therapy (LLLT) reduced the intensity of the attacks during laser irradiation without significantly affecting the frequency of attacks. Additionally, after laser irradiation, the temperature gradient after cold exposure was reduced, but there was no effect on the number of fingers showing prolonged rewarming. It is hypothesized that the effects of LLLT on vasoregulation are based on an endothelium-independent pathway by acting on cell membrane permeability.

Treatment of primary Raynaud's syndrome with traditional Chinese acupuncture. Appiah R, Hiller S, Caspary L, et al. *J Intern Med* 1997; 241: 119–24.

Thirty-three patients with primary Raynaud disease (16 controls, 17 treatment) were studied. Overall, attacks were reduced by 63%.

Evening primrose oil (Efamol) in the treatment of Raynaud's phenomenon: a double-blind study. Belch JJ, Shaw B, O'Dowd A, et al. *Thromb Haemost* 1985; 54: 490–4.

Twenty-one patients were studied. Evening primrose oil (12 capsules daily) provided symptomatic improvement.

Fish-oil dietary supplementation in patients with Raynaud's phenomenon: a double blind controlled, prospective study. DiGiacomo RA, Kremer JM, Shah DM. *Am J Med* 1989; 86: 158–64.

In this trial involving 32 patients, supplementation with omega-3 fatty acids (3.96 g eicosapentaenoic acid and 2.64 g docosahexaenoic acid) was shown to be of benefit in patients with primary, but not secondary, RP.

Statins: potentially useful in therapy of systemic sclerosis-related Raynaud's phenomenon and digital ulcers. Abou-Raya A, Abou-Raya S, Helmii M. *J Rheumatol* 2008; 35: 1801.

This randomized trial involving 84 patients demonstrated that atorvastatin 40 mg daily for 4 months reduced the overall number of digital ulcers, severity, and pain in SSC-related RP.

Long-term low molecular weight heparin therapy for severe Raynaud's phenomenon: a pilot study. Denton CP, Howell K, Stratton RJ, Black CM. *Clin Exp Rheumatol* 2000; 18: 499.

Low-molecular-weight heparin was used as an add-on therapy for patients with primary or secondary RP already receiving at least one oral therapy for Raynaud phenomenon. There was an improvement in attack severity after 4 weeks of heparin therapy, which reached maximal improvement by 20 weeks, compared with the control group.

Reactive arthritis

Saakshi Khattri, Clinton W. Enos, Sara Samimi,
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Reactive arthritis (ReA), formerly known as *Reiter syndrome*, is a type of sterile synovitis that follows an enteric or urogenital infection. It is a type of seronegative spondyloarthropathy. This condition is thought to arise in a susceptible host following an environmental trigger with skin and joint manifestations that develop 2–4 weeks after an enteric or urogenital infection. Commonly implicated gastrointestinal pathogens include *Yersinia*, *Salmonella*, *Shigella*, *Campylobacter*, and *Clostridium difficile*; common urogenital pathogens include *Chlamydia trachomatis*, *Neisseria gonorrhea*, and *Ureaplasma urealyticum*. Rarely, ReA can manifest after a respiratory infection with *Chlamydia pneumoniae* or group A β -hemolytic streptococcus. ReA is a relatively rare condition that is more common in young adults ages 20–40. There is no predilection for either sex when a gastrointestinal pathogen is the inciting agent; however, males have a greater incidence after *Chlamydia trachomatis* infection. The HLA-B27 allele has been associated with ReA, although it is not a diagnostic criterion.

ReA is a clinical diagnosis characterized by a triad of urethritis, conjunctivitis, and oligoarthritis; however, only roughly one-third of patients present with a complete triad, making the diagnosis largely dependent on patient history. General guidelines set forth by the American College of Rheumatology (ACR) proposed major and minor criteria to aid in a definite diagnosis (see later). Similarly, European guidelines for sexually acquired ReA incorporate the recognition of a monoarthritis or oligoarthritis preceded by a symptomatic urethritis. Additional extraarticular findings can include enthesitis, tendinitis, bursitis, conjunctivitis, anterior uveitis, and keratitis. The classic skin manifestations include keratoderma blennorrhagica and circinate balanitis. Nail changes, oral lesions, and ulcerative vulvitis may also be seen. Erythema nodosum can also occur and is more common in the

setting of a *Yersinia* infection. The differential diagnosis may include atopic dermatitis, Behçet disease, contact dermatitis, and pustular psoriasis.

MANAGEMENT STRATEGY

The mucocutaneous lesions of uncomplicated ReA are usually self-limited and clear within a few months. Severe, extensive, and chronic cutaneous presentations, which are more common in the setting of human immunodeficiency virus (HIV) infection, are generally treated in the same manner as pustular psoriasis. Initial therapy for limited skin disease includes *topical steroids*, *topical vitamin D preparations*, *tacrolimus*, and *tazarotene*. Second-line agents include *ultraviolet B (UVB)* and *systemic retinoids*. Severe disease can be treated with *psoralen plus ultraviolet A (PUVA)* and *immunosuppressive agents such as methotrexate and ciclosporin*. *Anti-tumor necrosis factor (TNF)* agents have also been used successfully in patients with refractory disease as well as those with HIV, but data from randomized, placebo-controlled trials are lacking.

In most patients, the symptoms of arthritis and inflammation of the peripheral ligamentous or muscular attachments (entheses) dictate the focus of treatment. *Non-steroidal antiinflammatory drugs (NSAIDs)* are the first-line therapy. *Corticosteroid injections* can provide temporary relief of the pain caused by arthritis or bursitis, and oral corticosteroids may also be beneficial when severe. *Sulfasalazine* and *methotrexate* have been shown to be effective and well tolerated in cases refractory to both NSAIDs and steroids. *TNF inhibitors* have also shown efficacy in treating severe disease. Only one case report of use of an IL-17 blocker (secukinumab) and another with an IL-6 receptor blocker (tocilizumab) in ReA was found. Of note, other biologics such as ustekinumab, apremilast, guselkumab, and risankizumab have not been investigated in the treatment of ReA.

Transient and mild conjunctivitis does not require specific therapeutic intervention. Symptoms of eye pain or blurry vision require immediate referral to ophthalmology to determine whether these symptoms are due to conjunctivitis or a more serious eye problem such as uveitis, iritis, or keratitis. Treatment often involves topical and/or systemic corticosteroids and immunosuppressive medications such as methotrexate.

The effects of short-term and long-term *antibiotic therapy* for ReA are controversial. Although there is some evidence that antibiotics may be beneficial during the infectious phase before arthritis has developed, it is not clear whether the introduction of antibiotics after the development of arthritis will modify the disease course. A meta-analysis of 10 trials indicated that there is no significant benefit for the use of antibiotics in ReA. However, due to the heterogeneity of trials included in this analysis, the possible benefit of antibiotics in certain subgroups or at certain time points cannot be completely excluded. For example, a double-blind, placebo-controlled study suggested no advantage of combination antibiotics (roxithromycin and ofloxacin) over placebo in the treatment of recent-onset ReA, but another small study reports a beneficial effect of combination treatment with *doxycycline* and *rifampin* for chronic spondyloarthritis. If the inciting organism is documented by culture or polymerase chain reaction (PCR), antibiotics are indicated. The true benefits of antibiotics, their dosage, and their duration remain to be clarified. However, when evaluating a patient with ReA after a urogenital infection, it is also important to consider treatment of the patient's partner for further disease prevention.

ReA in HIV-infected individuals may be more prevalent, severe, and progressive because it is more refractory to treatment. However, one report describes ReA as part of an immune reconstitution

syndrome that is rapidly responsive to a 2-week course of doxycycline. Another case report describes the resolution of ReA symptoms upon initiating antiretroviral therapy. The pathogenic link between HIV and ReA is not completely understood; however, case reports highlight the benefit of closely comanaging HIV-1 infection and the symptoms of ReA.

Specific Investigations

- Recent history of gastrointestinal or genitourinary infection or symptoms
- Skin biopsy
- Urinalysis
- Urethral, cervical, and stool cultures
- Serum antibodies to chlamydia
- Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count
- HIV testing/status
- Rheumatoid factor and antinuclear antibody (ANA) (negative in reactive arthritis)
- Synovial fluid analysis
- Radiographic imaging
- HLA-B27 typing
- Ophthalmologic slit lamp examination
- Electrocardiogram (ECG) in chronic disease

Proposed Diagnostic Criteria by the ACR (1999)

Major criteria:

1. Arthritis with at least two of the following: asymmetry, monoarthritis or oligoarthritis, lower limb involvement
2. Preceding symptomatic infection
 - a. Enteritis that consists of diarrhea for at least 1 day, 3 days to 6 weeks before onset of arthritis
 - b. Urethritis that consists of dysuria for at least 1 day, 3 days to 6 weeks before onset of arthritis

Minor criteria:

1. Evidence of a triggering infection via one or both of the following:
 - a. Positive nucleic acid amplification test in morning urine or urethral/cervical swab positive for *Chlamydia trachomatis*
 - b. Positive stool cultures for pathogens associated with ReA
2. Evidence of persistent synovial infection via immunohistochemical or PCR studies for *Chlamydia*

A definite diagnosis includes both major criteria and a relevant minor criterion. A probable diagnosis consists of both major criteria with no minor criteria, or one major criterion and one or more relevant minor criteria.

First-Line Therapies

Cutaneous disease

• Topical steroids	C
• Calcipotriene (calcipotriol)	E
• Tazarotene	E
• Tacrolimus	E

Reiter Syndrome

Mucocutaneous lesions may necessitate only local care for mucosal erosions and topical steroids for psoriasiform lesions. Rothe MJ, Kerdel FA. *Int J Dermatol* 1991; 30: 173–80.

Because treatment in ReA is typically directed toward the musculoskeletal component and urethritis, there is a paucity of studies designed for the treatment of cutaneous disease. However, despite the lack of controlled studies, topical steroids are accepted as first-line therapy for mild cutaneous lesions.

Successful treatment of chronic skin disease with clobetasol propionate and a hydrocolloid dressing. Volden G. *Acta Derm Venereol* 1992; 72: 69–71.

Two patients with skin lesions of reactive arthritis and 19 patients with palmoplantar pustulosis responded to clobetasol propionate lotion once weekly under occlusion. The mean interval to remission was 3 weeks for the skin lesions of ReA and 2.2 weeks for palmoplantar pustulosis.

Reiter's disease in a homosexual HIV-positive male. Vaughan Jones SA, McGibbon DH. *Clin Exp Dermatol* 1994; 19: 430–3.

A case report of a 32-year-old male with AIDS whose psoriasiform lesions improved after 2 weeks of topical corticosteroids and a course of flucloxacillin.

Tacrolimus therapy for circinate balanitis associated with reactive arthritis. Herrera-Esparza R, Medina F, Avalos-Diaz E. *J Clin Rheumatol* 2009; 15: 377–9.

A report of three patients with evidence of circinate balanitis refractory to systemic therapy with corticosteroids and sulfasalazine but responsive to treatment with topical tacrolimus 0.1%.

Reiter's disease in a 6-year-old girl. Arora S, Arora G. *Indian J Dermatol Venereol Leprol* 2005; 71: 285–6.

A case report of a 6-year-old child with ReA whose primary keratoderma blennorrhagicum lesions were treated with topical salicylic acid and hydrocortisone with complete resolution in 3 weeks.

The use of topical calcipotriene/calcipotriol in conditions other than plaque-type psoriasis. Thiers BH. *J Am Acad Dermatol* 1997; 37: S69–71.

A 47-year-old man with relapsing ReA, with pustules and hyperkeratotic plaques on his palms and soles, as well as circinate balanitis, responded to 14 days of doxycycline (100 mg twice a day) and topical calcipotriene.

Treatment of keratoderma blennorrhagicum with tazarotene gel 0.1%. Lewis A, Nigro M, Rosen T. *J Am Acad Dermatol* 2000; 43: 400–2.

A case report of a 64-year-old man with ReA who responded to daily application of tazarotene gel 0.1% to his soles.

Second-Line Therapies

Cutaneous disease

• Systemic retinoids	D
• UVB/PUVA	D
• Antiretroviral therapy	E

Acitretin and AIDS-related Reiter's disease. Blanche P. *Clin Exp Rheum* 1999; 17: 105–6.

A case report of a 46-year-old patient with AIDS and ReA whose arthritis and skin lesions responded to 2 weeks of acitretin (25 mg daily). Therapy was continued for 5 months; a recurrence occurred several months after the acitretin was stopped despite maintenance on antiretroviral therapy. Acitretin was resumed,

resulting in prompt resolution of disease, and continued for 6 months. No recurrence was observed after 13 months.

Reiter's syndrome-like pattern in AIDS-associated psoriasiform dermatitis. Romani J, Puig L, Baselga E. *Int J Dermatol* 1996; 35: 484–8.

A retrospective review of seven HIV-positive patients with Reiter-like psoriasiform dermatitis. Etretinate alone and RePUVA (etretinate 1 mg/kg daily, 8-methoxypsoralen 0.6 mg/kg followed by UVA) were safe and effective in controlling skin disease. Methotrexate (15 mg weekly in three divided doses) was effective but complicated by hematologic toxicity in two patients. Cyclosporin (2.5 mg/kg daily) was moderately effective and not associated with progression of AIDS.

Successful treatment of severe Reiter's syndrome associated with human immunodeficiency virus infection with etretinate. Report of 2 cases. Louthrenoo W. *J Rheumatol* 1993; 20: 1243–6.

A report of two cases of HIV-related ReA responding dramatically to 4 weeks of etretinate (0.5–1.0 mg/kg daily).

Reactive arthritis responding to antiretroviral therapy in an HIV-1-infected individual. Scott C, Brand A, Natha M. *Int J STD AIDS* 2012; 23: 373–4.

A report of an HIV-1 infected patient with severe ReA who failed conventional therapy with steroids, disease-modifying antirheumatic agents, and NSAIDs but experienced resolution of ReA symptoms after initiation of antiretroviral therapy. Antiretroviral use may be beneficial for symptomatic relief, suggesting that patients should be managed closely by both rheumatology and infectious disease.

Human immunodeficiency virus associated spondyloarthritis: pathogenic insights based on imaging findings and response to highly active antiretroviral treatment. McGonagle D, Reade S, Emery P. *Ann Rheum Dis* 2001; 60: 696–8.

Case report of a 31-year-old HIV-positive man with ReA with extensive polyarthralgia and osteitis. The patient's arthritis worsened despite treatment, including indomethacin, tramadol, and sulfasalazine, but improved dramatically after antiretroviral treatment (lamivudine, zidovudine, and zalcitabine). Improvement was accompanied by a significant rise in CD4 T-lymphocyte counts.

Clinical improvement of HIV-associated psoriasis parallels a reduction of HIV viral load induced by effective antiretroviral therapy. Fischer T, Ramadori G. *AIDS* 1999; 13: 628–9.

Case report of a 38-year-old HIV-positive male with viremia and psoriasis. The patient was started on multiple antiretroviral agents in addition to topical steroids and vitamin D₃ analogs. Despite antiretroviral therapy, his viral load remained high and his psoriasis persisted. It was not until his viral load decreased below 400 that his skin lesions started to improve.

Third-Line Therapies

Cutaneous disease

• Methotrexate	C
• Cyclosporin	E
• TNF inhibitors	C
• Other biologics	E

A review of methotrexate therapy in Reiter syndrome. Lally EV, Ho G Jr. *Semin Arthritis Rheum* 1985; 15: 139–45.

A case report and review of the literature. Eighteen of 20 patients noted dramatic improvement in skin lesions within 2 weeks of receiving methotrexate; 15 of 20 patients had significant improvement in arthritis, although the response was generally slower. Methotrexate was generally well tolerated, but the drug had to be discontinued in three cases due to adverse effects. Methotrexate was used for exacerbations and was then discontinued after clinical improvement. The usual dosage was 10–50 mg/week administered either orally or parenterally.

Successful treatment of Reiter's syndrome in a patient with AIDS with methotrexate and corticosteroids. Berenbaum F, Duvivier C, Prier A. *Br J Rheumatol* 1996; 35: 295.

A case report of a 37-year-old man with AIDS and severe ReA who responded to prednisone 20 mg daily and methotrexate 20 mg/week. This was combined with antiretroviral therapy, chemoprophylaxis of infection, and aggressive therapy of Kaposi sarcoma without exacerbation of his AIDS.

Successful treatment of severe recurrent Reiter's syndrome with cyclosporine. Kiyohara A, Ogawa H. *J Am Acad Dermatol* 1997; 36: 482–3.

A case report of a 48-year-old man with postchlamydia ReA not responsive to topical steroids and etretinate treated successfully with 5 mg/kg daily cyclosporin that was slowly tapered. No recurrence of the disease was noted at 18 months.

Infliximab in the treatment of an HIV positive patient with Reiter's syndrome. Gaylis N. *J Rheumatol* 2003; 30: 2.

A case report of a 41-year-old man with ReA who responded to infliximab, methotrexate, and systemic corticosteroid treatment regimens. During therapy his arthritis resolved, as did the onycholysis and keratoderma blennorrhagica of the soles. The patient was able to discontinue systemic corticosteroids and was maintained on intravenous infliximab at a dose of 300 mg (3 mg/kg) every 6–7 weeks and intramuscular methotrexate at a dose of 15 mg/week for 18 months without a decrease in his CD4 cells or a rise in his viral load.

Decreased pain and synovial inflammation after etanercept therapy in patients with reactive and undifferentiated arthritis: an open-label trial. Flagg S, Meador R, Schumacher HR. *Arthritis Rheum* 2005; 53: 613–7.

Describes a 6-month open-label trial of 16 patients with undifferentiated or reactive arthritis treated with etanercept (25 mg subcutaneous twice weekly). Seven patients met the criteria for ReA, and nine had a similar pattern of arthritis without evidence of infection. Ten patients completed the trial. Three patients tested positive for HLA-B27. All patients had been on NSAIDs, and 11 had been treated with sulfasalazine and/or methotrexate. Of the 10 completers, nine were classified as responders with less tender joints and decreased swelling of joints. The tenth had improvement in pain but no change in the number of tender or swollen joints.

Successful use of infliximab in the treatment of Reiter's syndrome: a case report and discussion. Gill H, Majithia V. *Clin Rheumatol* 2008; 27: 121–3.

A case report of a 28-year-old man with HIV with ReA complicated by circinate balanitis and arthritis, as well as onycholysis and keratoderma blennorrhagica who did not respond to aggressive treatment with NSAIDs, prednisone (60–20 mg/day), and methotrexate (15 mg/week) for 3 months. He was treated with infliximab 200 mg (3 mg/kg) intravenously with rapid improvement

of skin lesions and arthritis. This regimen was well tolerated. The patient was subsequently lost to follow-up.

Use of adalimumab in poststreptococcal reactive arthritis. Sanchez-Cano D, Callejas-Rubio JL, Ortego-Centeno N. *J Clin Rheum* 2007; 13: 176.

A case report describing a 21-year-old female with oligoarthritis affecting the lower extremities after pharyngitis 2 weeks before the onset of arthritis. NSAIDs, prednisone (1 mg/kg/day), hydroxychloroquine (6 mg/kg/day), and methotrexate (25 mg/weekly) were not effective. Clinical response was achieved 8 weeks after introduction of adalimumab (40 mg subcutaneously every 2 weeks) and was maintained. Steroids and methotrexate were discontinued; no side effects were observed after 1 year of treatment with adalimumab.

The use of antitumor necrosis factor therapy in HIV-positive individuals with rheumatic disease. Cepeda E, William F, Ishimori M, et al. *Ann Rheum Dis* 2008; 67: 710–2.

Eight HIV-positive patients with rheumatic diseases (two with rheumatoid arthritis, three with psoriatic arthritis, one with ReA, one with undifferentiated spondyloarthritis, and one with ankylosing spondyloarthritis) refractory to disease-modifying antirheumatic drugs who had a CD4 count $>200\text{ mm}^3$ and an HIV viral load of $<60,000$ copies/ mm^3 and no active concurrent infections were treated with TNF blockers. No significant clinical adverse effect was noted over 28 months. CD4 counts and HIV viral loads remained stable. Three patients on etanercept and two on infliximab had sustained improvement in their rheumatic disease.

Prolonged remission of chronic reactive arthritis treated with three infusions of infliximab. Wechalekar M, Rischmueler M, Whittle S, et al. *J Clin Rheumatol* 2010; 16: 79–80.

A case report of a 25-year-old female with an 11-month history of progressive oligoarthritis and increasing CRP after *Chlamydia trachomatis* infection. She failed treatment with azithromycin, NSAIDs, corticosteroid injections, methotrexate, sulfasalazine, and hydroxychloroquine. Subsequently, infliximab at a dose of 6 mg/kg was given. After the first two doses her symptoms resolved with normalization of her CRP. Methotrexate, sulfasalazine, and hydroxychloroquine were tapered without evidence of recurrent disease.

Safety and efficacy of antitumor necrosis factor α therapy in ten patients with recent-onset refractory reactive arthritis. Meyer A, Chatelus E, Wendling D, et al. *Arthritis Rheum* 2011; 63: 1274–80.

A retrospective review of anti-TNF- α therapy in 10 patients with evidence of new-onset ReA. Five patients were given infliximab (4 received 5 mg/kg and 1 received 3 mg/kg), four etanercept (50 mg/week), and one adalimumab (40 mg every 2 weeks). Concomitant therapies included NSAIDs (7 patients), oral corticosteroids (8 patients), methotrexate (7 patients), and sulfasalazine (3 patients). No severe adverse events were reported during the median 20.6 months. Nine of 10 patients had improvement in their rheumatic symptoms with a median of 15 days for $>30\%$

improvement in their pain score and tender joint count, and a median of 33 days for $>30\%$ improvement in their swollen joint count. Improvement of anterior uveitis (in 5 patients after 6 months) and cutaneous manifestations were also noted.

Spectacular evolution of reactive arthritis after early treatment with infliximab. Thomas-Pohl M, Tissot A, Banal F, et al. *Joint Bone Spine* 2012; 79: 524.

A case report describing a 32-year-old male with acute febrile polyarthritis 1 month after gastrointestinal infection. After failing NSAIDs, ofloxacin (200 mg twice daily for 16 days), rifampin (300 mg twice daily for 4 days), and methylprednisone, he was given infliximab (5 mg/kg). Immediately after the infusion, he reported a decrease in pain with improvement of inflammatory markers.

Antibiotics

Antibiotics for treatment of reactive arthritis: a systematic review and meta-analysis. Barber CE, Kim J, Inman RD, et al. *J Rheumatol* 2013; 40: 916–28.

A meta-analysis of 10 out of 12 eligible trials. There was no significant benefit comparing antibiotic use and disease remission. The authors also reported substantial heterogeneity in the results and attributed this to differences in study design. Ultimately, the efficacy of antibiotics remains uncertain.

Combination antibiotics as a treatment for chronic *Chlamydia*-induced reactive arthritis: a double-blind, placebo controlled, prospective trial. Carter JD, Espinoza LR, Inman RD, et al. *Arthritis Rheum* 2010; 62: 1298–307.

A prospective randomized trial with 42 patients who had evidence of chronic postchlamydial reactive arthritis. Patients were randomized to receive either doxycycline and rifampin (12 patients), azithromycin and rifampin (15 patients), or matching oral placebos (15 patients) for 6 months; 22% of subjects on combination antibiotic therapy achieved complete resolution of their symptoms in comparison to 0% of those receiving placebo. An increased number of patients in the antibiotic group became PCR negative for *Chlamydia* compared with the placebo group.

Retrospective case series of 12 patients with chronic reactive arthritis with emphasis on treatment outcome with biologics. Gupta V, Mohta P, Sharma VK, Indian J. *Dermatol Venereol Leprol* 2019 Jul 11 [Epub ahead of print].

A retrospective case series of 12 patients with reactive arthritis who received different biologics for the treatment of chronic reactive arthritis. One out of 12 received secukinumab. Other biologics in the study were infliximab, etanercept, and adalimumab. Biologic use was associated with skin and joint improvement.

Successful treatment of reactive arthritis with a humanized anti-interleukin-6 receptor antibody, tocilizumab. Tanaka T, Kuwahara Y, Shima Y, et al. *Arthritis Rheum* 2009; 61(12): 1762–4.

Case report of use of tocilizumab in a patient with reactive arthritis with rapid improvement in joint symptoms after two injections.

Relapsing polychondritis

Sumera Qureshi, David P. D'Cruz



Relapsing polychondritis is an autoimmune rheumatic disorder characterized by cartilage inflammation. Characteristic features include nasal bridge, auricular and ocular inflammation, and major airway disease. It is rare with an incidence of 0.71/million/year, with an estimated increased mortality rate of 2–3 times that of the general population, and there is often a delay in establishing a diagnosis. There is an associated autoimmune condition in 8–20% of patients with relapsing polychondritis.

The diagnosis is established by the presence of chondritis in two of three characteristic anatomic sites: auricular, nasal, laryngotracheal, or one of these sites and two other features, including ocular inflammation, audiovestibular damage, or seronegative inflammatory arthritis. In most patients, histologic confirmation is not necessary for diagnosis.

Auricular chondritis manifests as ear pain, redness, and swelling with sparing of the non-cartilaginous lobule. After repeated relapses, the pinnae may be floppy and distorted or have a cauliflower-like appearance. The ear may become rigid after extensive calcification. Hearing loss, either sensory or conductive, can occur in up to 50% of cases.

Recurrent nasal chondritis results in a saddle-nose deformity.

Skin manifestations include oral ulceration, sometimes with genital ulceration, nodules, purpura, papules, sterile pustules, superficial phlebitis, livedo reticularis, skin ulcers, and distal necrosis.

Laryngotracheal chondritis presents with hoarseness, tracheal ring tenderness, cough, breathlessness, and stridor. All patients with suspected pulmonary disease should undergo computed tomography (CT) imaging, including end-inspiratory and dynamic expiratory volumetric imaging. End-inspiratory scanning may reveal tracheal and bronchial stenosis, wall thickening, and calcification. Expiratory scans may demonstrate tracheobronchial malacia with airway collapse and air trapping. Airway

manifestations are ultimately present in over 50% of patients and are the leading cause of death. Cardiovascular complications eventually occur in half of all patients and are the second most frequent cause of mortality. Aortic involvement, leading to aneurysmal disease, is the most common cardiac manifestation. Cardiac manifestations can also include aortic regurgitation, aortic aneurysm, atrioventricular block, mitral regurgitation, and acute pericarditis, making periodic cardiac examination mandatory.

Central and peripheral nerve involvement is rare. Cranial nerve lesions are the most common, but other complications include seizures, cerebral dysfunction, confusion, headaches, cerebral aneurysm, and rhombencephalitis.

All patients should be monitored for the development of renal disease with routine urine dip testing for blood and protein.

Disease activity is assessed clinically by standard methods. There is an objective scoring system, the Relapsing Polychondritis Disease Activity Index (RPDAI), that provides objective disease assessment for use in clinical studies. An updated new scoring system to assess damage, relapsing polychondritis disease activity (RPDAM), based on expert opinions has been developed but this has yet to be validated.

Otologic manifestations of relapsing polychondritis. Review of literature and report of nine cases. Bachor E, Blevins NH, et al. *Auris Nasus Larynx* 2006; 33: 135–41.

A good description of the broad spectrum of ear manifestations. No patients died, suggesting patients with limited disease have a good prognosis.

Up to 46% of patients have impaired hearing, and inadequately treated patients can suffer permanent hearing loss. Screening audiometry should be mandatory.

Aortic involvement in relapsing polychondritis: case-based review. Erdogan M, Esatoglu S, Hatemi G, Hamuryudan V. *Rheumatol Int.* 2021; 41: 827–837.

This paper highlights a case series of 114 patients, where aortic disease was the predominant feature.

In total, 93 (82%) patients had aortic vessel involvement, while aortic valve involvement was identified in 41 patients (36%). At the time of aortic involvement diagnosis, 19% of the patients were asymptomatic. Aortic dissection and rupture were the most frequent causes of mortality.

Tracheobronchial involvement of relapsing polychondritis. de Montmollin N, Dusser D, et al. *Autoimmun Rev* 2019 Sep; 18(9). <https://doi.org/10.1016/j.autrev.2019.102353>.

This article reviewed the frequency of respiratory involvement, with recommended investigations and monitoring schedules in this group of patients.

Pulmonary function tests should be routinely performed at diagnosis and during follow-up on a yearly basis. A chest CT scan should include the cervical portion of the trachea and dynamic expiratory scans. It should be performed, even in asymptomatic patients, at the time of diagnosis and repeated as necessary during the evolution of the disease.

Relapsing polychondritis: prevalence of expiratory CT airway abnormalities. Lee KS, Ernst A, et al. *Radiology* 2006; 240: 565–73.

Dynamic expiratory CT scans demonstrated abnormalities such as tracheomalacia and air trapping in 94% of relapsing polychondritis patients who had pulmonary symptoms, yet only half the patients demonstrated abnormalities on routine inspiratory CT scans. The most common findings were air trapping (94%), malacia (72%), and calcification (39%).

Expiratory CT scans show clinically relevant bronchopulmonary abnormalities earlier than standard inspiratory CT scans, mandating earlier institution of aggressive therapy to prevent disease progression.

Fluorodeoxyglucose positron emission tomography/computed tomography in the diagnosis, assessment of disease activity and therapeutic response in relapsing polychondritis. Sharma A, Kumar R, et al. *Rheumatology (Oxford)* 2020 Jan 1; 59.

In this case series positron emission tomography/CT (PET-CT) was performed in 25 adult patients, with a confirmed diagnosis of relapsing polychondritis. It was found to positively correlate with the clinical symptoms and detected asymptomatic large airway involvement in seven patients (28%).

Ten patients had a follow-up PET-CT to assess disease activity, which demonstrated remission in five cases.

PET-CT is now increasingly recognized as the gold standard for assessing disease activity in clinically inaccessible sites. Baseline evaluation with PET-CT should be considered in all patients, particularly with apparently limited clinical symptoms.

Dermatologic manifestations of relapsing polychondritis. A study of 200 cases at a single center. Francés C, el Rassi R, et al. *Medicine (Baltimore)* 2001; 80: 173–9.

Cutaneous manifestations of patients with relapsing polychondritis: an association with extracutaneous complications. Shimizu J, Oka H, Yamano Y, et al. *Clin Rheumatol* 2016; 35: 781–3.

Two of the largest series in the literature of >200 patients described a variety of skin manifestations, including oral ulceration sometimes with genital ulceration, nodules, purpura, papules, sterile pustules, superficial phlebitis, livedo reticularis, neutrophilic dermatoses including Sweet syndrome, skin ulcers, and distal necrosis. In Francés et al.'s paper, oral ulceration was the most common finding in patients with relapsing polychondritis who did not have any other disease, and in seven patients genital ulcers were also seen. The acronym MAGIC (mouth and genital ulceration with inflamed cartilage) has previously been coined to describe patients who appear to have relapsing polychondritis with oral and genital ulceration. However, this syndrome is controversial, and these patients are more likely to be an overlap of Behçet disease with relapsing polychondritis, especially as relapsing polychondritis may occur in association with other autoimmune rheumatic diseases.

Nodules on the limbs were the most common skin lesions and have been described as erythema nodosum-like lesions with septal panniculitis. Histologic findings included vasculitis in 19 patients (leukocytoclastic in 17 and lymphocytic in two), neutrophil infiltrates in six, thrombosis of skin vessels in four, septal panniculitis in three, and minor non-specific changes in two patients. Both these studies described patients with myelodysplastic syndromes and relapsing polychondritis, and these patients were much more likely to have dermatologic manifestations, most commonly limb nodules, purpura, papules, and livedo reticularis, as well as neutrophilic dermatoses including Sweet syndrome.

Association of myelodysplastic syndrome and relapsing polychondritis: further evidence. Hebbbar M, Brouillard M, et al. *Leukemia* 1995; 9: 731–3.

Twenty-eight percent (5 of 18) of relapsing polychondritis patients over a period of 13 years were found to have myelodysplastic syndromes.

Anemia is a poor prognostic sign in patients with relapsing polychondritis; those with concurrent myelodysplasia often develop refractory anemia requiring transfusions. Several patients have progressed to leukemia.

MANAGEMENT STRATEGY

Treatment of relapsing polychondritis is aimed at reducing inflammation, which may progressively destroy the ears, nose, eyes, joints, respiratory tract, and cardiovascular system. A multidisciplinary approach, including referral to specialist centers, is crucial to evaluate and treat multiple organ involvement. There are no controlled trials: treatment is empiric and should be tailored to the severity of disease.

Mildly affected patients may be managed using *non-steroidal antiinflammatory agents*. They should be used sparingly and for short periods given the long-term risks of gastrointestinal, renal, and cardiovascular complications. *Colchicine* 0.5 mg twice daily and *dapsone* 50–100 mg daily have also provided benefit, but toxicity may occur, especially with dapsone and G6PD (glucose-6-phosphate dehydrogenase) deficiency.

Corticosteroids are widely used for more severe disease. Life-threatening airway obstruction may be treated with *pulsed intravenous methylprednisolone* (500 mg to 1 g/day for 3 days). The traditional dose of 1 mg/kg/day is completely non-evidence based, is excessive, and should be abandoned. High-dose corticosteroids contribute significantly to long-term damage, which is associated with premature mortality. Most patients with moderate disease will benefit from doses of prednisolone between 10 and 20 mg daily in a tapering dose irrespective of body weight. The lowest possible maintenance dose should be used, and some patients may be able to use *intermittent short courses of prednisolone 20 mg daily for 1–2 weeks*. Osteoporosis prevention with calcium and vitamin D supplementation and bisphosphonates should be considered in corticosteroid-dependent patients.

Second-line therapies should be considered for patients unable to taper corticosteroid doses. The most commonly used agents are *methotrexate* (considered first line by most experts) 5–25 mg weekly, *azathioprine* 1.5–2 mg/kg/day, *cyclosporin* 5 mg/kg/day, *mycophenolate mofetil* 2–3 g/day, *leflunomide*, and *chlorambucil*. Intravenous *cyclophosphamide* has been used for severe, rapidly progressive, and life-threatening disease, especially for aortitis or glomerulonephritis. Plasma exchange and *intravenous immunoglobulin* (IVIG) therapy are usually not successful, but isolated case reports have described clinical benefit.

Biologic agents are increasingly being used off label for treatment-resistant patients with some success. *Infliximab*, *adalimumab*, *etanercept*, *tocilizumab*, and *anakinra* have all been reported to improve disease control described most recently in a multicenter case series from France, where 41 patients with refractory disease were treated (see below).

Topical steroids may be used to treat skin manifestations and are standard therapy for ocular inflammation. Inhaled steroids may be useful in mild airway inflammation and nebulized ephedrine has been used occasionally.

Respiratory support with continuous positive airway pressure and other non-invasive ventilation devices may improve quality of life for patients where surgical intervention or stenting is not feasible.

Surgical intervention may be needed acutely when tracheostomy is needed for tracheal stenosis. Other surgical interventions to manage fibrotic or stenotic complications should only be considered electively when the disease is in remission. Tracheal surgery, including reconstruction procedures, may be needed for

localized stenosis. Balloon dilatation may be used either alone or in combination with other surgical procedures. Large airway stenting has been successfully used, although metallic stents may erode the airways and silicon stents are more likely to migrate.

Cardiac valve replacement and aortic surgery are associated with significant surgical morbidity and mortality, but several case reports describe successful outcomes. Any general anesthetic that requires intubation and ventilation before surgery requires careful preoperative anesthetic review.

Specific Investigations

- Otolaryngologic evaluation
- Audiometry
- Pulmonary evaluation
- Chest radiograph and/or CT/magnetic resonance imaging (MRI)
- Dynamic expiratory CT examination
- PET-CT of large airways
- Pulmonary function tests (especially flow/volume loops)
- Endobronchial ultrasonography
- Cardiovascular examination
- Electrocardiogram and/or echocardiogram (CT/MRI may also be useful)
- Ophthalmologic examination
- Urinalysis
- Bloods: immunological serology (e.g., rheumatoid factor, antinuclear antibody [ANA], antineutrophil cytoplasmic antibodies [ANCA]), hematological screen (e.g., full blood count, blood film), and myeloma screen

First-Line Therapies

• NSAIDs	D
• Colchicine	C
• Dapsone	C
• Systemic corticosteroids	C

Treatment of relapsing polychondritis with dapsone. Baranco VP, Monor DB, Solomon H. Arch Dermatol 1976; 112: 1268–88.

Three patients were successfully treated with dapsone (100–200 mg daily), each showing complete resolution of an acute attack of relapsing polychondritis within 2 weeks of starting therapy.

Although not all patients respond to dapsone, those who do may improve dramatically within 1–2 weeks. The effectiveness of dapsone seems to be dose dependent, with 200 mg daily being the most commonly reported effective dose. G6PD levels should be measured before treatment to avoid the risk of dapsone-induced hemolytic anemia.

Use of inhaled fluticasone propionate to control respiratory manifestations of relapsing polychondritis. Tsuburai T, Suzuki M, Tsurikisawa N, et al. Respirology 2009; 14: 299–301.

A 19-year-old patient with relapsing polychondritis used high-dose fluticasone propionate, which reduced oral corticosteroid requirements and dramatically decreased the patient's obstructive airway impairment.

Relapsing polychondritis. Kent PD, Michet CJ Jr, Luthra HS. Curr Opin Rheumatol 2004; 16: 56–61.

A well-written and comprehensive review of the clinical features, assessment, and management of relapsing polychondritis.

Recommendations for corticosteroid doses are given, ranging from 10 to 20 mg daily of prednisolone for mild-to-moderate disease up to high-dose prednisolone and intravenous methylprednisolone 500 mg to 1 g/day for 3 days.

Second-Line Therapies

• Azathioprine	D
• Ciclosporin	D
• Methotrexate	D
• Mycophenolate mofetil	D
• Leflunomide	D
• Cyclophosphamide	E
• Intravenous immunoglobulin	E
• Infliximab	D
• Adalimumab	E
• Etanercept	E
• Inhaled fluticasone	E
• Continuous positive airway pressure	E
• Tracheobronchial stents	E

Relapsing polychondritis: a clinical update. Longo L, Greco A, Rea A, et al. Autoimmun Rev 2016; 15: 539–43.

An excellent clinical review of relapsing polychondritis and its treatment, covering the use of corticosteroids, immunosuppressive agents, and biologics in some depth.

Efficacy and safety of biologics in relapsing polychondritis: a French national multicentre study. Moulis G, Pugnet G, et al. Ann Rheum Dis 2018; 77(8): 1172–8.

This multicenter, retrospective cohort study described patients treated with biologics for relapsing polychondritis. Clinical response (partial or complete) during the first 6 months, of treatment, plus daily corticosteroid dose at 6 months were assessed.

In the study, 41 patients were treated with 105 biologics (tumor necrosis factor (TNF) inhibitors, $n=60$; tocilizumab, $n=17$; anakinra, $n=15$; rituximab, $n=7$; abatacept, $n=6$). Overall response rate during the first 6 months of exposure was 62.9%. Complete response rate was 19.0%.

The highest persistence among TNF inhibitors was observed with adalimumab. Differences in clinical response rates were observed depending on biologics and organ involvement. There were trends toward a lower response rate in cases with associated myelodysplastic syndromes and higher response rates were also achieved for nasal/auricular chondritis, sternal chondritis, and with the concomitant use of non-biologic disease-modifying antirheumatic drugs.

The use of biologics, especially TNF antagonists, has been increasingly recognized as effective, particularly in refractory patients with high-dose steroid requirements. The choice of biologic should be considered by experienced clinicians, as coexisting morbidities and other autoimmune conditions can significantly impact treatment strategies.

Complete remission in refractory relapsing polychondritis with intravenous immunoglobulins. Terrier B, Aouba A, et al. Clin Exp Rheumatol 2007; 25: 136–8.

A young woman with relapsing episodes of nasal chondritis and severe scleritis with scleromalacia received IVIG every 3 weeks and then every 4 weeks (2 g/kg on 2 days) in association with 25 mg/day of prednisone after treatment with corticosteroids, infliximab, methotrexate, mycophenolate, and cyclophosphamide failed to control her symptoms. Dramatic improvement of symptoms was sustained for 11 months, but when IVIG treatments

were spaced every 6 weeks, hearing loss and episcleritis recurred. Reinstitution treatment every fourth week brought her symptoms under control.

Management of airway manifestations of relapsing polychondritis: case reports and review of the literature. Sarodia SD, Dasgupta A, Mehta AC. *Chest* 1999; 116: 1669–75.

Five patients with severe respiratory involvement (three of whom required continuous mechanical ventilation due to airway collapse) benefited from placement of self-expandable metallic tracheobronchial stents. A total of 17 stents of varying sizes were placed in these patients over a period of 3 years, with favorable outcomes in four patients.

When severe, progressive disease leads to extensive destruction of the tracheobronchial tree despite maximal medical therapy. Tracheostomy or tracheobronchial stent placement may preserve or improve respiratory function and reduce patients' reliance on mechanical ventilation.

Surgical treatment of the cardiac manifestations of relapsing polychondritis: overview of 33 patients identified through literature review and the Mayo Clinic records. Dib C, Moustafa SE, et al. *Mayo Clin Proc* 2006; 81: 772–6.

Clinically important aortic or mitral regurgitation occurs in about 10% of relapsing polychondritis patients, with aortic

regurgitation being the more common and more urgent. In this retrospective series and literature review the mean time between initial onset of relapsing polychondritis and surgery was about 5 years. In contrast to previous reports of 70% 1-year mortality after valve replacement, in this analysis 50% of patients were alive 1 year after surgery.

Aortic regurgitation is a serious complication of relapsing polychondritis. Baseline chest CT, MR angiography, cardiac MRI, or trans-thoracic echocardiography should be performed upon diagnosis and repeated at intervals as clinically indicated. All aortic segments should be regularly evaluated because involvement of multiple thoracic and abdominal aneurysms has been reported in several patients.

Relapsing polychondritis can be characterized by 3 different clinical phenotypes: analysis of a recent series of 142 patients. Dion J, Costedoat-Chalumeau N, et al. *Arthritis Rheumatol* 2016; 68: 2992–3001.

This study used cluster analysis to define three groups that were clinically relevant in terms of prognosis: cluster 1, which had the highest mortality, included more men who were older at diagnosis, with myelodysplasia, general symptoms, and cutaneous and cardiac disease; cluster 2 had younger patients with predominant large airway disease; and cluster 3 had patients with mild disease and long-lasting remissions.

Rhinophyma

Donald J. Grande



Rhinophyma is a benign cutaneous condition that is the result of hypertrophy of the pilosebaceous units of the nasal skin. This overgrowth and subsequent fibrosis can be the end result of rosacea. The Greek word *phyma* means 'growth' and this hypertrophic tissue adds bulk and weight to the nasal skin that can lead to obstruction of air flow and ptosis. Males are more greatly affected than females, 12:1, and the condition is rare among individuals of Asian or African heritage. While most cases arise in the setting of rosacea, it is not always a precursor. While rhinophyma does not predispose the patient to skin cancer, any non-healing or fast-growing lesion should be biopsied to rule out a malignancy.

MANAGEMENT STRATEGY

The hyperplastic tissue is best treated with ablative modalities. Topical treatment is not effective; while oral antibiotics and retinoids (isotretinoin) may slow the progression, ultimately they do not reduce the bulk of tissue. All ablation treatments are destructive and scarring and hypopigmentation can result. Surgical techniques involve paring the tissue and contouring either with a scalpel or a 'cutting loop' of an electrosurgical unit. The Shaw scalpel uses a heated blade to remove the phymatous tissue, in a relatively bloodless field. Energy-based devices such as the CO₂ laser, pulsed dye laser, and yttrium-aluminum-garnet (YAG) lasers can be used to vaporize or refine nasal contours. Liquid nitrogen (cryosurgery) and ionizing radiation have also been used; the former can cause hypopigmentation and scarring, while the latter may induce a skin cancer.

Specific Investigation

- Biopsy is occasionally indicated to exclude malignancy

Rhinophyma and coexisting occult skin cancers. Lutz ME, Otley CC. *Dermatol Surg* 2001; 27: 201–2.

Rhinophyma can be complicated by the development of a malignancy, which can be difficult to recognize.

Rhinophyma and nonmelanoma skin cancer: an update. Lazzeri D, Agostini T, Pantaloni M, et al. *Ann Chir Plast Esthet* 2012; 57: 183–4.

In addition to basal cell, squamous cell, and basosquamous carcinomas, rarely, angiosarcoma and sebaceous carcinoma may occur.

First-Line Therapy

- Surgical paring

C

Triple approach to rhinophyma. Curnier A, Choudhary S. *Ann Plast Surg* 2002; 49: 211–4.

The authors report pleasing results in six patients treated by tangential excision for debulking, the use of scissors for sculpting, and mild dermabrasion for final contouring.

Second-Line Therapies

• Electrosurgery	C
• Pulsed dye laser	C
• CO ₂ laser	C
• Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser	E
• Erbium-doped:yttrium-aluminum-garnet (Er:YAG) laser	D
• Cryotherapy	D
• Isotretinoin	C
• Microdebrider	E
• Shaw scalpel	E
• Radiotherapy	E
• Hydrosurgery	D

Electrosurgical treatment of rhinophyma. Clark DP, Hanke CW. *J Am Acad Dermatol* 1990; 22: 831–7.

This treatment was inexpensive, associated with few complications, and gave good or excellent cosmetic results in 13 cases.

Surgical management of rhinophyma: report of eight patients treated with electrosection. Rex J, Ribera M, Bielsa I, et al. *Dermatol Surg* 2002; 28: 347–9.

Eight male patients were treated using radiofrequency electrosurgery to remove thin layers of tissue until the nose shape was recreated. All patients achieved acceptable cosmetic results.

Rhinophyma: "Less is more" and "Old is gold". Marcasciano M, Vaia N, Rituffo D, et al. *Aesthetic Plast Surg* 2017; 41(1): 232–3.

Ten patients with moderate-to-severe rhinophyma were treated with decortication with a Valley Lab electrosurgical loop with good results.

Diode laser treatment of rhinophyma. Tahery J, Zakaria R, Natt RS. *Clin Otolaryngol* 2010; 35(5): 442–4.

Mild disease was treated due to the depth of the rhinophymatous tissue.

Carbon dioxide laser treatment of rhinophyma: a review of 124 patients. Madan V, Ferguson JE, August PJ. *Br J Dermatol* 2009; 161: 814–8.

Exuberant sebaceous tissue was ablated using the Sharplan 40°C CO₂ laser under local anesthesia. The laser was used in a continuous mode to debulk the larger rhinophymas and in a resurfacing mode (Silk Touch scanner; Sharplan, 4–7-mm spot at 20–40 W) or continuous mode (10–20 W using a defocused 2–3-mm beam) to reshape the nasal contours. Results were classified as good to excellent in 118 and poor in six patients.

Spectrum of results after treatment of rhinophyma with the carbon dioxide laser. El Azhary RA, Roenigk RK, Wang TD. *Mayo Clin Proc* 1991; 66: 899–905.

A review of 30 patients treated with the CO₂ laser and followed up for 1–4 years. Milder cases were treated with laser vaporization, and more severe cases with CO₂ laser excision and then vaporization. Dilated pores developed in many patients. Leukoderma, unilateral alar lift, and mild hypertrophic scarring developed in single cases.

Surgical correction of rhinophyma: comparison of two methods in a 15-year-long experience. Lazzeri D, Larcher L, Huemer GM, et al. *J Craniomaxillofac Surg* 2013; 41: 429–36.

Long-term results in 45 cases treated with tangential excision and 22 treated with the CO₂ laser. Minor complications, including scarring and hypopigmentation, were seen in six patients. All patients were satisfied with their outcomes at the follow-up visit, and no major complications were detected. The authors did not consider the extra cost of laser treatment to be justified.

Surgical treatment of rhinophyma using carbon dioxide laser and pulsed dye laser. Moreira A, Leite I, Guedes R, et al. *Cosmet Laser Ther* 2010; 12(2): 73–6.

A single case of a combined treatment with 12-month follow-up.

Use of a dual-mode erbium:YAG laser for the surgical correction of rhinophyma. Fincher EF, Gladstone HB. *Arch Facial Plast Surg* 2004; 6: 267–71.

In each of these reports six cases of rhinophyma were treated with satisfactory outcomes. The Er:YAG laser provides both controlled ablation of tissue and hemostasis.

Rhinophyma treated by liquid nitrogen spray cryosurgery. Sonnex TS, Dawber RPR. *Clin Exp Dermatol* 1986; 11: 284–8.

Five cases were treated using two freeze–thaw cycles, each freeze lasting 30 seconds after the ice field was established, with a 4-minute intervening thaw. Pethidine and diazepam premedication was used. In three cases, small residual prominent areas responded to further treatment after 2 months. The final result was satisfactory in each case, with no scarring.

Rhinophyma: successful treatment with low dose oral isotretinoin. Pohl L, Karsai S, Raulin C. *Hautarzt* 2018; 69(10): 853–6.

A 78-kg man was treated successfully with isotretinoin dosed at 20 mg every third day for 2 years; it was anticipated to keep him on this low dose for another year.

Down-regulating causes of fibrosis with tamoxifen: a possible cellular/ molecular approach to treat rhinophyma. Payne WG, Ko F, Anspaugh S, et al. *Ann Plast Surg* 2006; 56(3): 301–5.

Fibrosis is a prominent feature of severe rhinophyma. This may represent a new cellular/molecular approach for severe rhinophyma. Fibroblast activity was reduced.

Treatment of severe rhinophyma using scalpel excision and wire loop tip surgery. Prado R, Runke A, Bingham J, et al. *Dermatol Surg* 2013; 39(10): 1556.

Surgical treatment of rhinophyma with the Shaw scalpel. Eisen RF, Katz AE, Bohigian RK, et al. *Arch Dermatol* 1986; 122: 307–9.

The Shaw scalpel is a device in which a scalpel blade can be heated. A rhinophyma was treated using a temperature of 150°C to achieve hemostasis while paring. Contours were then refined using a CO₂ laser and light dermabrasion.

Rhinophyma, associated with carcinoma, treated successfully with radiation. Plenk HP. *Plast Reconstruct Surg* 1995; 95: 559–62.

Two patients with basal cell carcinoma complicating rhinophyma had complete control of both conditions by radiotherapy using orthovoltage X-radiation. The authors suggest that this modality might be useful for rhinophyma alone.

Rhinophyma treated with kilovoltage photons. Skala M, Delaney G, Towell V, et al. *Australas J Dermatol* 2005; 46: 88–9.

A rhinophyma was successfully treated with 90-kV photons to a total dose of 40 Gy in 20 daily fractions.

Treatment of rhinophyma with the Versajet Hydrosurgery System. Taghizadeh R, Mackay SP, Gilbert PM. *J Plast Reconstruct Aesthet Surg* 2008; 61: 330–3.

Six patients with moderate-to-severe rhinophyma were successfully treated with this device. The device itself is expensive.

A new surgical technique of rhinophyma (gull-wing technique). Karacor-Altuntas Z, Dadaci M, Ince B, et al. *J Craniofac Surg* 2015; 26: e28–30.

A severe rhinophyma underwent full-thickness excision using gull-wing elevation of the nasal tip and dorsal skin. The patient was very satisfied with the result.

Giant rhinophyma: a rare case of total nasal obstruction and restitutio ad integrum. Andreas W, Scholz T, Liebau Aesthetic *Plast Surg* 2017; 41(4): 905–9.

A single case report of complete nasal obstruction treated by decorication and electrosurgical wire loop. The area was allowed to heal by second intention with good cosmesis and improved function.

Rocky Mountain spotted fever and other rickettsial infections

Amer Ali Almohssen, Robert A. Schwartz



Courtesy of Frederick A. Pereira, MD

The taxonomy of the Rickettsiales order has been reclassified based upon updated genetic and molecular analysis. *Coxiella* genus and *Bartonella* genus are no longer considered to be a part of the Rickettsial order. *Coxiella* is now a part of the Legionellales Gram-negative order and *Bartonella* is in the Rhizobiales Gram-negative bacteria order. The Rickettsiales order comprises Gram-negative bacteria and includes the genera *Rickettsia*, *Neorickettsia*, *Anaplasma*, *Ehrlichia*, and *Orientia*. These different bacterial orders remain mentioned together in this chapter, as they are vectorborne diseases that have similar clinical presentations and treatments. These diseases are divided into the spotted fevers (including Rocky Mountain spotted fever [RMSF]), the typhus group, rickettsialpox, Q fever, and ehrlichiosis.

RICKETTSIAL SPOTTED FEVERS

These infections include African tick bite fever (*Rickettsia africae*), Astrakhan fever (*R. conorii*), Flinders Island spotted fever (*R. honei*), Indian tick typhus (*R. conorii*), Israeli spotted fever (*R. conorii*), Japanese spotted fever (*R. japonica*), Mediterranean spotted fever (*R. conorii*), Queensland tick typhus (*R. australis*), Siberian tick typhus (*R. sibirica*), and RMSF (*R. rickettsii*). All of the spotted fevers are first evident with a maculopapular rash; 50–90% of them worldwide have an eschar, except for RMSF, with less than 1% of patients developing an eschar.

RMSF is caused by *Rickettsia rickettsii* and is endemic to most areas of the United States with a high degree of prevalence in North Carolina, Tennessee, and Oklahoma. RMSF is transmitted by *Dermacentor andersoni* in the western United States and by *D. variabilis* in the eastern United States. The classic triad of fever, headache, and rash is only seen in about 3% of the patients during the first 3 days of the disease, but by day 14 up to 70% of them may have this triad. The tick bite is typically painless, so the patient may not

recall it happening. The infection is characterized by an acute onset of fever (95%), headache (90%), and myalgia (85%), followed by vomiting (60%) and a rash (90%). The rash first appears as erythematous blanching macules over the forearms, wrists, and ankles 2–4 days after the onset of fever. These macules often spread to include the trunk, palms, hands, and feet. After the 5th day of illness, the macules change to petechiae. Antibiotic treatment should be initiated before the development of the petechial rash, as this is a sign of severe disease. Bilateral calf pain is the most common presenting complaint. Gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, and vomiting occur in nearly half of patients, usually early in the course of the illness. These findings often lead to a misdiagnosis or delay in therapy. Vascular injury to the small intestine, appendix, and gallbladder may occur, in some cases mimicking acute cholecystitis, or even appendicitis.

Diagnosis is most often based on clinical presentation, as patients may have a history of a tick bite after spending time in an endemic area. Clinical suspicion requires rapid initiation of therapy even while skin biopsies and confirmatory tests are pending. Serologic tests, including indirect immunofluorescence, latex agglutination, and enzyme immunoassay that detect antirickettsial antibodies, are available. However, these tests usually yield negative readings in the critical first days of the disease, as antibodies are not detectable until 7–10 days after the onset of the illness. Confirmation of the diagnosis using acute- and convalescent-phase serum samples is possible with these tests. The indirect hemagglutination antibody and immunofluorescent antibody tests are most useful because of their high sensitivity and specificity. The immunofluorescent test is especially beneficial because of its capacity to assess IgG and IgM levels. Highly specific and sensitive pan-*Rickettsia* and *R. rickettsii*-specific polymerase chain reaction (PCR) assays for the detection of the spotted fever and typhus group of Rickettsiae have been developed for rapid diagnostic confirmation when rickettsial loads are low. Detection by PCR of DNA in cutaneous lesional specimens or an acute phase whole blood specimen should be considered with testing available at some local and state health departments in the United States. A complete blood count and liver function tests should be obtained. Most patients will have some degree of anemia or leukopenia, though in some cases the white blood count may be elevated. Thrombocytopenia may occur in severe cases. Hepatic enzymes, bilirubin, and lactate dehydrogenase may be elevated. Skin biopsy can aid in the diagnosis of RMSF; Giemsa staining and direct immunofluorescence (DIF) can facilitate the diagnosis. Blood cultures or a skin biopsy specimen may be used to confirm the diagnosis, but are not helpful in the initial diagnosis of spotted fevers due to the length of time they require for results.

MANAGEMENT STRATEGY

Clinical suspicion of a spotted fever is sufficient to warrant treatment. Serologic confirmation should not delay the initiation of appropriate therapy. Diagnosis is difficult, as the characteristic rash is not a reliable sign, and the classic triad of a tick bite, rash, and fever is often not evident.

Specific Investigations

- Skin biopsy, direct immunofluorescence/immunoperoxidase
- Serologic testing for antirickettsial antibodies
- PCR

See <https://www.cdc.gov/rmsf/healthcare-providers/ClinLab-Diagnosis.html> (accessed June 2020).

Immunofluorescence antibody (IFA) assay for IgG against the *R. rickettsii* antigen should be performed twice to show a four-fold seroconversion to establish the diagnosis. The first serology should be done 7–10 days after the beginning of symptoms and the second IFA should be done 2–4 weeks later. Antibodies to *R. rickettsii* may continue to be elevated for years after the disease is cured and a single serological test may lead to the misdiagnosis of the disease, as more than 10% of the population in endemic areas may have elevated antibody titer.

Diseases from North America: focus on tick-borne infections. Nathavitharana RR, Mitty JA. Clinical Medicine 2015; 15: 74–7.

The sensitivity of serology is poor during the first days of infection, and only starts to reach a substantial sensitivity of 94% on days 14–21. CSF shows mild elevation in protein levels and an elevation of lymphocytes. Direct immunofluorescence on skin biopsies has an approximate sensitivity of 70% and a specificity of 100%.

As spotted fevers progress rapidly, immediate treatment is required, ideally in the first 3–4 days. Doxycycline is the best first-line agent for treating RMSF and other spotted fevers. Doxycycline is administered at a dose of 100 mg twice daily orally in adults. Children under 45.4 kg should receive 2.2 mg/kg twice daily orally. The therapeutic benefit provided by doxycycline in the treatment of RMSF outweighs the potential risk for tooth discoloration in children receiving doxycycline. These oral antibiotics are taken for a minimum of 7 days and are continued until the patient is afebrile for 72 hours. Within 24 hours of the initiation of treatment, a response may be observed. Within the first 48 hours, considerable clinical improvement is seen; apyrexia is often achieved by 72 hours. In severe cases requiring hospitalization, a loading dose of doxycycline at a dose of 200 mg every 12 hours is given intravenously for the first 72 hours followed by the normal dose of 100 mg every 12 hours.

Azithromycin at a dose of 500 mg once daily by mouth can also be used as a second-line treatment. Chloramphenicol can be employed at a dose of 50–100 mg/kg divided into four doses for 7 days; however, close monitoring is prudent due to the increased risk of complications including gray baby syndrome in pregnant women and aplastic anemia in children. Thus, the use of chloramphenicol is recommended with caution as a third-line treatment option.

Death occurs at a higher rate if patients are untreated beyond the 5th day of illness onset. Of note, early discontinuation of therapy may result in relapse. RMSF has a case-fatality rate as high as 30% in certain untreated patients. Even with treatment, hospitalization rates of 72% and case-fatality rates of 4% are seen.

Supportive care is also an important component in successful treatment. A high-protein diet, adequate hydration, and continuous monitoring of blood volume are critical. In cases in which renal, pulmonary, or cardiac complications occur, other specialized therapies may be required.

Prognosis is related to the timely diagnosis and initiation of effective treatment. Prevention is achieved by avoiding areas with ticks. Covering skin with long protective clothing reduces the risk of exposure. Clothing may be impregnated with acaricidal compounds for added protection. Any uncovered skin should be treated with a topical insect repellent before activities in high-risk areas. Unfortunately, most insect repellents are effective for only short periods and need to be reapplied frequently. Thorough skin examinations should be conducted regularly, at least twice daily in endemic areas, and any ticks removed. The scalp, axillary, and

pubic hair require particularly careful examination. There is currently no effective vaccine, although immunogenic surface protein antigens have been cloned and sequenced.

First-Line Therapy

- Doxycycline (in adults, pregnant patients, and children)

A

The evaluation and management of Rocky Mountain spotted fever in the emergency department: a review of the literature. Gottlieb M, Long B, Koyfman A. J Emerg Med 2018; 55(1): 42–50.

Two-thirds of cases occur in patients younger than 15 years old; males are more likely to be affected than females. The majority of experts recommend doxycycline as the first-line treatment for children, adults, and pregnant women.

No visible dental staining in children treated with doxycycline for suspected Rocky Mountain spotted fever. Todd SR, Dahlgren FS, Traeger MS, et al. J Pediatr 2015; 166: 1246–51.

This study failed to demonstrate enamel hypoplasia, dental staining, or tooth color changes in children under 8 years of age who received short-term courses of doxycycline. Confidence in the use of doxycycline for children suspected of having RMSF may be improved if the drug's label was changed to reflect these findings.

Fatal Rocky Mountain spotted fever in the United States, 1999–2007. Dahlgren FS, Holman RC, Paddock CD, et al. Am J Trop Med Hyg 2012; 86: 713–9.

The study highlights several risk groups who are more likely to die of RMSF: children 5–9 years of age, American Indians, immunosuppressed patients, and severe cases experiencing delayed diagnosis and/or treatment. Doxycycline should be used as the first-line drug against RMSF for all ages, even in children less than 8 years old.

Rocky Mountain spotted fever in children. Woods CR. Pediatr Clin North Am 2013; 60: 455–70.

RMSF is often undifferentiated from many infections during the first days of illness. Accordingly, doxycycline should not be delayed pending confirmation even in children under the age of 8 years.

Risk factors for fatal outcome from Rocky Mountain spotted fever in a highly endemic area—Arizona, 2002–2011. Regan JJ, Traeger MS, Humpherys D, et al. Clin Infect Dis 2015; 60: 1659–66.

Treatment with doxycycline during the first 3 days of the disease can decrease morbidity and mortality from RMSF in this region. Risk factors associated with doxycycline delay and fatal outcomes include 1) gastrointestinal symptoms, 2) alcoholism, and 3) chronic lung disease. There should be a low threshold for initiating doxycycline, especially in endemic areas like tribal lands in Arizona.

Revisiting doxycycline in pregnancy and early childhood – time to rebuild its reputation? Cross R, Ling C, Day NP, et al. Expert Opin Drug Saf 2016; 15: 367–82.

A systematic review of the literature on the use of doxycycline during pregnancy and in children revealed that there is no correlation between the use of doxycycline and teratogenic effects during pregnancy or dental staining in children.

Second-Line Therapy

- Azithromycin (adults, pregnant patients, and children)

B

Bilateral sensorineural deafness in a young pregnant female presenting with a fever: a rare complication of a reemerging disease-spotted fever group rickettsioses. Kariyawasam AGTA, Palangasinghe DR, Fonseka CL, et al. *Case Rep Infect Dis* 2019; Article ID 5923146. doi: 10.1155/2019/5923146.

Sensorineural deafness is a rare complication in spotted fever group rickettsioses. In rickettsial diseases complicated with organ involvement, a prolonged course of antibiotics is recommended. This patient was treated successfully with azithromycin for 10 days, although bilateral sensorineural deafness took several months to resolve.

Third-Line Therapy

- Chloramphenicol (pregnant and non-pregnant adults)

B

Rocky Mountain spotted fever and pregnancy: four cases from Sonora, Mexico. Licona-Enriquez JD, Delgado-de la Mora J, Paddock CD, et al. *Am J Trop Med Hyg* 2017; 97: 795–8.

Chloramphenicol has been effective in the treatment of some cases of RMSE, but it is also associated with many side effects including gray baby syndrome, bone marrow suppression, and aplastic anemia. It has also been associated with increased mortality in some cases of RMSE.

TYPHUS GROUP

Epidemic Typhus

Also known as louseborne typhus, prison fever, famine fever, and ship fever, epidemic typhus is caused by *R. prowazekii*, transmitted via the body louse. It is associated with poor hygiene, poverty, and overcrowding, with most outbreaks seen in prisons, homeless shelters, and refugee camps. Because this is the only typhus disease for which humans are the main reservoir, untreated patients can become asymptomatic survivors of epidemic typhus and can suffer reinfection decades after the initial infection, a recurrence known as Brill–Zinsser disease.

Recommended treatment is doxycycline taken orally 200 mg daily and continued for 3 days after the patient is afebrile. Prevention is crucial and can be achieved through bathing, washing clothes, and the use of permethrin or dichlorodiphenyltrichloroethane (DDT).

Endemic Typhus

Also known as murine typhus or fleaborne typhus, murine typhus (or endemic typhus) is due to *R. typhi* and *R. felis*, transmitted via the rat flea and the rat louse, and has been found in southern Texas, southern California, and Mexico. Treatment is recommended with antibiotic options similar to the treatments of RMSE. Untreated cases often resolve within 2 weeks.

Scrub Typhus

Scrub typhus (aka tsutsugamushi fever or chigger fever) is caused by *Orientia tsutsugamushi*, transmitted via the larval stage of the

Leptotrombidium mite species. This disease is endemic in Pakistan, India, and extends to include all of east and southeast Asia plus Australia and Japan. Treatment with doxycycline for 14 days is recommended. Azithromycin can also be used in cases that are resistant to doxycycline; ciprofloxacin has also been reported to be effective in such cases. Lastly, chloramphenicol can be utilized with caution, but is less effective and associated with more side effects.

MANAGEMENT STRATEGY

Specific Investigations

Epidemic typhus

- Serology: microimmunofluorescent and plate microagglutination tests

Murine typhus

- Serology: indirect fluorescent antibody, latex agglutination, solid-phase immunoassay

Scrub typhus

- Serology: indirect fluorescent antibody test

Eschar and IgM ELISA in the diagnosis of scrub typhus. Perumalla SK, Paul S, Abhilash KPP, et al. *Indian J Med Microbiol* 2019; 37: 113–5.

Of the 116 patients that were diagnosed with scrub typhus, 50.8% had an eschar, 49% had a fever, 38% had multiorgan dysfunction syndrome, 31% had abdominal pain, and 21.5% had difficulty breathing with 7.7% requiring ventilation and ICU admission. In 91% of cases there was an eschar and also a positive IgM ELISA test.

First-Line Therapies

Epidemic typhus

- Doxycycline **A**

Murine typhus

- Doxycycline **A**

Scrub typhus

- Doxycycline **A**

Rickettsioses and Q fever in travelers (2004–2013). Delord M, Socolovschi C, Parola P. *Travel Med Infect Dis* 2014; 12: 443–58.

Doxycycline remains the standard treatment for all spotted fever group rickettsioses. Doxycycline is also the standard of treatment for scrub, murine, and epidemic typhus infections.

Comparative effectiveness of azithromycin for treating scrub typhus: a PRISMA-compliant systematic review and meta-analysis. Lee SC, Yu-Jyun Cheng YJ, Lin CH, et al. *Medicine* (Baltimore) 2017; 96(36): e7992.

Azithromycin is effective against rickettsial infections and scrub typhus with limited side effects. It is reasonable to use azithromycin as the first-line treatment against scrub typhus.

Second-Line Therapies

All typhus groups

- Rifampicin
- Chloramphenicol

A
A
D

RICKETTSIALPOX

Rickettsialpox is due to *R. akari*. The house mouse is the reservoir; mites transmit the bacteria to humans. This disease is self-limiting. It manifests as headache, fever, and a papulovesicular rash over the trunk and extremities. An eschar is seen in up to 90% of cases. Treatment in adults is doxycycline 200 mg daily for 10 days.

MANAGEMENT STRATEGY

Specific Investigation

- Serology: complement fixation

First-Line Therapy

- Doxycycline

A

Investigating the histopathological findings and immunolocalization of rickettsialpox infection in skin biopsies: a case series and review of the literature. Vyas NS, Shieh WJ, Phelps RG. *J Cutan Pathol* 2020; 47: 451–8.

Six biopsy specimens were studied, revealing a granulomatous vasculitis involving the reticular dermis and vessel walls in five of the six specimens. All showed vacuolar interface dermatitis at the dermoepidermal junction and a perivascular lymphocytic and neutrophilic vasculitis. Rickettsialpox skin biopsy specimens can be used to diagnose the disease in an appropriate clinical context.

Q FEVER

Q fever is caused by *Coxiella burnetii*. Transmission to humans occurs via aerosolized urine, feces, or birth products of ungulates (hoofed mammals). This disease usually has no skin findings. Patients often present with febrile illness, severe headache, and with or without pneumonia, hepatitis, or endocarditis. Vaccines for this occupational disease of sheep and dairy workers are not available in the United States.

MANAGEMENT STRATEGY

Acute Q Fever

The primary treatment of choice in adults is doxycycline (100 mg orally twice a day for 14 days). Moxifloxacin (400 mg daily for 14 days) may be used as an alternative. In vitro, the disease has been susceptible to fluoroquinolones, chloramphenicol, rifampin, and trimethoprim-sulfamethoxazole.

Chronic Q Fever

The most common chronic manifestation is endocarditis, which is often resistant to treatment, due to the bacteriostatic rather than

the bactericidal effects of antibiotics on *C. burnetii*. Currently, combination therapy with doxycycline (100 mg twice daily) and hydroxychloroquine (200 mg three times daily) is the mainstay of treatment given their bactericidal activity. Treatment must be carried out for a minimum of 18 months. The duration must further be tailored to the individual clinical response.

Specific Investigations

Acute Q fever

- Serology: complement fixation, immunofluorescent antibody
- PCR

Chronic Q fever

- Echocardiography
- Serology

Who is at risk of occupational Q fever: new insights from a multi-profession cross-sectional study. Groten T, Kuenzer K, et al. *BMJ Open* 2020; 10(2): e030088.

Obstetricians are not at increased risk, even with exposure to infected birth products during the delivery of Q fever-infected women. Shepherds, veterinarians, and cattle farmers are at high risk of *C. burnetii* infection.

Clinical characteristics of acute Q fever patients in South Korea and time from symptom onset to serologic diagnosis. Heo JY, Choi YW, Kim EJ, et al. *BMC Infect Dis* 2019; 19(1): 903.

Most acute Q fever patients have non-specific clinical presentations including fever, and mild elevation of transaminases and usually no history of an animal or occupational risk. The fever usually subsides before the immunofluorescence assay becomes positive.

First-Line Therapies

Acute Q fever

- β-Lactams B
- Doxycycline B
- Macrolides B
- Quinolones B

Chronic Q fever

- Doxycycline and hydroxychloroquine B

Doxycycline desensitization in chronic Q fever – a critical tool for the clinician. Caplunik-Pratsch AL, Potasman I, Kessel A, et al. *IDCases* 2018; 11: 70–2.

Macrolides (clarithromycin), β-lactams, doxycycline, and moxifloxacin can all be used for the treatment of Q fever. However, doxycycline desensitization can be an option if there are no alternative treatments available. This is the third case report showing successful desensitization to doxycycline for the treatment of Q fever. Desensitization of doxycycline was also used for the treatment of ehrlichiosis.

Second-Line Therapy

Chronic Q fever

- Quinolone and doxycycline

B

EHRlichiosis

Ehrlichiosis consists of two tickborne diseases: human monocytic ehrlichiosis due to *Ehrlichia chaffeensis* (the most common form in the United States) and human granulocytic ehrlichiosis due to *E. equi*. Both are found in mammalian reservoirs such as deer, dogs, and horses and are transmitted via ticks. Commonly encountered symptoms include fever, headaches, lack of appetite, and a highly variable exanthema. There are many similarities in clinical presentations and laboratory findings between ehrlichiosis and RMSF. Moreover, one-third of these patients do not recall a history of a tick bite. If inappropriately treated, ehrlichiosis can progress to life-threatening respiratory failure and meningoencephalitis.

MANAGEMENT STRATEGY

Doxycycline 100 mg orally twice daily for adults, or 4 mg/kg daily in children 8 years of age and older, is the treatment of choice. The treatment should be continued for a minimum of 7 days and for 3 days after defervescence.

Specific Investigation

- Serology: immunofluorescent antibody

First-Line Therapy

- Doxycycline

A

Fatal ehrlichial myocarditis in a healthy adolescent: a case report and review of the literature. Havens NS, Kinnear BR, Mató S. Clin Infect Dis 2012; 54: e113–4.

There should be a low threshold for treatment with doxycycline during the peak season in endemic areas, as a delay increases both morbidity and mortality. Therapy becomes even less effective if delayed beyond 1 week.

Second-Line Therapy

- Rifampin (rifampicin)

D

Successful treatment of human monocytic ehrlichiosis with rifampin. Abusaada K, Ajmal S, Hughes L. Cureus 2016; 8: e444.

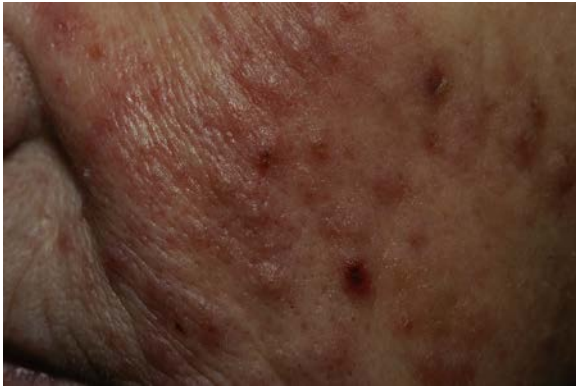
Rifampin (rifampicin) was successfully used in the treatment of a patient who had doxycycline allergy.

Arthropod-borne bacterial diseases in pregnancy. Doters-Katz SK, Kuller J, Heine RP. Obstet Gynecol Surv 2013; 68: 635–49.

The preferred treatment is doxycycline, but rifampin is also effective in treating human monocytic ehrlichiosis and human granulocytic ehrlichiosis. Rifampin crosses the placenta, and may be useful in treating the fetus. Rifampin does not cause birth defects or fetal complications. Doxycycline and rifampin are suitable with breastfeeding.

Rosacea

James Q. Del Rosso



Courtesy of Jason Smith MD, Rome, Georgia

Rosacea is a common, chronic, heterogenous, inflammatory skin disease, seen most often in adults of both genders and all skin types. It predominantly involves the central face and is characterized by intermittent flares that present with transient findings (flushing, papules/pustules) and by persistence of some fixed clinical manifestations (telangiectasias, persistent facial erythema). Individuals who develop rosacea are innately affected by rosacea-prone skin that exhibits physiochemical and ultrastructural differences from normal facial skin. These include altered colocalization of cutaneous nerves and vessels, increase in perivascular mast cells, aberrant patterns of cutaneous receptor distribution and magnitude, altered gene expression patterns that appear to correlate with clinical features, aberrant response to environmental exposures ('triggers'), increased serine protease activity, diminished antioxidant reserve (superoxide dismutase), augmented immunologic and inflammatory responses via the cathelicidin cascade and other pathways, and progressive alterations in superficial cutaneous vasculature. The collective effects of these changes observed within rosacea-prone skin are neurovascular dysregulation and augmented immune detection-response. These dominant pathophysiologic mechanisms correlate with specific clinical manifestations that lead to different phenotypic expressions among patients affected by rosacea, which may progress over time and directly impact upon management of individual cases of rosacea.

The most common presentations of cutaneous rosacea seen by clinicians in real-world practice are central facial erythema with or without papulopustular lesions. Patients may also present with phymatous changes, usually affecting the nose (rhinophyma) and/or ocular rosacea, often described by patients as sensations of dry eyes, grittiness, itchiness, and/or irritation. The latter may include blepharitis, conjunctivitis, and less commonly chalazion, hordeolum, and keratitis. Facial telangiectasias are characteristic visible signs of rosacea. Rosacea flares are associated with episodic facial vasodilation (flushing of rosacea), and papulopustular lesions in some patients, both which are transient clinical features that distinguish rosacea from chronic photodamage.

Persistent erythema involving the central face is commonly observed between flares of rosacea, due to proliferation and fixed dilatation of superficial facial vasculature. Sensory symptoms of facial burning and/or stinging can accompany rosacea, especially during flares. Dry facial skin, sometimes with fine scaling, is often noted ('rosacea dermatitis') due to increased transepidermal water loss inherent to rosacea-affected skin, which is distinct from seborrheic dermatitis. Marked chronic facial edema, solitary plaque rosacea, granulomatous rosacea, and extrafacial rosacea are relatively uncommon clinical variants of the disease.

MANAGEMENT STRATEGY

Rosacea is diagnosed clinically, with a usual onset in early adulthood. Importantly, the clinical manifestations of rosacea vary among affected individuals, with central facial erythema and episodic flushing being the two most consistent diagnostic features. Papulopustular lesions are noted in some patients during flares. The presence and the intensity of individual manifestations of rosacea vary in affected individuals over time.

As both neurovascular dysregulation and augmented immune detection-response are integral components of rosacea-prone skin, avoidance of 'triggers' that can induce facial vasodilation (i.e., alcohol, spicy food, hot drinks, hot ambient temperature) is suggested, as is avoidance of common skin irritants. Consistent use of gentle skin care, moisturizer application, and photoprotection are integral components of cutaneous rosacea management. Cosmetic camouflage of the erythema and telangiectasia may be helpful for some patients. Papulopustular lesions can be effectively treated with specific 'antiinflammatory' topical or oral agents, either as monotherapy, or in combination, which are described later. Agents used to treat papulopustular lesions also reduce perilesional erythema; none have shown efficacy in reducing persistent facial erythema of rosacea (PFE; background vascular erythema), which is due to fixed dilation of superficial facial vasculature. With regard to using oral agents that can improve papulopustular rosacea, but can induce antibiotic resistance as an unwanted consequence, guidelines suggest that subantibiotic treatment is used initially if deemed to be indicated and if accessible. Use of topical corticosteroids of any potency for treatment of rosacea, although tempting due to initial benefit, is best avoided due to the high potential for 'cutaneous steroid addiction' characterized by a marked rosaceaform eruption and other persistent adverse effects. Persistent facial erythema can be treated with topical application of an α -adrenoreceptor agonist or with designated physical modalities, such as *intense pulsed light* or *vascular lasers*. The latter are more effectively utilized to treat telangiectasias, which are not responsive to available topical or oral agents used to treat rosacea. Flushing of rosacea, a major hallmark of a flare, is usually the most difficult manifestation to treat; however, the frequency and intensity of episodic flaring appear to be reduced by available medical therapies when used consistently. Ocular rosacea is often managed with emollient ophthalmic preparations ('artificial tears') and an oral tetracycline agent. Increased *Demodex* mite density may occur in some patients with cutaneous rosacea with or without papulopustular lesions, and in ocular rosacea, with the mites apparently serving as a trigger factor in some cases, or inducing a rosaceaform papulopustular facial eruption. Some reports have suggested that eradication of *Helicobacter pylori* infection with antibiotic therapy improves rosacea, although others refute these findings; this subject area remains controversial. The use of physical devices, such as laser and light-based therapies, is rapidly evolving with some guidance provided in available publications and consensus recommendations. Specific treatments are

shown below in sections on papulopustular rosacea, erythematotelangiectatic rosacea, flushing, lymphedema, ocular rosacea, and rosacea fulminans. Treatments for rhinophyma and perioral dermatitis are described in separate chapters.

Specific Investigations

In selected cases

- Exclude carcinoid syndrome: history, physical examination, laboratory testing
- Exclude cutaneous lupus: history, serology, histology
- Exclude chronic photodamage: history, physical examination
- Exclude contact dermatitis: history, physical examination, patch testing
- Exclude seborrheic dermatitis: history, physical examination

PAPULOPUSTULAR ROSACEA

First-Line Therapies

• Topical metronidazole	A
• Topical azelaic acid	A
• Topical ivermectin	A
• Topical minocycline	A
• Oral tetracyclines (including subantibiotic-dose doxycycline)	A

Managing rosacea: a review of the use of metronidazole alone and in combination with oral antibiotics. Conde JF, Yelverton CB, Balkrishnan R, et al. *J Drugs Dermatol.* 2007; 6(5): 495–8.

The efficacy and safety of topical metronidazole used as monotherapy or in combination with oral antibiotic therapy was demonstrated in several studies for papulopustular rosacea. A variety of metronidazole 0.75% and 1% vehicle formulations are available (gel, cream, lotion) for once daily or twice daily use. Combination therapy induces a faster onset of inflammatory lesion reduction and perilesional erythema, especially in cases of greater severity.

Topical metronidazole maintains remissions of rosacea. Dahl MV, Katz HI, Krueger GG, et al. *Arch Dermatol* 1998; 134: 679–83.

Eighty-eight subjects who had responded to treatment with systemic tetracycline and topical metronidazole were randomized to receive 0.75% metronidazole gel or placebo gel for 6 months. In those using metronidazole, 23% developed a relapse of papulopustular lesions and 55% noted worsening of erythema, compared with 42% and 74% of subjects in the placebo group, respectively.

Azelaic acid in the treatment of papulopustular rosacea: a systematic review of randomized trials. Liu RH, Smith MK, Basta SA, et al. *Arch Dermatol.* 2006; 142(8): 1047–52.

This is a thorough analysis of randomized controlled studies of topical azelaic acid 15% gel and 20% cream with their vehicles, and with metronidazole gel. Topical azelaic acid is effective for papulopustular rosacea, evidenced by reduction in mean

inflammatory lesion counts and perilesional erythema. Comparison with topical metronidazole showed azelaic acid to be at least equally effective, if not a better treatment option.

Cathelicidin, kallikrein-5, and serine protease activity is inhibited during treatment of rosacea with azelaic acid 15% gel. Coda AB, Hata T, Miller J, et al. *J Am Acad Dermatol* 2013; 69(4): 570–7.

Gene expression and protease activity were measured in a 16-week, prospective, multicenter study of patients with papulopustular rosacea treated with azelaic acid 15% gel. Murine and keratinocyte models have shown that azelaic acid downregulates kallikrein-5 and cathelicidin (LL37). This study performed in patients with papulopustular rosacea showed that azelaic acid downregulated kallikrein-5 and cathelicidin and identified rosacea subsets with high or low baseline serine protease activity. This supports apparent modes of action for topical azelaic acid in rosacea.

Impact of order of application of moisturizers on percutaneous absorption kinetics: evaluation of sequential application of moisturizer lotions and azelaic acid gel 15% using a human skin model. Del Rosso JQ, Lehman PA, Raney SG. *Cutis* 2009; 83(3): 119–24.

This study addressed a common clinical question about the preferred order of moisturizer application. Data were collected ex vivo using human skin and tested with three commonly used moisturizer lotions. The results showed that moisturizer application can be either before or after azelaic acid 15% gel with no significant change in the percutaneous absorption profile of azelaic acid, at least with the moisturizers that were tested.

Azelaic acid topical formulations: differentiation of 15% gel and 15% foam. Del Rosso, JQ. *J Clin Aesthet Dermatol* 2017; 10(3): 37–40.

Efficacy and safety with both formulations in papulopustular rosacea has been substantiated in randomized, controlled trials. Differences in vehicle technology and potential clinical impact on potential neurosensory skin tolerability reactions between the formulations are explained. The foam formulation appears to reduce the potential for neurosensory symptoms (i.e., stinging, burning) that may occur in a subset of patients after skin application compared to the gel. The importance of proper skin care in rosacea treatment is discussed.

Efficacy and safety of ivermectin 1% cream in treatment of papulopustular rosacea: results of two randomized, double-blind, vehicle controlled, pivotal studies. Stein L, Kircik L, Fowler J, et al. *J Drugs Dermatol* 2014; 13: 316–23.

Nearly 700 subjects were enrolled in each study; a high mean inflammatory lesion count (≈ 30) was present at baseline in all study arms. Treatments were applied once daily. At 12 weeks, assessments of 'clear' or 'almost clear' were noted in 38.4% and 40.1% of the ivermectin group and 11.6% and 18.8% of the vehicle group, respectively ($p < 0.001$). Skin tolerability was very favorable and systemic safety signals were noted.

Superiority of ivermectin 1% cream over metronidazole 0.75% cream in treating inflammatory lesions of rosacea: a randomized, investigator-blinded trial. Taieb A, Ortonne JP, Ruzicka T, et al. *Br J Dermatol* 2015; 172: 1103–10.

In a 16-week study ($n = 962$), subjects applying ivermectin cream experienced an 83% reduction in inflammatory lesions (the primary end point), compared with a 74% reduction in the

metronidazole group ($p < 0.001$). A longer duration of remission posttreatment (median 115 vs. 85 days) was noted in the ivermectin-treated study arm. Skin tolerability was highly favorable in both groups. The likelihood of achieving clear skin based on investigator assessment is higher with topical ivermectin, though both agents are effective and well tolerated.

Dual anti-inflammatory and anti-parasitic action of topical ivermectin 1% in papulopustular rosacea. Schaller M, Gonser L, Belge K, et al. *J Eur Acad Dermatol Venereol* 2017; 31(11): 1907–11.

In a pilot study ($n = 20$), ivermectin 1% cream was used once daily for ≥ 12 weeks to treat papulopustular rosacea of at least moderate severity and a minimum *Demodex* density $\geq 15/\text{cm}^2$. Outcomes were evaluated clinically, by change in *Demodex* density, and via biomarker measurement. Both antiinflammatory and antiparasitic modes of action were shown. Mean *Demodex* density was significantly reduced at weeks 6 and 12 ($p < 0.001$). Biomarkers (i.e., IL8, LL37, TLR4) were markedly downregulated. Clear or almost clear skin by investigator global assessment was achieved in 80% of subjects.

Minocycline 1.5% foam for the treatment of moderate to severe papulopustular rosacea: results of 2 phase 3, randomized, clinical trials. Stein Gold LS, Del Rosso JQ, Kircik L, et al. *J Am Acad Dermatol* 2020; 82(5): 1166–73.

Two double-blind, randomized, 12-week, multicenter studies completed in subjects treated once daily with minocycline 1.5% foam ($n = 1009$) or vehicle foam ($n = 513$) evaluated efficacy, tolerability, and safety. Minocycline 1.5% foam showed significantly greater reductions in papulopustular lesions ($p = .0031$; $p < .0001$) and higher rates of treatment success ($p = 0.0273$; $p = .0077$) than vehicle. Skin tolerability was favorable in both study arms. No serious treatment-related adverse events were noted; no major systemic side effects reported to occur with oral minocycline were observed.

Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg doxycycline, USP capsules, modified release) administered once daily for treatment of rosacea. Del Rosso JQ, Webster GF, Jackson M, et al. *J Am Acad Dermatol* 2007; 56: 791–802.

Doxycycline 40 mg modified-release capsule once daily used as monotherapy vs. placebo was proven to be effective and well tolerated for papulopustular rosacea in two large-scale phase III studies. This dosing formulation mitigates antibiotic resistance by avoiding bacterial selection pressure. Cases of phototoxicity were not observed, and no reports of vaginal candidiasis were noted among actively treated females ($n = 185$).

Comparison of anti-inflammatory dose doxycycline versus doxycycline 100 mg in the treatment of rosacea. Del Rosso JQ, Schlessinger J, Werschler P. *J Drugs Dermatol*. 2008; 7(6): 573–6.

In this randomized, double-blind, head-to-head, 16-week trial, subjects ($n = 91$) received subantibiotic-dose doxycycline 40 mg daily or antibiotic-dose doxycycline 100 mg daily. Efficacy was equivalent in both groups at all time points based on investigator global assessment and inflammatory lesion count reductions. Gastrointestinal side effects of nausea, vomiting, diarrhea, esophageal pain, and abdominal pain occurred only in the group treated with doxycycline 100 mg.

An open-label, community-based, 12-week assessment of the effectiveness and safety of monotherapy with doxycycline

40 mg (30-mg immediate-release and 10-mg delayed-release beads). Webster GF. *Cutis* 2010; 86(5 Suppl): 7–15.

This report of a large phase 4 community-based (open), 12-week trial assessed outcomes with the 40-mg, once-daily, subantibiotic-dose doxycycline formulation used as monotherapy in adults with mild-to-severe papulopustular rosacea. The primary outcome measure was a change in investigator global assessment (IGA) score from baseline to week 12. Among the 826 monotherapy participants who completed the trial, approximately 75% of participants were clear or near clear by week 12. Adverse events that occurred in $>1\%$ included diarrhea (1.2%), nausea (1.3%), and headache (1.0%); fungal/yeast infections were noted in 0.4%. These data support the efficacy and safety of this formulation in this patient population.

Among participants who received subantibiotic-dose doxycycline as ‘add-on therapy’ to topical rosacea treatments that presented with persistent rosacea at baseline, therapeutic outcomes were very similar to these monotherapy results.

Efficacy of extended-release 45mg oral minocycline and extended-release oral minocycline plus 15% azelaic acid in the treatment of acne rosacea. Jackson JM, Kircik LH, Lorenz DJ. *J Drugs Dermatol* 2013; 12(3): 292–8.

The use of an extended-release low-dose minocycline 45 mg tablet once daily, with or without topical azelaic acid, for the treatment of papulopustular rosacea is reported. This is an antibiotic-dose of minocycline; subantibiotic dosing with oral minocycline has not been established.

Minocycline is not as commonly used as doxycycline for treatment of rosacea, likely due to the potential for vertigo, need for chronic administration, cutaneous pigmentation changes with prolonged use, lack of a proven subantibiotic-dose/formulation, and rare association with drug hypersensitivity syndrome, autoimmune reactions such as hepatitis and systemic lupus-like syndrome, and higher potential for benign intracranial hypertension.

Second-Line Therapies

• Topical macrolides/lincosamides	C
• Topical benzoyl peroxide (with or without clindamycin)	A
• Alternative oral antibiotics (azithromycin, erythromycin, metronidazole)	A, B

Treatment of rosacea: topical clindamycin versus oral tetracycline. Wilkin JK, DeWitt S. *Int J Dermatol* 1993; 32: 65–7.

A randomized, blinded 12-week trial compared topical clindamycin lotion twice daily with oral tetracycline ($n = 43$). Efficacy outcomes were similar in both groups, although clindamycin was superior in pustule reduction.

Current published recommendations by multiple organized groups that discuss acne and rosacea management, and antibiotic therapy use, advise against monotherapy with topical clindamycin due to increased emergence of antibiotic-resistant bacterial strains. In the case of rosacea, there are several other approved topical therapy options available.

Randomized, phase 2, dose-ranging study in the treatment of rosacea with encapsulated benzoyl peroxide gel. Leyden JJ. *J Drugs Dermatol* 2014; 13(6): 685–8.

Once-daily application of encapsulated benzoyl peroxide 1% and 5% formulations were evaluated in a multicentered randomized, double-blind, vehicle-controlled, 12-week study in patients

with predominantly moderate papulopustular rosacea ($n=92$). Both 1% and 5% encapsulated benzoyl peroxide gel were significantly superior to vehicle in reducing papulopustular lesions ($p=0.01$; $p=0.02$); the 5% formulation was significantly superior to vehicle based on IGA ratings of achieving clear or almost clear ($p=0.0013$).

Double-blind, randomized, vehicle-randomized clinical trial of once-daily benzoyl peroxide/clindamycin topical gel in the treatment of patients with moderate to severe rosacea. Breneman D, Savin R, VandePol C, et al. *Int J Dermatol* 2004; 43: 381–7.

Use of 5% benzoyl peroxide/1% clindamycin gel once daily was shown to be effective ($n=52$). Mean percentage reduction in inflammatory lesions from baseline to the end of treatment was 71.3% in the benzoyl peroxide/clindamycin group and 19.3% in the vehicle group ($p=0.0056$). Application site reactions were noted in four of 26 patients in the benzoyl peroxide/clindamycin study group.

Oral use of azithromycin for treatment of acne rosacea. Fernandez-Obregon A. *Arch Dermatol* 2004; 140: 489–90.

Ten patients responded to azithromycin 250 mg/day for 3 days each week (Monday, Wednesday, and Friday) within 4 weeks. Ocular symptoms also improved. The long half-life of azithromycin supports intermittent administration.

Papulopustular rosacea: response to treatment with oral azithromycin. Lova Navarro M, Sánchez-Pedreño Guillen P, Victoria Martínez AM, et al. *Actas Dermosifiliogr* 2018; 109(6): 529–35.

This prospective pilot study evaluated oral azithromycin use after inadequate response to oral doxycycline and metronidazole gel ($n=16$). Fourteen patients showed complete or almost complete improvement (complete clearance of papules/pustules; marked reduction in perilesional erythema). The authors concluded that oral azithromycin could be effective for short-term and long-term treatment in refractory cases.

Caution with oral azithromycin is suggested in older patients and those with a history of cardiac disease.

Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 3: a status report on systemic therapies. Del Rosso JQ, Thiboutot D, Gallo R, et al. *Cutis* 2014; 93(1): 18–28.

This thorough review provides study data and recommendations on oral agents for treatment of rosacea (i.e., tablets, capsules). Subantibiotic-dose doxycycline, a modified-release doxycycline 40-mg capsule once daily, is the only oral agent approved by the US Food and Drug Administration (FDA) for rosacea (papulopustular lesions). Other non-FDA-approved oral agents with supporting publications are discussed, including other tetracyclines, macrolides, azalides, metronidazole, and isotretinoin (discussed later). Data on antibiotic-dose doxycycline use are based on several studies for papulopustular rosacea, including combinations with topical agents. Data with minocycline are more limited. Tetracycline use is limited based on poor accessibility and dietary interactions. Caution with oral azithromycin is suggested in older patients and those with a history of cardiac disease. Erythromycin use warrants caution due to gastrointestinal side effects and potentially significant drug–drug interaction with coingestion including carbamazepine toxicity, ciclosporin toxicity, and myalgias/rhabdomyolysis in patients taking lipid-lowering agents ('statins') metabolized by CYP3A4. Oral metronidazole may be effective in some refractory papulopustular cases; use can be limited by disulfiram-type reactions with alcohol ingestion, an

unacceptable persistent metallic taste, and peripheral neuropathy with prolonged use.

Third-Line Therapies

• Systemic isotretinoin	B
• Topical retinoids (adapalene, tretinoin)	B
• Topical sulfur ± sulfacetamide	B
• Photodynamic therapy	D
• <i>Demodex</i> eradication	B
• Topical calcineurin inhibitors (pimecrolimus, tacrolimus)	C, D
• Oral nicotinamide with zinc	C
• Zinc sulfate	B

Use of oral isotretinoin in the management of rosacea. Park H, Del Rosso JQ. *J Clin Aesthet Dermatol* 2011; 4(9): 54–61.

Thorough review of 'off-label' uses for isotretinoin with emphasis on data from studies on management of rosacea, especially refractory papulopustular disease. Continuous 'micro-dose' isotretinoin (CMI) treatment (0.04–0.11 mg/kg/day) has been used to treat recalcitrant papulopustular rosacea, including patients previously treated with topical metronidazole and several cycles of oral antibiotic therapy. For recalcitrant disease, isotretinoin 10–20 mg/day was initiated and continued over a period of 4–6 months; daily dosage was then decreased to an individualized continuous minimal dosage range of 0.03–0.17 mg/kg/day (mean, 0.07 mg/kg/day). The CMI regimen produced marked improvement supported by positive changes in the Dermatology Life Quality Index scores ($p=0.0001$). Annual cumulative doses fell below those projected to have higher potential to produce bone changes. Use of CMI may be considered in selected patients who wish to avoid repeated cycles of oral antibiotic therapy or want to avoid relapse upon discontinuation of isotretinoin. A rational approach including patient consent after thorough discussion of potential risks, a long-term monitoring plan, and effective contraception in premenopausal female patients of childbearing potential are inherent to the use of isotretinoin.

A randomized-controlled trial of low-dose isotretinoin for difficult-to-treat papulopustular rosacea. Sbidian E, Vicaute É, Chidiack H, et al. *J Invest Dermatol* 2016; 136: 1124–9.

Isotretinoin 0.25 mg/kg/day or placebo was used over 4 months for recalcitrant disease ($n=156$). A 90% reduction in inflammatory lesions was observed in 57% using isotretinoin vs. 10% on placebo ($p<0.0001$). The proportions of patients discontinuing therapy due to adverse events were similar in the two groups.

Adapalene vs metronidazole gel for the treatment of rosacea. Altinyazar HC, Koca R, Tekin NS, et al. *Int J Dermatol* 2005; 44: 252–5.

An investigator-blinded, parallel-group trial ($n=55$) showed similar outcomes with adapalene 0.1% gel or metronidazole 0.75% gel.

Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 2: a status report on topical agents. Del Rosso JQ, Thiboutot D, Gallo R, et al. *Cutis* 2013; 92(6): 277–84.

This thorough review discusses studies and recommendations with topical agents for rosacea. Data on topical retinoids, including tretinoin and adapalene, are limited though therapeutic benefit has been reported; skin irritation is a potential adverse effect. Information on topical calcineurin inhibitors (pimecrolimus, tacrolimus) is limited to small studies/case reports with

inconsistent efficacy outcomes observed among available publications; exacerbation of rosacea has been reported with these agents.

The treatment of rosacea: the safety and efficacy of sulfacetamide 10% and sulfur 5% lotion is demonstrated in a double-blind study. Saunder DN, Miller R, Gratton D, et al. *J Dermatol Treat* 1997; 8: 79–85.

Sodium sulfacetamide 10% and sulfur 5% lotion was shown to be effective and well tolerated in an 8-week randomized, vehicle-controlled, multicenter trial for papulopustular rosacea ($n=103$).

Photodynamic therapy for rosacea in Chinese patients. Fan L, Yin R, Lan T, et al. *Photodiagnosis Photodyn Ther* 2018; 24: 82–7.

Patients with either erythematotelangiectatic or papulopustular rosacea ($n=20$) received photodynamic therapy using 5-aminolevulinic acid 5% (ALA-PDT) under plastic film occlusion with 2 hours of incubation followed by red light exposure over 15 min in each session, with four total sessions completed at 10-day intervals. Assessments were completed at baseline and at weeks 4, 12, and 24 after the last ALA-PDT treatment. Inflammatory lesions and flushing episodes resolved completely in all patients after 24 weeks. Subjective symptoms (i.e., itching, burning, stinging) also resolved with no relapses noted during the follow-up period.

Permethrin 5% cream versus metronidazole 0.75% gel for the treatment of papulopustular rosacea: a randomized double-blind placebo-controlled study. Koçak M, Yagli S, Vahapoglu G, et al. *Dermatology* 2002; 205: 265–70.

Both treatments were applied twice daily for 2 months. Permethrin was superior in efficacy to placebo in reducing papules and perilesional erythema with effectiveness equivalent to metronidazole 0.75% gel. No effect was noted on telangiectasia, rhinophyma, or pustules. Decrease in *Demodex* mite counts was markedly greater with permethrin than with metronidazole or placebo.

The Nicamide Improvement in Clinical Outcomes Study (NICOS): results of an 8-week trial. Niren NM, Torok HM. *Cutis* 2006; 77: 17–28.

Oral zinc sulfate in the treatment of rosacea: a double-blind, placebo-controlled study. Sharquie KE, Najim RA, Al-Salman HN. *Int J Dermatol* 2006; 45: 857–61.

A combination oral formulation, comprising nicotinamide 750 mg, zinc 25 mg, copper 1.5 mg, and folic acid 500 mcg, was reported to be effective for rosacea and acne vulgaris in an open-label study ($n=198$). In a separate report from a crossover trial ($n=25$), zinc sulfate 100 mg/day was more effective than placebo.

PERSISTENT FACIAL ERYTHEMA (ERYTHEMATOTELANGIECTATIC ROSACEA)

First-Line Therapies

• Topical α -agonists (brimonidine gel, oxymetazoline cream)	A
• Light-based therapies (intense pulse light)	B
• Vascular lasers (pulse dye laser, others)	B

Efficacy and safety of once daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial

erythema of rosacea: results of two randomized, double-blind and vehicle-controlled pivotal studies. Fowler J Jr, Jackson M, Moore A, et al. *J Drugs Dermatol* 2013; 12(6): 650–6.

Brimonidine tartrate gel 0.5% (brimonidine 0.33%) was more effective than vehicle in reducing facial erythema over 12 hours of observation (days 1, 15, and 29) with rapid onset of ≥ 30 minutes (all $p < 0.001$). No tachyphylaxis or rebound was reported.

In the long-term (52-week) safety study required for FDA approval, reduced facial erythema with daily application was maintained throughout 12 months with no tachyphylaxis observed. When properly used, no systemic safety signals have emerged; however, worsening of facial erythema in 15%–20% of patients has been noted in real-world clinical practice.

Optimizing use of topical brimonidine in rosacea management: panel recommendations. Tanghetti EA, Jackson JM, Belasco KT, et al. *J Drugs Dermatol* 2015; 14(1): 33–40.

Topical brimonidine use in clinical practice has yielded observations that expand on the frequency and type of adverse cutaneous reactions that were reported in pivotal clinical trials. Real-world use shows that approximately 10%–20% of patients treated with brimonidine gel experience worsening of erythema, commonly referred to as ‘rebound’. This article clarifies the presentations of worsened facial erythema that have occurred including return of erythema to greater than baseline and paradoxical erythema (3–6 hours after application). Allergic contact dermatitis and irritant skin reactions are rare. Practical strategies such as proper skin care, thin layer application, and avoidance of overapplication are discussed based on anecdotal observations from panelists experienced with topical brimonidine use in clinical practice.

Topical oxymetazoline cream 1.0% for persistent facial erythema associated with rosacea: pooled analysis of the two phase 3, 29-day, randomized, controlled reveal trials. Stein-Gold L, Kir-cik L, Draelos ZD, et al. *J Drugs Dermatol* 2018; 17(11): 1201–8.

Oxymetazoline 1% cream applied once daily effectively reduced moderate-to-severe persistent facial erythema of rosacea ($p < 0.001$) and was well tolerated; no systemic safety signals emerged. The primary efficacy end point was ≥ 2 -grade improvement from baseline agreed upon by the investigator and the subject at 3, 6, 9, and 12 hours postdose at day 29.

This study, along with the long-term (52-week) safety study required by the FDA for approval, showed no tachyphylaxis and worsening of facial erythema was negligible.

Topical α -agonist therapy for persistent facial erythema of rosacea and the addition of oxymetazoline to the treatment armamentarium: where are we now? Del Rosso JQ. *J Clin Aesthet Dermatol* 2017; 10(7): 28–32.

This article differentiates α -adrenoreceptor activation between brimonidine and oxymetazoline and discusses potential clinical correlations. Rates of worsening of facial erythema with oxymetazoline 1% cream in clinical studies are low: 1% in pivotal trials ($n=489$) vs. $<1\%$ with vehicle ($n=483$) and 2% in the 52-week extension study ($n=440$), which had no vehicle arm. Paradoxical erythema has not been observed with oxymetazoline 1% cream; both allergic and irritant contact dermatitis do not appear to be clinical concerns based on available studies and pharmacovigilance to date.

Update on the management of rosacea from the American Acne & Rosacea Society. Del Rosso JQ, Tanghetti E, Webster G, et al. *J Clin Aesthet Dermatol* 2019; 12(6): 17–24.

This thorough review discusses publications and recommendations with physical devices. As this subject area is a moving

target, with new and updated devices constantly emerging, recommendations may be subject to change faster than with medical therapies. Additionally, results in practice are dependent on the experience of the operator; dosing; machine settings; hand pieces; treatment intervals; use of adjunctive devices; and differences among various machines, including those using the same fundamental technology. For telangiectasias and persistent facial erythema of rosacea (PFE), pulsed-dye laser (PDL) is commonly used; later PDL generations have an updated pulse format, which reduces bruising seen with early PDL devices. Intense pulsed light (IPL) devices can treat both PFE and telangiectasias, with comparable efficacy to PDL noted in some reports.

Early studies with long-pulsed 532-nm neodymium-doped yttrium aluminum garnet (Nd:YAG) laser show efficacy for telangiectasias; a more powerful 532-nm laser has been reported to treat telangiectasias and PFE, with results comparable to PDL devices. Overall, the use of vascular lasers and light-based devices have shown better results treating telangiectatic vessels compared to those obtained treating PFE. More data are needed on the use of physical devices for the treatment of papulopustular lesions. Publications are limited on topical α -agonist therapy utilized in combination with IPL or lasers for rosacea, although some suggest that such use is complementary.

Second-Line Therapies

• Botulinum toxin	D
• Cromolyn sodium	D

Botulinum toxin for the treatment of refractory erythema and flushing of rosacea. Park KY, Hyun MY, Jeong SY, et al. *Dermatology* 2015; 230: 299–301.

Impact of intradermal abobotulinumA on facial erythema of rosacea. Bloom BS, Payongayong L, Mourin A, et al. *Dermatol Surg* 2015; 41 (Suppl 1): S9–16.

Two reports of facial erythema and probably flushing responding to facial botulinum toxin injection in 2 and 15 cases, respectively.

Mast cells are key mediators of cathelicidin-initiated skin inflammation in rosacea. Muto Y, Wang Z, Vandenberghe M, et al. *J Invest Dermatol* 2014; 134: 2728–36.

This is a randomized, vehicle-controlled trial ($n=10$). Erythematotelangiectatic rosacea was treated with application of cromolyn sodium 4% solution or placebo twice daily for 8 weeks. Diffuse facial erythema was reduced in the active-treatment group.

FLUSHING OF ROSACEA

Flushing of rosacea exhibits an acute–subacute pattern of onset and reflects underlying augmented vasodilation induced by a known or unknown trigger(s). This occurs during intermittent flares of rosacea with or without concurrent papulopustular lesions. Flushing is often the most bothersome and difficult manifestation of rosacea to treat; however, therapies that reduce the frequency and magnitude of rosacea flares can indirectly reduce flushing episodes when used consistently. When a flare of rosacea resolves, and flushing-associated vasodilation and papulopustular lesions (if present) abate, the baseline state of fixed, dilated superficial facial vasculature remains present as diffuse central facial erythema, referred to as persistent facial erythema of rosacea (PFE). Some approaches to flushing of rosacea are reviewed below. When using agents such as clonidine or carvedilol, it is important to recognize that these agents are antihypertensive and may lower blood pressure.

First-Line Therapies

• Clonidine	D
• Carvedilol	D
• Naloxone	D
• Botulinum toxin	D

Clonidine and facial flushing in rosacea. Cunliffe WJ, Dodman B, Binner JG. *Br Med J* 1977; 1: 105.

In a crossover trial comparing clonidine 0.05 mg twice daily and placebo ($n=17$), five patients with rosacea experienced improvement in frequency and severity of flushing while on clonidine.

Effect of subdepressor clonidine on flushing reactions in rosacea: change in malar thermal circulation index during provoked flushing reactions. Wilkin JK. *Arch Dermatol* 1983; 119: 211–4.

Oral clonidine 0.05 mg twice daily did not mitigate provoked flushing reactions; tested triggers included water at 60°C, red wine, and chocolate. Clonidine did decrease malar skin temperature, suggesting a possible vasoconstrictor effect.

Long-term management of distinct facial flushing and persistent erythema of rosacea by treatment with carvedilol. Pietschke K, Schaller M. *J Dermatolog Treat* 2018; 29(3): 310–3.

The non-selective oral β -blocker carvedilol, dosed at 12.5 mg twice daily over at least 6 months, was evaluated for flushing and persistent facial erythema of rosacea ($n=5$). Grading of severity by both clinicians and patients showed marked reductions in facial erythema in all five cases. Major improvements in level of satisfaction and the absence of feelings of embarrassment were also noted in all five patients. Treatment was reported to be well tolerated.

Alcohol-induced rosacea flushing blocked by naloxone. Bernstein JE, Soltani K. *Br J Dermatol* 1982; 107: 59–61.

In an experimental setting ($n=5$), subcutaneous naloxone 0.8 mg effectively prevented alcohol-induced rosacea flushing. This suggests a potential role for opioid antagonism for the treatment of flushing of rosacea. Oral chlorpheniramine 12 mg or placebo demonstrated no consistent effect on flushing.

ROSACEA LYMPHEDEMA (MORBIHAN DISEASE)

Morbihan disease is considered an uncommon variant of rosacea of unknown etiology characterized by chronic/persistent edema of periorbital soft tissue, nose, cheeks, and the forehead/glabella region. Due to the limited number of cases overall, most information on treatment comes from case reports. A consistently successful therapeutic recommendation has not been identified, though successful approaches have been reported.

First-Line Therapies

• Oral antibiotic therapy (especially tetracycline agents)	E
• Isotretinoin	D
• Oral corticosteroid with an oral antibiotic (metronidazole; doxycycline)	E
• Surgery (CO ₂ laser blepharoplasty; eyelid debulking)	E

Morbihan disease treatment: two case reports and a systematic literature review. Boparai RS, Levin AM, Lelli GJ Jr. *Ophthalmic Plast Reconstr Surg* 2019; 35(2): 126–32.

The efficacy of treatments for Morbihan disease was systematically reviewed encompassing 87 patients from 49 publications and two cases treated by the authors ($n=89$). Median age was 51 years (range 14–79 years) and 74% were male. Presence of papulopustular lesions correlated with complete treatment response (odds ratio: 4.07; $p=0.03$); males tended to respond less favorably. Longer durations of antibiotic therapy (usually a tetracycline agent) correlated with response to treatment ($p=0.03$), favoring complete over partial response ($p=0.02$). Mean antibiotic duration in patients who responded was 4.4 months with complete responders requiring 6.5 months. Use of oral corticosteroids, isotretinoin, and combination therapies did not consistently correlate with treatment response.

Effective treatment of Morbihan disease with long-term isotretinoin: a report of three cases. Olivera-Cortes V, Pulido-Diaz N. *J Clin Aesthet Dermatol* 2019; 12(1): 32–4.

Three adult patients were treated with isotretinoin with an initial dose of 40 mg/day for ≥ 12 months, achieving substantial clinical improvement within 4–8 months. Once marked clinical improvement was determined, the daily dosage was then reduced to 20 mg for 6–12 months. Adverse effects were negligible. Successful clinical response was maintained with no recurrences, including one patient followed for 1 year and another patient for 3 years.

Successful long-term use of oral isotretinoin for the management of Morbihan disease: a case series report and review of the literature. Smith LA, Cohen DE. *Arch Dermatol* 2012; 148: 1395–8.

Isotretinoin 40–80 mg/day was used for 10–24 months ($n=5$). Marked improvement was not observed before 6 months of therapy; treatment was successful with disease-free follow-up ranging from 1 to 24 months.

Persistent facial swelling in a patient with rosacea. Scerri L, Saihan EM. *Arch Dermatol* 1995; 131: 1069–74.

Successful treatment of Morbihan disease with oral prednisolone and doxycycline. Ranu H, Lee J, Hee TH. *Dermatol Ther* 2010; 23: 682–5.

Two individual cases were successfully treated with oral prednisolone and either oral metronidazole or doxycycline. Marked decrease in facial swelling was noted with a tapering course of prednisolone (30 mg daily starting dose) and metronidazole 400 mg/day over a 4-month period followed by metronidazole 200 mg/day. A second patient responded to doxycycline 100 mg daily with oral prednisolone added on after 6 weeks (20 mg daily for 2 weeks, then 10 mg daily for 1 week).

Morbihan disease: treatment with CO₂ laser blepharoplasty. Bechara FG, Jansen T, Losch R, et al. *J Dermatol*. 2004; 31: 113–5.

Chronic eyelid lymphedema and acne rosacea: report of two cases. Bernardini FP, Kersten RC, Khouri LM, et al. *Ophthalmology* 2000; 107: 2220–3.

Favorable cosmetic results and reduced visual impairment were achieved with CO₂ laser blepharoplasty. In a separate publication, surgical debulking of affected soft tissue produced highly favorable cosmetic and functional improvement in both patients.

OCULAR ROSACEA

Ocular rosacea is reported to occur in approximately 30–50% of patients with cutaneous rosacea, presenting most often as blepharitis, conjunctivitis, episcleritis, hordeolum (stye), and chalazion. Fortunately, severe keratitis is uncommon but can lead to visual changes if cases of greater clinical significance are not expeditiously managed. Meibomian gland dysfunction with reduced lipid production and evaporative loss of the aqueous content of tear film leads to adverse changes to tear film integrity and breakup time. Physiochemical changes occur within the eye unit affected by ocular rosacea analogous to what has been described for cutaneous rosacea. Symptoms of ocular rosacea include sensations of dryness, grittiness, itchiness, and irritation, which patients attribute to ‘allergies’, so they do not usually voice the complaint to a dermatologist. Ophthalmologic consultation is warranted in cases of diagnostic concern, and with refractory or more severe cases. This is especially warranted if keratitis of increased clinical significance is suspected, with pain, discomfort with raising the upper eyelid, photophobia, marked or worsening erythema, blurred vision, and/or impaired vision being suggestive symptoms. Caution is recommended if oral isotretinoin is used for refractory papulopustular rosacea as systemic retinoid use impairs meibomian gland secretion. Similarly to proper skin care for cutaneous rosacea, artificial tears and ocular lubricants are recommended as integral components in the management for ocular rosacea, and omega-3 fatty acid (O3FA) oral supplements may reduce symptoms, prolong tear breakup time, and improve Schirmer test results. Compresses, careful eyelid cleansing/hygiene, and intermittent use of topical antibiotic therapy may also be beneficial.

First-Line Therapies

• Oral antibiotics (especially doxycycline including subantibiotic-dose doxycycline)	A
• Topical ciclosporin	A
• Topical antimicrobial agents (azithromycin, ivermectin)	C, D

Meibomian gland dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. Geerling G, Tauber J, Baudouin C, et al. *Invest Ophthalmol Vis Sci* 2011; 52: 2050–64.

The authors discuss a comprehensive practical approach with supporting evidence that can provide benefit for ocular rosacea management. A helpful treatment algorithm is included.

Ocular rosacea: signs, symptoms and tear studies before and after treatment with doxycycline. Quarterman MJ, Johnson DW, Abele DC, et al. *Arch Dermatol* 1997; 133: 49–54.

Doxycycline 100 mg daily for 12 weeks markedly improved signs and symptoms of both cutaneous and ocular rosacea ($n=39$). Average tear breakup time was 5.7 seconds prior to treatment, which improved to 10.8 seconds after 12 weeks ($p=0.007$).

This study showed that all patients with cutaneous rosacea exhibit at least subclinical ophthalmologic measurement changes that occur to a greater magnitude with clinically evident ocular rosacea; a subset of patients develop clinical manifestations of ocular rosacea.

Treatment of ocular rosacea with once-daily low-dose doxycycline. Sobolewska B, Doycheva D, Deuter C, et al. *Cornea* 2014; 33(3): 257–60.

Patients with ocular rosacea were enrolled in a retrospective observational case series ($n=15$). Clinical manifestations included blepharitis with telangiectasia, meibomian gland dysfunction, and conjunctival erythema. Subantibiotic-dose doxycycline 40 mg modified-release capsule once daily was used over a mean duration of 8 months (range 5–12 months); mean duration of follow-up was 9 months (range 6–17 months). Despite use of artificial tears and eyelid hygiene, severe symptoms and blepharitis were present in 73.3% and 80% of patients at baseline and improved to 13.3% and 20% after 12 weeks of therapy, respectively ($p=0.01$).

Systemic therapy of ocular and cutaneous rosacea in children. Gonser LI, Gonser CE, Deuter C, et al. *J Eur Acad Dermatol Venereol* 2017; 31(10): 1732–8.

A retrospective study of children with ocular rosacea treated with oral antibiotic therapy with mean follow-up duration of 30.2 months: 17 patients (89.5%) with blepharitis, 15 (78.9%) with conjunctivitis, 12 (63.2%) with chalazia/styes, and 9 (47.4%) with corneal involvement at baseline. Oral treatment was erythromycin ($n=9$) or roxithromycin ($n=1$) in patients age ≤ 8 years, and doxycycline ($n=8$) or minocycline ($n=1$) in patients age >8 years. Results showed that 7/9 patients treated with erythromycin, 1/8 treated with doxycycline, and 1/1 treated with minocycline achieved complete remission of ocular and cutaneous symptoms, and 2/9 patients treated with erythromycin, 7/8 patients treated with doxycycline, and 1/1 treated with roxithromycin achieved a partial remission. Relapses occurred in the patient treated with minocycline (cutaneous), 2/8 patients treated with doxycycline (ocular and cutaneous), and 1/9 treated with erythromycin (cutaneous).

The limited data available suggest that although both cutaneous and ocular rosacea in children are uncommon, these conditions can be difficult to treat and may require prolonged management and combination therapy approaches. Affected children often have a strong family history of rosacea.

Treatment of ocular rosacea: comparative study of topical ciclosporin and oral doxycycline. Arman A, Demirseren DD, Takmaz T. *Int J Ophthalmol* 2015; 8: 544–9.

Patients with ocular rosacea were randomized to receive topical ciclosporin twice daily for 3 months or oral doxycycline 100 mg twice daily for 1 month, then once daily for 2 months. Equal efficacy was noted in rosacea-associated ocular changes; ciclosporin was more effective in relieving symptoms ($p=0.01$) and in improving mean Schirmer test scores and tear breakup time scores compared with doxycycline ($p<0.05$). Topical ciclosporin may be more effective overall in treating ocular rosacea complications than oral doxycycline with avoidance of oral therapy.

Efficacy of topical ciclosporin for the treatment of ocular rosacea. Schechter BA, Katz RS, Friedman LS. *Adv Ther.* 2009; 26: 651–9.

Double-blind, randomized, 3-month trial ($n=37$) comparing ciclosporin 0.05% ophthalmic emulsion twice daily with an artificial tear solution (control). Marked improvement in objective parameters (Schirmer scores, tear breakup time, corneal staining) and quality of life (Ocular Surface Disease Index) were seen in the actively treated group compared to the control group.

Topical azithromycin as a novel treatment for ocular rosacea. Mantelli F, Di Zazzo A, Sacchetti M, et al. *Ocul Immunol Inflamm* 2013; 21(5): 371–7.

Among 37 patients with ocular rosacea, 12 were treated with systemic doxycycline and 16 with azithromycin eye drops. Marked improvement in symptoms, tear film breakup time, and meibomian gland plugging were observed at 1 month with both therapies. Topical azithromycin may serve to avoid exposure to systemic therapy for ocular rosacea in some patients.

Successful therapy of ocular rosacea with topical ivermectin. Schaller M, Pietschke K. *Br J Dermatol.* 2018; 179(2): 520–1.

Case report of an adult male with severe papulopustular rosacea and mild-to-moderate ocular rosacea (blepharoconjunctivitis without keratitis) treated with topical ivermectin 1% cream once daily, including application to closed eyelid skin. After 14 weeks, both facial and ocular rosacea improved, the latter favorably progressing to mild severity. By week 35, both cutaneous and ocular rosacea were completely clear, with no relapse over 20 months of follow-up. Quantification of *Demodex* mite density at baseline by skin-surface biopsy technique showed complete eradication at week 14 and week 35.

ROSACEA FULMINANS/PYODERMA FACIALE

Rosacea fulminans, also referred to as pyoderma faciale, although presenting clinically like a ‘cousin’ of acne fulminans, is a distinct entity. It is characterized by abrupt onset of multiple coalescing facial inflammatory lesions, predominantly pustules, nodules, and abscesses. This entity is fortunately rare and of unknown etiology, most often affecting female patients with an age distribution of usually between the second through fifth decades of life. As this entity is rare, information on treatment is gleaned from case reports and case series. Similarly to acne fulminans, oral corticosteroid therapy is recommended initially and tapered judiciously with monitoring of response. Concurrent use of oral isotretinoin appears to be of therapeutic benefit with both cautious initiation and daily dosing to mitigate unwanted exacerbation. It does appear that the duration of oral corticosteroid therapy is likely to be shorter than what is often needed for acne fulminans to achieve clearance or adequate disease control. There is no current evidence strongly supporting use of antibiotic therapy for rosacea fulminans, although data are limited, and this may be an option in selected cases, especially when oral isotretinoin cannot be used. Topical corticosteroid therapy may be an option in selected cases, especially when limitations exist with systemic corticosteroid use. A short course of oral corticosteroid therapy in combination with oral isotretinoin appears to be effective in many cases of rosacea fulminans, although treatment is best individualized based on monitoring of response and patient-specific considerations.

First-Line Therapies

• Systemic corticosteroids	C
• Isotretinoin	C
• Oral antibiotic therapy	D

Pyoderma faciale: a review and report of 20 additional cases: is it rosacea? Plewig G, Jansen T, Kligman AM. *Arch Dermatol* 1992; 128: 1611–7.

Oral prednisolone was initiated at 1 mg/kg/day for 1–2 weeks. Isotretinoin 0.2–0.5 mg/kg/day was then added. Prednisolone was then tapered over 2–3 weeks. Isotretinoin continued for 3–4 months.

Diagnosis and treatment of rosacea fulminans: a comprehensive review. Walsh RK, Endicott AA, Shinkai K. *Am J Clin Dermatol* 2018; 19(1): 79–86.

This comprehensive review evaluated 135 cases of rosacea fulminans and reported management strategies. The average age at onset was 31.3 years and 91% were females. In 81% of cases, the reported duration of symptoms was <3 months and recurrences were uncommon. Most patients had a prior history of rosacea or flushing; hormonal shifts were a common trigger. Extrafacial and systemic involvement were rare. Regarding management, use of oral and topical antibiotics shifted after reports using isotretinoin emerged in the late 1980s, with increased reliance on isotretinoin along with corticosteroid therapy as recommended treatment.

Rosacea fulminans during pregnancy. Markou AG, Alessandrini V, Muray JM, et al. *Clin Exp Obstet Gynecol* 2017; 44(1): 157–9.

A 37-year-old woman during the 37th week of pregnancy presented with rosacea fulminans with ocular manifestations. Isotretinoin use was contraindicated. She was treated with oral prednisone and oral azithromycin. After delivery at 38 weeks, there was significant improvement.

Close communication with the patient's obstetrician was recommended as varying obstetrical outcomes have been reported in pregnant women affected by rosacea fulminans.

Sarcoidosis

Carlos Vieira, Bilal Fawaz, Lacy L. Sommer



Sarcoidosis is a multisystem disease of unknown etiology characterized histologically by non-caseating granulomas. It is an immune-mediated disease, with a Th1-predominant cytokine profile. Skin manifestations are observed in approximately 25% of cases. Sarcoidosis has been reported to develop after exposure to inorganic particles in the environment. The use of polymerase chain reaction techniques has also led to the identification of mycobacterial and propionibacterial DNA and RNA in sarcoidal tissue. Sarcoidosis may be the end result of immune responses to those or other specific triggers. Therapy for erythema nodosum associated with sarcoidosis is addressed in the chapter on erythema nodosum.

Cutaneous sarcoidosis (CS) has also been reported as a paraneoplastic phenomenon, most frequently in the setting of hematologic malignancies. Improvement of cutaneous disease is noted in the majority of patients following treatment of the underlying lymphoproliferative disorders, suggesting a potential pathogenic link between both conditions.

Medications including immune checkpoint inhibitors, tumor necrosis factor- α (TNF- α) inhibitors, ustekinumab, antiretrovirals, and interferons have been associated with sarcoidosis-like reactions in the skin. While discontinuation of the medication often leads to the resolution of cutaneous disease, therapeutic adjustments are not mandatory in the absence of organ dysfunction or quality of life impairment. Some studies suggest a benefit to continuation of therapy with the addition of other antisarcoidosis medication to the regimen.

MANAGEMENT STRATEGY

The treatment of CS depends on the types and extent of lesions and is directed at suppressing granuloma formation. Guidelines for treating extracutaneous involvement can be found elsewhere,

but it should be recognized that therapy for internal involvement may take precedence over skin disease and that response to treatment may be variable, depending on the type of tissue involved.

In small papular or localized sarcoidosis, treatment with *potent topical corticosteroids*, *intralesional triamcinolone acetonide* (3.3–10 mg/mL), or *topical calcineurin inhibitors* is reasonable. If this is ineffective or involvement is more diffuse, *tetracyclines* (100 mg minocycline twice daily), *oral chloroquine* (up to 3.5 mg/kg/day), *hydroxychloroquine* (up to 6.5 mg/kg/day), or *methotrexate* may be effective. If no response is seen or disfiguring lesions are present, *oral prednisone* can be used at a dose of 1 mg/kg daily (maximum 60 mg) for up to 3 months and then tapered if improvement or a stable level is reached, to a maintenance dose of 5–10 mg on alternate days for several months. Periodic escalations in dose are necessary with flares of the disease.

Methotrexate may be used as a corticosteroid-sparing agent or as monotherapy in those patients with lupus pernio, ulcerative sarcoidosis, or severe disease that has not responded to prednisone. Initial doses of 15–20 mg weekly are favored. *Mycophenolate mofetil* has also shown promise as a steroid-sparing agent. *Thalidomide*, *azathioprine*, *chlorambucil*, *isotretinoin*, or *allopurinol* could be considered if methotrexate or mycophenolate mofetil fails in this subset of patients. Azathioprine and chlorambucil are better studied in patients with pulmonary sarcoidosis. Thalidomide seems to be more effective than isotretinoin and allopurinol in cutaneous disease. Reported failures are described with etretinate.

Biologic agents that inhibit TNF- α should be considered in patients with lupus pernio or CS recalcitrant to systemic steroids or steroid-sparing agents. Specifically, *infliximab* and *adalimumab* have demonstrated efficacy in treating CS. Etanercept, golimumab, and certolizumab, however, do not appear to be useful for the treatment of sarcoidosis. Discontinuation of anti-TNF therapy has been linked to relapse of cutaneous disease in approximately half of patients.

Leflunomide and *apremilast* have shown promise in the treatment of CS unresponsive to other therapies. Janus kinase (JAK) inhibitors have gained particular interest in recent years, with early reports suggesting *tofacitinib* may have the potential to revolutionize treatment for refractory disease; however, further studies are needed to establish long-term safety and efficacy.

Localized disease that does not respond to topical or intralesional corticosteroids, or in those cases in which the use of systemic medications is undesirable, may represent a niche for other modalities, such as *excision*, *laser*, *photodynamic therapy*, *PUVA*, *intralesional 5-fluorouracil*, or *intralesional chloroquine*.

Specific Investigations

- Special stains, cultures, and polarization of biopsy specimens
- Electrolytes, blood urea nitrogen, creatinine, serum calcium, liver function tests, complete blood count, 24-hour urine calcium, and serum angiotensin-converting enzyme
- Ophthalmologic evaluation, including slit-lamp examination
- Chest radiograph, pulmonary function tests
- Electrocardiogram
- FDG PET (18-fluoro-deoxyglucose positron-emission tomography) is useful in identifying sites for diagnostic biopsy (for patients without apparent lung involvement)
- MRI with gadolinium (neurologic sarcoidosis may occur without any other internal organ involvement)
- DEXA (dual X-ray absorptiometry) bone density scans in patients on long-term oral corticosteroids

Sarcoidosis: a comprehensive review and update for the dermatologist – part I. Cutaneous disease. Haimovic BA, Sanchez M, Judson MA, et al. J Am Acad Dermatol 2012; 66: 699, e1–18.

An extensive review of CS, including epidemiology, pathogenesis including the Th1 pathway, morphologies, and treatment. The discussion includes a proposed treatment algorithm.

Cutaneous sarcoidosis: a new subset in the spectrum of paraneoplastic dermatoses. El-Khalawany M, Mosbeh A, Aboeldahab S, et al. Clin Exp Dermatol 2018; 43: 683–91.

This is an observational cohort prospective study of 94 patients with CS that identified 12 patients (12.8%) with paraneoplastic sarcoidosis (PS). The most commonly associated malignancies were Hodgkin lymphoma ($n=6$), multiple myeloma ($n=5$), and non-Hodgkin lymphoma ($n=1$). Patients with PS did not respond well to monotherapy with prednisone and had a moderate response to combination therapy with adjuvant immunosuppressive agents. After treatment of the associated malignancy, 58.3% of patients with PS demonstrated complete remission of lesions while the remaining cohort showed moderate improvement, with histologic regression of granulomas.

Poor response to conventional therapy and presence of frequent mitoses on histologic evaluation should alert the clinician to the possibility of PS. Most of the associated hematologic malignancies developed 1–2 years after the diagnosis of sarcoidosis.

Immune checkpoint inhibitor-induced sarcoidosis-like granulomas. Rambhia PH, Reichert B, Scott JF, et al. Int J Clin Oncol 2019; 24: 1171–81.

A review article identified 55 cases of sarcoidosis-like granulomas (SLG) attributed to immune checkpoint inhibitor-related reactions. Only one patient had a prior known diagnosis of sarcoidosis. Patients were treated with programmed cell death protein 1 (PD-1) inhibitors (45%), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors (27%), or a combination of both (27%). Reactions most commonly involved the lungs, skin, and lymph nodes. Cutaneous findings occurred in 55% of cases and included subcutaneous nodules, papules, and plaques.

Outcomes were reported in 89% of cases, and SLG resolved with discontinuation of immune checkpoint inhibitors in 41% of cases. The remaining cases resolved with a combination of treatment withdrawal and steroids, steroids alone, or no intervention.

Drug-induced sarcoidosis-like reactions. Chopra A, Nautiyal A, Kalkanis A, et al. Chest 2018; 154: 664–77.

Drug-induced sarcoidosis-like reactions (DISR) have been attributed to immune checkpoint inhibitors, TNF- α antagonists, antiretroviral therapy, and interferons, among others. These reactions typically resolve spontaneously or with discontinuation of the drug. While switching to an alternate drug within the same class (as in TNF- α blockers) results in resolution of DISR, it may be useful to continue therapy with the addition of a corticosteroid or other antisarcoidosis therapy when the benefits of treatment outweigh the potential burden of DISR. Adjunctive antigranulomatous therapy led to over 60% resolution across DISR cases in each offending drug category. Many cases used an initial dose of 20 mg daily prednisone and adjusted according to the patient's underlying condition.

First-Line Therapies

Localized disease

- Topical corticosteroids **C**
- Intralesional corticosteroids **C**

Diffuse disease or limited response to local treatment

- Oral corticosteroids **C**
- Minocycline, doxycycline **D**
- Chloroquine **B**
- Hydroxychloroquine **C**
- Methotrexate **B**

Verrucous cutaneous sarcoidosis in an adolescent with dark skin. Corradin MT, Forcione M, Fiorentino R, et al. Eur J Dermatol 2010; 20: 659–60.

A 16-year-old boy presented with violaceous, verrucous nodules on his forehead, chest, and arm. The patient was treated with topical mometasone furoate 0.1% cream daily with clearance of lesions in 3 weeks.

Potent topical corticosteroid use is reported to be of some value in anecdotal reports. Most authors believe that intralesional corticosteroids are more effective, yet this, too, is anecdotal. Small lesions are optimal candidates; however, lupus pernio has also been reported to respond.

Sarcoidal foreign body reaction as a severe side-effect to permanent makeup: successful treatment with intralesional triamcinolone. Tittelbach J, Peckruhn M, Schliemann S, et al. Acta Derm Venereol 2018; 98(4): 458–9.

A 41-year-old female presented with a granulomatous foreign body reaction of the bilateral eyebrows several years after permanent cosmetic tattooing. Topical clobetasol cream was ineffective; however, satisfactory response occurred with a series of five intralesional triamcinolone injections administered at 3- to 4-week intervals.

Anecdotal reports suggest small, papular sarcoid responds best. The strength of triamcinolone acetonide varies from 2 to 40 mg/mL, and frequency varies from weekly to monthly.

Evidence-based therapy for cutaneous sarcoidosis. Baughman RP, Lower EE. Clin Dermatol 2007; 25: 334–40.

Whereas the recommended starting dose of prednisone for pulmonary sarcoidosis is suggested to be 20–40 mg daily, the dose and duration of treatment for CS have not been established. The authors suggest using this as a benchmark and tapering the steroid dose after 1 or 2 months to one that controls the disease while avoiding toxicity. The authors report that the need for long-term systemic corticosteroids for treatment of chronic sarcoidosis occurs in about 25% of patients.

Another suggested regimen for prednisone in CS is 30 mg orally on alternate days until the granulomas fade. The dose is then tapered over several months to 15 mg orally on alternate days. Other protocols report a good response with prednisone 30–40 mg orally daily, with a gradual taper to 10–20 mg orally on alternate days for 1 year, or prednisone 1 mg/kg orally daily (maximum 60 mg) for 8–12 weeks, with a taper to 0.25 mg/kg daily continued for 6 months.

With long-term treatment, prevention of corticosteroid-induced osteoporosis with bisphosphonates and Pneumocystis pneumonia prophylaxis with trimethoprim-sulfamethoxazole should be considered.

Oral minocycline in treatment of cutaneous sarcoidosis.

Steen T, English JC. JAMA Dermatol 2013; 149(6): 758–60. Twenty-seven patients with biopsy-proven CS were included in the study. Seven patients had sarcoidosis of skin only; 17 had pulmonary and skin involvement; and one had ocular, pulmonary, and skin involvement. Minocycline was prescribed as first-line treatment in 18 patients. In total, 20 of 27 (74%) patients showed response to the treatment ($p = 0.02$) with six patients (22%) demonstrating complete remission. Six patients experienced hyperpigmentation, limited in four of these cases to the site of CS.

Despite the lack of large published studies, due to the low cost, safety profile, and moderate success, tetracyclines can be considered a first-line therapy in cutaneous disease.

Treatment of cutaneous sarcoidosis with chloroquine: review of the literature.

Zic JA, Horowitz DH, Arzubiaga C, et al. Arch Dermatol 1991; 127: 1034–40. The review article cites four studies (three open clinical trials and one case series) that support the use of chloroquine. The authors recommend an initial dose of 250 mg twice daily for 14 days, then 250 mg daily for long-term suppression, though most studies have used 500 mg daily for several months. Relapses after discontinuation of treatment are frequent.

Hydroxychloroquine is effective therapy for control of cutaneous sarcoid granulomas.

Jones EJ, Callen JP. J Am Acad Dermatol 1990; 23: 487–9. A total of 17 patients were treated with 200 mg or 400 mg daily of hydroxychloroquine. Cutaneous lesions regressed in 12 patients within 4–12 weeks, and three patients had a partial response. Of the 12 patients with the best response, six had a recurrence after a dosage reduction or discontinuation.

Hydroxychloroquine may have a better safety profile than chloroquine; however, chloroquine has been better studied in sarcoidosis. Although retinal toxicity is rare, in order to prevent this complication, doses of chloroquine should not exceed 3.5 mg/kg/day, and hydroxychloroquine should not exceed 6.5 mg/kg/day. A solitary case report of multiple injections of intralesional chloroquine hydrochloride (50 mg/mL) at 3–4-week intervals showed efficacy in a single patient, with minimal side effects (Liedtka JE. Intralesional chloroquine for the treatment of CS. Int J Dermatol 1996; 35: 682–3).

Methotrexate is steroid sparing in acute sarcoidosis: results of a double blind, randomized trial.

Baughman RP, Winget DB, Lower EE. Sarcoidosis Vasc Diffuse Lung Dis 2000; 17: 60–6. In this trial, 24 patients with new-onset symptomatic pulmonary disease were randomized to receive either methotrexate or placebo in addition to their prednisone. Although only 15 patients received at least 6 months of therapy, the methotrexate group required less prednisone than the placebo group. There was no difference in toxicity between the methotrexate and the placebo groups.

A favorable response is usually expected after several months of therapy, and the dose can be tapered weekly after 4–6 months. Some studies indicate that methotrexate may be particularly useful for those with ulcerative sarcoidosis.

Infliximab for chronic cutaneous sarcoidosis: a subset analysis from a double-blind randomized clinical trial.

Baughman RP, Judson MA, Lower EE, et al. Sarcoidosis Vasc Diffuse Lung Dis 2016; 15: 32: 289–95. A subset analysis of 17 patients with chronic CS from a larger study of 138 patients with pulmonary disease reviewed their response to infliximab (3 or 5 mg/kg) versus placebo over 24 weeks. The Sarcoidosis Activity and Severity Index (SASI) scoring system found significant improvement in desquamation and induration at week 24, but erythema, percentage of area involved, and evaluation of paired photographs did not show a significant difference.

Infliximab, although potentially effective, has been shown to increase the risk of tuberculosis reactivation, the risk of other granulomatous infections, lymphomas, and autoimmune disease. Therapy is expensive, costing up to thousands of dollars per infusion. One must be aware of the side effects and cost.

Anti-tumor necrosis factor agents in sarcoidosis: a systematic review of efficacy and safety.

Adler BL, Wang CJ, Bui TL, et al. Semin Arthritis Rheum 2019; 48: 1093–104. A systematic review of anti-TNF agents in sarcoidosis. One randomized controlled trial demonstrated adalimumab (80 mg week 0, 40 mg weeks 1–12) to have a greater response after 12 weeks of treatment as well as a significantly lower target lesion area compared with placebo. Non-randomized studies of infliximab (3–5 mg/kg every 4–8 weeks) demonstrated 31% complete remission rate and a 58% partial remission rate in 84 patients. Use of anti-TNF therapy was found to slightly increase the risk of serious infections, particularly infliximab, but the concomitant use of other immunomodulators was not accounted for.

Infliximab has become a second-line agent, particularly in cases of lupus pernio and neurocutaneous sarcoidosis. Studies suggest that infliximab can be used as an induction agent with long-term methotrexate. Superiority to etanercept has been demonstrated. Alternatively, adalimumab may also be considered given the established efficacy and convenience of administration when compared with infliximab, although rare reports exist of adalimumab inducing sarcoidosis in certain patients.

Randomized controlled trials involving etanercept ($n=1$) and golimumab ($n=1$) did not demonstrate efficacy in the treatment of sarcoidosis. Numerous case reports exist on etanercept and certolizumab inducing sarcoidosis. Therefore, etanercept, golimumab, and certolizumab do not appear to be useful in the treatment of sarcoidosis.

Mycophenolate mofetil as an alternative treatment in sarcoidosis.

Papiris S, Stagaki E, Papadaki G, et al. Pulm Pharmacol Ther 2019; 58: 101840. Eight patients with pulmonary and extrapulmonary sarcoidosis were treated with mycophenolate mofetil (MMF) at 2 g daily for at least 1 year. Three patients had CS that significantly improved on treatment.

The absence of lung toxicity and considerable safety profile of MMF permits its use as an alternative drug in sarcoidosis.

Second-Line Therapies

• Infliximab	B
• Adalimumab	B
• Mycophenolate mofetil	D

Third-Line Therapies

• Topical calcineurin inhibitors	D
• Intralesional 5-fluorouracil	E
• Excision	D
• PUVA	D
• Medium-dose ultraviolet A1 (UVA1)	E
• Photodynamic therapy	D

Continued

Third-Line Therapies—cont'd

• Laser	E
• Apremilast	C
• Pentoxifylline	E
• Isotretinoin	E
• Allopurinol	D
• Tofacitinib	D
• Azathioprine	E
• Leflunomide	D
• Thalidomide	C
• Chlorambucil	B

Lichenoid type of cutaneous sarcoidosis: great response to topical tacrolimus. Vano-Galvan S, Fernandez-Guarino M, Carmona LP, et al. *Eur J Dermatol* 2008; 18: 89–90.

A 33-year-old female with lichenoid-type CS was treated with 0.1% tacrolimus ointment twice daily. Near-complete resolution was noted at 2 months, and the patient remained free of disease at 4 months.

Topical pimecrolimus as a new optional treatment in cutaneous sarcoidosis of lichenoid type. Tammaro A, Abruzzese C, Narcisi A, et al. *Case Rep Dermatol Med* 2014; 2014: 976851.

A 66-year-old woman with violaceous, lichenoid sarcoidosis previously unresponsive to clobetasol resolved with topical 1% pimecrolimus cream (applied twice daily) after 6 months of treatment with no adverse effects.

Cutaneous sarcoidosis successfully treated with intralesional 5-fluorouracil. Gharavi N, Diehl J, Soriano T. *Dermatol Surg* 2015; 41: 1082–5.

A 48-year-old Caucasian male with large, periorbital sarcoidal nodules significantly improved with three monthly treatments of 0.5–1.0 mL of 50 mg/mL of intralesional 5-fluorouracil. The exact mechanism by which 5-fluorouracil resolves granulomas remains unclear.

Cutaneous nasal sarcoidosis: treatment by excision and split-skin grafting. Goldin JH, Jawad SMA, Reis AP. *J Laryngol Otol* 1983; 97: 1053–6.

Split-thickness and full-thickness skin grafts, dermabrasion, and primary closure have been attempted, with mixed results. Surgery has been used in ulcerative and non-ulcerative sarcoidosis.

Several reports utilizing primary closure, a paramedian forehead flap, and a full-thickness graft continue to show mixed long-term results.

Light and laser modalities in the treatment of cutaneous sarcoidosis: a systematic review. Lima AL, Goetze S, Illing T, et al. *Acta Derm Venereol* 2018; 98(5): 481–3.

This systematic review summarizes light and laser therapy for CS. Six patients with recalcitrant CS were treated with topical gel psoralen and UVA (PUVA) twice weekly at 0.2 J/cm². Three patients (50%) had a complete response, and three patients had greater than 50% improvement. Two cases demonstrate considerable improvement with UVA1 therapy. Photodynamic therapy and intense pulse light have been used successfully. Pulsed dye laser and Q-switched ruby laser have shown efficacy in lupus pernio; however, exacerbations of lupus pernio – namely, generalized ulceration in treated and untreated lesions – have been reported after this therapy. CO₂ laser resurfacing has been used in four patients with lupus pernio with a favorable cosmetic result.

Efficacy and safety of apremilast in chronic cutaneous sarcoidosis. Baughman RP, Judson MA, Ingledue R, et al. *Arch Dermatol* 2012; 148: 262–4.

In this study of 15 patients on systemic steroids treated with 20 mg twice daily (once daily if not tolerated) apremilast, a phosphodiesterase type 4 inhibitor, a significant reduction in SASI induration score was observed at 4 and 12 weeks. Relapse was noted in three patients at the 3-month follow-up. *Pentoxifylline*, a non-selective cyclic nucleotide phosphodiesterase inhibitor, has been reported as an effective treatment for pulmonary sarcoidosis; however, efficacy in CS needs further investigation.

Cutaneous sarcoidosis: complete remission after oral isotretinoin therapy. Georgiou S, Monastirli A, Pasmatzis E, et al. *Acta Derm Venereol* 1998; 78: 457–9.

A 31-year-old woman with nodules and plaques on the trunk and extremities showed a complete remission with 8 months of isotretinoin at 1 mg/kg daily; 15-month follow-up revealed continuing remission.

Two other cases report improvement with a 30-week course (0.67–1.34 mg/kg daily) and a 6-month course (0.4–1 mg/kg daily), respectively, of isotretinoin.

Low-dose allopurinol in the treatment of cutaneous sarcoidosis: response in four of seven patients. Bregnhoej A, Jemec GB. *J Dermatolog Treat* 2005; 16(2): 125–7.

Seven patients with CS were treated with low-dose allopurinol at either 100 or 200 mg daily. After treatment for 2–16 weeks, four of seven patients (57%) responded: one patient achieved complete remission, three achieved partial remission, and three had no response. Two of the three non-responders were only treated with 100 mg allopurinol daily while all of the responding patients were treated with 200 mg allopurinol daily. One non-responder had a short duration of treatment at 2 weeks, whereas responders were treated with a longer period.

A few case reports demonstrate a dose–response and a time–response relationship of allopurinol in the treatment of sarcoidosis, suggesting the minimum dose of allopurinol to be 200 mg daily, and the minimum treatment period to be 4 weeks.

Janus kinase inhibition induces disease remission in cutaneous sarcoidosis and granuloma annulare. Damsky W, Thakral D, McGeary MK, et al. *J Am Acad Dermatol* 2020; 82: 612–21.

A prospective study that followed four patients (3 with CS, 1 with granuloma annulare) treated with tofacitinib (5 mg twice daily). There was a mean of 96% improvement from baseline Cutaneous Sarcoidosis Activity and Morphology Instrument with three out of four patients demonstrating complete response to treatment (2 with CS and 1 with granuloma annulare) and histologic resolution of granulomatous inflammation. Clinical improvement was noted as early as 2 months into therapy, and remission was observed within 6–10 months. Two patients experienced interruption in therapy resulting in relapse of clinical disease, followed by improvement upon restarting tofacitinib. No adverse events were noted.

Tofacitinib appears to be a promising therapeutic option for patients with refractory sarcoidosis via downregulation of the JAK–STAT pathway. Randomized controlled trials are needed, however, to further evaluate the safety and efficacy of JAK inhibitors in the treatment of sarcoidosis.

Tofacitinib treatment and molecular analysis of cutaneous sarcoidosis. Damsky W, Thakral D, Emeagwali N, et al. *N Engl J Med* 2018; 379: 2540–6.

A case report of a patient treated with tofacitinib, a Janus kinase (JAK) 1 and 3 inhibitor, who was refractory to therapy with topical corticosteroids, oral tacrolimus, minocycline, hydroxychloroquine, methotrexate, apremilast, and adalimumab. Treatment with tofacitinib (5 mg twice daily) led to remission of her disease both clinically and histologically. A 3-month lapse in treatment resulted in the return of cutaneous disease, but the skin lesions abated once again after tofacitinib was restarted. No adverse events were noted.

Long-term use of azathioprine as a steroid-sparing treatment. Hof DG, Hof PC, Godfrey WA. *Am J Respir Crit Care Med* 1996; 153: 870A.

Of the 21 patients in this study, eight had multisystem involvement and one had skin-only involvement. All patients with extrapulmonary disease achieved a complete remission with azathioprine and a tapering dose of prednisone.

Effectiveness and safety of leflunomide for pulmonary and extrapulmonary sarcoidosis. Sahoo DH, Bandyopadhyay D, Xu M, et al. *Eur Respir J* 2011; 38(5): 1145–50.

This retrospective chart review analyzed 79 patients who were prescribed leflunomide for sarcoidosis over a 5-year period. Leflunomide was initiated at 20 mg daily for a mean duration of 16 ± 13 months. Of the 12 patients treated for CS, 50% (n=6) had a complete response (>90% clearance), 42% (n=5) had a partial (50–89% clearance) response, and one had no response (<49% clearance). Side effects, though usually minor, occurred in 34% of patients; however, they required discontinuation of leflunomide in 17% of patients.

Adverse events, including gastrointestinal problems, hepatic enzyme elevation, neuropathy, and hypersensitivity reactions, including erythema multiforme and Stevens–Johnson syndrome, have been reported.

Thalidomide for improving cutaneous and pulmonary sarcoidosis in patients resistant or with contraindications to corticosteroids. Fazzi P, Manni E, Cristofani R, et al. *Biomed Pharmacother* 2012; 66(4): 300–7.

Nineteen patients with CS with either contraindications or resistance to steroids were treated with thalidomide for 24 months. Patients received 200 mg/day for 2 weeks, followed by a reduction to 100 mg/day for 11 weeks, and then a maintenance dose of 100 mg on alternate days for 35 weeks followed by a gradual tapering to discontinuation. Remarkable improvement was observed in all patients within 3 months of treatment. After 3 months of treatment, skin lesions resolved in 32% of patients, which increased to 67% of patients at 6 months and then plateaued for the remainder of the treatment period. The most common side effects were drowsiness–sedation (74%), constipation (68%), weight gain (53%), peripheral neuropathy (42%), skin rash (11%), and deep venous thrombosis (5%). Treatment was abandoned for the eight patients who developed peripheral neuropathy (mean time 17.6 months, range 9–24 months).

Chlorambucil treatment of sarcoidosis. Israel HL, McComb BL. *Sarcoidosis* 1991; 8: 35–41.

In this study, 31 patients received chlorambucil, either because complicating diseases prevented them from receiving corticosteroids or they did not respond to them. Marked improvement was noted in 15 patients and moderate improvement in 13 patients, but relapses were very common upon discontinuation after a 6-month course of treatment. No immune suppression–related side effects were noted.

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Scabies

Carmen Maria Salavastru, George Sorin Tiplica



Human scabies is a pruritic condition caused by infestation with the host-specific mite *Sarcoptes scabiei* var. *hominis*, which lives its entire life within the epidermis. Transmission typically occurs via direct close contact with an infested person. Fomite transmission is also possible and is much more common in severe cases.

The scabies mite is not a known vector for any systemic disease; however, secondary local or systemic bacterial infections with *S. pyogenes* (may lead to acute poststreptococcal glomerulonephritis) or *S. aureus* may develop.

Toward the global control of human scabies: introducing the International Alliance for the Control of Scabies. Engelman D, Kiang K, Chosidow O, et al. *PLoS Negl Trop Dis* 2013; 7: e2167.

Scabies affects around 100–300 million people worldwide, but accurate figures of its prevalence are difficult to obtain.

Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. *Lancet* 2018; 392(10159): 1789–858.

MANAGEMENT STRATEGY

Public Health Considerations

1. Reporting and surveillance

The Council for Outbreak Response: Healthcare-Associated Infections and Antimicrobial-Resistant Pathogens

Investigation and Control Workgroup. CORHA general guidance for the outbreak detection and reporting of scabies. Available at: <http://corha.org/resources/584/>.

Scabies is not a notifiable infectious disease as determined by Centers for Disease Control and Prevention (CDC). The outbreaks are reportable events.

2. Institutional outbreaks

Scabies outbreaks in ten care homes for elderly people: a prospective study of clinical features, epidemiology, and treatment outcomes. Cassell J, Middleton J, Nalabanda A, et al. *Lancet Infect Dis* 2018; 18: 894–902.

Control of scabies outbreaks in an Italian hospital: an information-centered management strategy. Capobussi M, Sabatino G, Donadini A, et al. *Am J Infect Control* 2014; 42: 316–20.

Scabies can spread rapidly under crowded conditions where close body contact is frequent and diagnosis of the index patient is delayed for numerous reasons.

3. Mass drug administration (MDA)

Efficacy of mass drug administration with ivermectin for control of scabies and impetigo, with coadministration of azithromycin: a single-arm community intervention trial. Romani L, Marks M, Sokana O, et al. *Lancet Infect Dis* 2019; 19: 510–8.

Scabies-targeted MDA has demonstrated efficacy in reducing scabies prevalence, decreasing secondary bacterial infection, and preventing systemic complications.

The study conducted by Romani et al. supports large-scale implementation of ivermectin-based MDA for control of scabies in locations where the condition is identified as a public health priority.

4. Scabies has been classified as a World Health Organization neglected tropical disease since 2017.

World Health Organization. Neglected tropical diseases. Available at: http://www.who.int/neglected_diseases/diseases/en/.

Consensus criteria for the diagnosis of scabies: a Delphi study of international experts. Engelman D, Fuller L, Steer A, et al. *PLoS Negl Trop Dis* 2018; 12: e0006549.

The International Alliance for the Control of Scabies reached a consensus on diagnostic criteria for scabies. Apart from classic scabies, the dermatologist is familiar with, there are clinical atypical forms and various particularities in subpopulations (infants, young children, elderly).

The 2019 network meta-analysis of 52 trials including 9917 patients, conducted by Thadanipon et al. (*see later*) indicated that permethrin had a significantly higher cure rate than sulfur, malathion, lindane, crotamiton, and benzyl benzoate. Combination permethrin plus oral ivermectin had a non-significantly higher cure rate than permethrin. Combination permethrin plus oral ivermectin was ranked highest in terms of cure, topical ivermectin in terms of persistent itching, and synergized pyrethrins in terms of adverse events. On the basis of clustered ranking, permethrin, oral ivermectin, and synergized pyrethrins seemed to retain balance between cure and adverse events.

Postscabetic pruritus commonly persists for 1–4 weeks, even after effective treatment, representing ongoing inflammation; it can be managed with emollients, oral antihistamines, and low-potency topical corticosteroids.

Crusted scabies requires repeated concomitant oral and topical treatments to decrease the high mite burden and penetrate thick scale. The CDC recommends oral ivermectin in three, five, or seven standard doses, topical permethrin or benzyl benzoate every 2–3 days for 1–2 weeks, and a keratolytic. Hospitalization may be considered to achieve isolation and optimize appropriate treatment.

Scabies in the age of increasing drug resistance. Khalil S, Abbas O, Kibbi AG, et al. *PLoS Negl Trop Dis* 2017; 11(11): e0005920.

Tolerance to standard topical scabicides is beginning to develop; therefore, potential solutions to the problem of resistance include newer drugs, insect growth regulators, natural products, and vaccination.

European guideline for the management of scabies. Salavastu C, Chosidow O, Boffa M, et al. *J Eur Acad Dermatol Venereol* 2017; 31: 1248–53.

The disease can be sexually transmitted. Partner management needs a look back period of 2 months. Screening for other STI is recommended. Patients and close contacts should avoid sexual contact until completion of treatment and should strictly observe personal hygiene rules when living in crowded spaces.

Specific Investigations

- Clinical examination for mites and burrows
- Skin scraping/adhesive tape test
- Dermoscopy
- Videodermoscopy

Visualization of Mites and Burrows

Comparison of dermoscopy, skin scraping, and the adhesive tape test for the diagnosis of scabies in a resource-poor setting. Walter B, Heukelbach J, Fengler G, et al. *Arch Dermatol* 2011; 147: 468–73.

Visualization of mites, eggs, or feces on light microscopy of skin scrapings confirms the diagnosis but has low sensitivity.

Visualization by Non-invasive Diagnostic Techniques

Diagnosis of scabies by high-magnification dermoscopy: the “delta-wing jet” appearance of *Sarcoptes scabiei*. Cinotti E, Perrot J, Labeille B, et al. *Ann Dermatol Venereol* 2013; 140: 722–3.

Dermoscopy rapidly identifies scabies (‘delta-wing’ sign); its use is limited by the operator experience and low sensitivity in mild disease.

High magnification videodermoscopy: a new noninvasive diagnostic tool for scabies in children. Lacarrubba F, Musumeci M, Caltabiano R, et al. *Pediatr Dermatol* 2001; 18: 439–41.

Videodermoscopy with its higher magnification (up to 1000×) is useful, especially to distinguish between burrows and excoriations.

Reflectance confocal microscopy and optical coherence tomography are expensive and time-consuming methods, and are not routinely used.

GENERAL MANAGEMENT CONSIDERATIONS

Centers for Disease Control and Prevention (CDC). Scabies fact sheet. Atlanta: CDC, 2005. http://www.cdc.gov/ncidod/dpd/parasites/scabies/factsht_scabies.htm.

Treatment should be prescribed to the patient and close physical contacts, even those who are asymptomatic.

Patients should be advised to avoid physical contact until they and their household members and sexual partners have been treated. Detailed verbal and written information about scabies infestation should be given to the patient.

Bedding, clothing, and towels used by infested persons or their household, sexual, and close contacts (as defined above) anytime during the 3 days before treatment should be decontaminated by washing in hot water and drying in a hot dryer, by dry-cleaning, or by sealing in a plastic bag for at least 72 hours. Scabies mites generally do not survive more than 2–3 days away from human skin.

Efficacy and safety of antiscabietic agents: a systematic review and network meta-analysis of randomized controlled trials. Thadanipon K, Anothaisintawee T, Rattanasiri S, et al. *J Am Acad Dermatol* 2019; 80(5): 1435–44.

Many drugs have been used to treat scabies, and so far there is no treatment that ranks highest in all aspects: efficacy, safety profiles, and ease of administration.

Combination permethrin plus oral ivermectin, topical ivermectin, and synergized pyrethrins had the strongest evidence for highest cure, lowest persistent itching, and lowest adverse events, respectively.

First-Line Therapies

• Oral ivermectin	A
• Permethrin 5% cream	A
• Benzyl benzoate	B

Ivermectin and permethrin for treating scabies. Rosumeck S, Nast A, Dressler C. *Cochrane Database Syst Rev* 2018; 4: CD012994.

Topical permethrin, topical ivermectin, and oral ivermectin are effective treatments for scabies with comparable rates of complete clearance at 2 and 4 weeks, though topical permethrin may lead to slightly higher complete clearance rates at 1 week.

Ivermectin versus permethrin in the treatment of scabies: a systematic review and meta-analysis of randomized controlled trials. Dhana A, Yen H, Okhovat JP, et al. *J Am Acad Dermatol* 2018; 78 (1): 194–8.

Oral ivermectin was associated with a significantly increased risk of treatment failure compared with topical permethrin. Meta-regression revealed no significant heterogeneity by various study characteristics: length of follow-up, treatment of family or close contacts, repetition of ivermectin dose, itch in definition of treatment failure, and microscopy in definition of treatment failure.

Thadanipon et al. found that the highest probability of cure at 3–6 weeks was associated with combination treatment with permethrin and oral ivermectin, followed by permethrin and topical ivermectin. For cure at 1–2 weeks, permethrin was significantly better than oral ivermectin.

Lower efficacy of oral ivermectin reported in some studies may reflect lack of ovicidal activity with single-dose administration.

Effect of high-fat meal intake on the pharmacokinetic profile of ivermectin in Japanese patients with scabies. Miyajima A, Hirota T, Sugioka A, et al. *J Dermatol* 2016; 43(9): 1030–6.

Ivermectin is metabolized primarily by cytochrome P-450 (CYP)3A4; therefore, dose adjustment is needed with biliary

obstruction. Bioavailability is increased when the drug is administered with a high-fat meal, and some authors have recommended dosing with food to increase absorption.

Systemic antiparasitic agents. Elston CA, Elston CM. In: Wolvertson SE, Wu JJ, eds. *Comprehensive Dermatologic Therapy*, 4th edn. Philadelphia, Elsevier, 2021; 126–32.

In the treatment of scabies (not approved by the US Food and Drug Administration [FDA]), 200 mcg/kg ivermectin is commonly given as a single dose, and repeated in 7–10 days as the drug has only scabicide and not ovicidal activity.

Hypersensitivity to ivermectin or components of formulation represents contraindications. The following reactions to ivermectin have been reported in >10% of patients in the setting of helminthic infestations: Mazzotti-type reaction, pruritus, fever, and lymphadenopathy, and less frequent reactions include tachycardia, facial edema, orthostatic hypotension, diarrhea, and nausea. Central nervous system (CNS) symptoms and Stevens–Johnson syndrome are rare. Liver function test abnormalities have been reported. A single Canadian report of increased deaths among nursing home patients using ivermectin has not been confirmed in other trials.

Based on 2015 FDA rulings, it poses a moderate–high risk when prescribed in pregnancy (pregnancy category C).

For crusted scabies, common in immune-compromised patients, ivermectin should generally be used in conjunction with keratolytics and topical therapy, but dosing is otherwise the same as in immune-competent patients.

Question 1: is it safe to use ivermectin in children less than five years of age and weighing less than 15 kg? Wilkins AL, Steer AC, Cranswick N, et al. *Arch Dis Child* 2018; 103(5): 514–9.

Ivermectin use is not recommended during lactation. It is not recommended for children weighing under 15 kg.

An undiagnosed index case leading to a nosocomial scabies outbreak: how mass single-dose ivermectin treatment can help control a nosocomial epidemic. Boyer PH, Debosker S, Hernandez C, et al. *Infect Control Hosp Epidemiol* 2018; 39(5): 631–2.

Ivermectin has been used in the control of institutional outbreaks of scabies and to decrease disease burden in highly endemic countries, and may be superior to topical treatment in the setting of mass infestation.

Cytochrome P450/ABC transporter inhibition simultaneously enhances ivermectin pharmacokinetics in the mammal host and pharmacodynamics in *Anopheles gambiae*. Chacour CJ, Hammann F, Alustiza M, et al. *Sci Rep* 2017; 7(1): 8535.

There is some potential for interaction with drugs that affect levels of CYP3A4.

Scabies in the age of increasing drug resistance. Khalil S, Abbas O, Kibbi AG, et al. *PLoS Negl Trop Dis* 2017; 11(11): e0005920.

Emerging evidence suggests that scabies mites are also becoming resistant to oral ivermectin, particularly in heavily endemic areas.

Bites and infestations. Chen TS. In: Teng JMC, Marqueling AL, Benjamin LT, eds. *Therapy in Pediatric Dermatology*. Chaim, Springer, 2017; 321–38.

Synthetic pyrethroids such as permethrin were developed to have a greater effectiveness and a wider range of activity against lice, scabies, ticks, and many other arthropods. FDA-approved

for scabies (not approved by the FDA for infants younger than 2 months of age given the theoretical risk of neurotoxicity), permethrin is available as a 5% cream for total body topical treatment of the condition by applying for 8 hours overnight from the neck down. The treatment should be repeated in 1 week.

Particular care should be paid to the hands and fingernail areas, because these sites harbor the greatest concentration of mites. In addition, intertriginous sites (including between digits) need careful application.

Because scabies can affect the scalp and face of infants and young children, the cream should be applied to these areas as well.

In pregnant women, the application should be shortened to 2 hours before rinsing off (pregnancy category B).

Pruritus can often persist for up to 1 month after treatment and should not be taken alone as a symptom of persistent infection. In severe cases, topical or systemic corticosteroids are prescribed to control the persistent itch.

Management of scabies. Monsel G, Chosidow O. *Skin Ther Lett* 2012; 17: 1–4.

WHO model lists of essential medicines. World Health Organization, 21st edn. Available at: <https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists>.

Although there are no commercially available preparations, benzyl benzoate is often compounded into a 10%–25% solution and is applied for 24 hours, then rinsed off; it may be repeated in 7–14 days.

There are few published human studies on its use for scabies, but it is commonly used in many countries, where it is reported to be a very inexpensive and effective compound being widely used globally; it is not available in North America but is a WHO essential medicine.

It can be used in pregnancy and children under the age of 2 years with only a 12-hour application. It may be diluted to 12.5% for children and 6.25% for infants to minimize irritation.

Adverse events are usually limited to skin irritation. Patients should be advised to avoid alcohol consumption for 48 hours after benzyl benzoate application because of the possibility of a disulfiram-like reaction. Safety in pregnancy has not been established.

Ivermectin versus benzyl benzoate applied once or twice to treat human scabies in Dakar, Senegal: a randomized controlled trial. Ly F, Caumes E, Ndaw AT, Mahé BNA. *Bull WHO* 2009; 87: 424–30.

The study showed benzyl benzoate was more effective for the treatment of scabies than oral ivermectin, irrespective of the number of applications; two applications gave a higher cure rate at day 14 than one application and only good compliance showed a statistically significant association with a cure.

Comparison of safety, efficacy, and cost effectiveness of benzyl benzoate, permethrin, and ivermectin in patients of scabies. Bachewar NP, Thawani VR, Mali SN, et al. *Indian J Pharmacol* 2009; 41: 9–14.

Prospective, randomized, comparative clinical trial conducted in 103 participants, randomly allocated to three groups: the first group received benzyl benzoate (BB) 25% lotion; the second group received permethrin 5% cream; whereas the third group received tablet ivermectin 200 mcg/kg as a single dose. The trial

concluded that the most economical regimen for treatment for scabies should start with benzyl benzoate for the first 2 weeks and then the uncured patients should be moved over to oral ivermectin therapy for the next 2 weeks.

Second-Line Therapies

• Topical ivermectin	A
• Crothamiton	A
• Sulfur	B
• Malathion	B

Topical antiparasitic agents. Martell DW, Lockshin BN. In: Wolverton SE, Wu JJ, eds. *Comprehensive Dermatologic Therapy*, 4th edn. Philadelphia, Elsevier, 2021; 504–9.

Ivermectin 0.5% lotion (not FDA-approved for scabies) is pregnancy category C.

It can be used by breastfeeding women, but patients should avoid applying the lotion directly on the nipple and areola.

A 2018 Cochrane review comparing the effectiveness of topical permethrin to topical ivermectin showed equal efficacy. One to three applications of 1% lotion or solution applied to affected areas spaced 1 week apart was sufficient to clear 96% of patients at 4 weeks.

No serious systemic or toxic adverse events have been reported with topical ivermectin. The most common reactions are skin irritation and localized burning.

Guideline for the diagnosis and treatment of scabies in Japan (third edition): Executive Committee of Guideline for the Diagnosis and Treatment of Scabies. Executive Committee of Guideline for the Diagnosis and Treatment of Scabies. *J Dermatol* 2017; 44: 991–1014.

In mass outbreaks in elderly resident facilities, crothamiton 10% cream monotherapy is not used in definitive cases of scabies, but efficacy is seen in the early stage of scabies infestation and in the incubation period; therefore, in cases where scabies has been definitively diagnosed and where scabies cases present with clinically typical symptoms, therapies that have a strong insecticidal effect are recommended.

Crothamiton is available as a 10% cream or lotion and is FDA-approved for the treatment of scabies. Apply for 24 hours, then rinse off, and repeat for 2 consecutive days. Rinse off 48 hours after second application; it may be repeated in 7–14 days.

This drug is minimally effective for scabies, but the medication is promoted for its antipruritic effects.

A comparative study between 10 per cent sulfur ointment and 0.3 per cent gamma benzene hexachloride gel in the treatment of scabies in children. Singalavanija S, Limpong-saturak W, Soponsakunkul S. *J Med Assoc Thai* 2003; 86(suppl 3): S531–6.

Precipitated sulfur as 2–10% ointment or cream (not FDA-approved for scabies) is applied for 24 hours for 3 consecutive days and may be repeated in 7–14 days, being considered safe in infancy and pregnancy, although the data are limited.

Ectoparasites. Thomas C, Coates SJ, Engelman D, et al. *Scabies* *J Am Acad Dermatol* 2020; 82: 533–48.

Malathion as 0.5% lotion or aqueous liquid (not FDA-approved for scabies) is applied for 24 hours; it may be repeated in 7–14 days. There are limited data in pediatric scabies, but malathion is contraindicated in infants younger than 2 years of age for lice treatment; safe in pregnancy; classified by the International Agency for Research on Cancer (IARC) as probably carcinogenic to humans.

Third-Line Therapies

• Synergized pyrethrins	B
• Tea tree oil	E
• Lindane – no longer used	N/A
• Moxidectin	E

Efficacy and tolerability of a new synergized pyrethrins thermofobic foam in comparison with benzyl benzoate in the treatment of scabies in convicts: the ISAC study (Studio Della scabbia in ambiente carcerario). Biele M, Campori G, Colombo R, et al. *J Eur Acad Dermatol Venereol* 2006; 20: 717–20.

Synergized pyrethrins: a 3-day treatment with pyrethrins thermophobic foam is at least as effective as a 5-day treatment with benzyl benzoate lotion.

Tea tree oil, a known antimicrobial, has demonstrated scabid activity.

Other agents with demonstrated scabid activity include *Tinospora cordifolia*, *Ligularia virgaurea*, and eugenols.

Melaleuca alternifolia (tea tree) oil: a review of antimicrobial and other medicinal properties. Carson C, Hammer K, Riley T. *Clin Microbiol Rev* 2006; 19: 50–62.

North American Regional Action Plan (NARAP) on lindane and other hexachlorocyclohexane (HCH) isomers. Commission for Environmental Cooperation. Available at: <http://www3-ccc.org/islandora/en/item/11602-north-american-regional-action-plan-narap-lindane-and-other-en.pdf> 2006.

Lindane is mentioned here only from a historic perspective because it has been banned by 52 US states. As a result, it is not recommended for the treatment of head lice or scabies.

Preclinical study of single-dose moxidectin, a new oral treatment for scabies: efficacy, safety, and pharmacokinetics compared to two-dose ivermectin in a porcine model. Bernigaud C, Fang F, Fischer K, et al. *PLoS Negl Trop Dis* 2016; 10: e0005030.

Given barriers to compliance with multidose regimens, new single-dose therapies are under investigation. Moxidectin is similar to ivermectin but has a longer half-life (20–35 days vs. 18 hours), enabling potential efficacy as a single-dose drug killing mites as they hatch.

Efficacy and pharmacokinetics evaluation of a single oral dose of afoxolaner against *Sarcoptes scabiei* in the porcine scabies model for human infestation. Bernigaud C, Fang F, Fischer K, et al. *Antimicrob Agents Chemother* 2018; 62(9): e02334–17.

Scleredema

Amy E. Flischel, Stephen E. Helms, Robert T. Brodell



Scleredema (scleredema adultorum or scleredema of Buschke) is characterized by progressive, symmetric induration and thickening of the skin secondary to deposition of collagen and glycosaminoglycans in the dermis. Clinically, scleredema commonly involves the posterior neck, shoulders, trunk, face, and arms. Three clinical categories are recognized: type I, postinfectious, usually resolves spontaneously within 6 months–2 years (55% of cases); type II, malignancy-associated, is linked to paraproteinemias and monoclonal gammopathy with or without multiple myeloma (25% of cases); and type III, scleredema diabetorum, is associated with poorly controlled insulin-dependent diabetes and persists indefinitely (20% of cases).

MANAGEMENT STRATEGY

Treatment of scleredema is usually unsatisfactory. However, case-based data demonstrates that several therapies can be effective. A candid discussion with the patient regarding limitations of treatment, cost, and side effects may lead to a decision to withhold treatment. This is particularly appropriate in patients with the postinfectious form, which often resolves spontaneously. Of course, identification of a specific etiology, such as streptococcal pharyngitis, should lead to appropriate antibiotic treatment, even in the absence of evidence that antibiotics alter the rate of clearance. In cases associated with diabetes mellitus and monoclonal gammopathy, progressive involvement can lead to discomfort, unsightly thickening, and systemic complications such as restrictive pulmonary

function, dysphagia secondary to tongue swelling, serositis, and cardiac arrhythmias.

Bath- or cream-PUVA (psoralen ultraviolet A) has been recommended as initial therapy in moderately severe disease. More recently, narrowband ultraviolet B (NB-UVB) and UVA1 have been shown to be effective. *Electron beam therapy* has been proposed for patients with severe disease, especially cases with restrictive pulmonary function. Alternative therapies include *ciclosporin*, *allopurinol*, *tamoxifen*, and *high-dose penicillin*. Control of serum glucose levels with antidiabetic therapy has no effect on disease progression in scleredema diabetorum.

Specific Investigations

- Fasting blood sugar, glucose tolerance test, hemoglobin A_{1c} (glycosylated hemoglobin)
- Serum protein electrophoresis, immunoelectrophoresis
- Antistreptolysin O, bacterial culture, C-reactive protein, erythrocyte sedimentation rate (ESR)

Scleredema adultorum. Not always a benign self-limited disease. Curtis AC, Shulak BM. Arch Dermatol 1965; 92: 526–41.

A review of 223 scleredema patients revealed 25% had symptoms more than 2 years. The following treatments demonstrated no benefit: calcium gluconate, estradiol, fever, hot baths, hyaluronidase, nicotinic acid, ovarian extract, p-aminobenzoate, penicillin, pituitary extract, corticosteroids, thyroid hormone, and vitamin D.

Scleredema adultorum due to streptococcal infection. Alp H, Orbak Z, Aktas A. Pediatr Int 2003; 45: 101–3.

In 65%–95% of cases, scleredema occurs within a few days to 6 weeks after an acute febrile illness. Of these infections, 58% are streptococcal. These infections may present as tonsillitis, pharyngitis, scarlet fever, erysipelas, cervical adenitis, pneumonia, otitis media, pyoderma, impetigo, or rheumatic fever. Appropriate studies will rapidly determine underlying infection associated with scleredema.

Monoclonal gammopathy in scleredema: observations in three cases. Kovary PM, Vakilzadeh F, Macher E, et al. Arch Dermatol 1981; 117: 536–9.

Many subsequent reports have confirmed this association. Skin manifestations often precede the development of the gammopathy.

Scleredema associated with carcinoma of the gall bladder. Manchanda Y, Das S, Sharma VK, et al. Br J Dermatol 2005; 152: 1373–4.

Scleredema has been associated with various internal malignancies. When clinically indicated, an evaluation for internal malignancies may be appropriate.

Scleredema associated with immunoglobulin A-κ smoldering myeloma: a case report and review of the literature. Keragala BSDP, Herath HMMTB, Janappriya GHDC, et al. J Med Case Rep 2018; 13: 145.

A 66-year-old Sri Lankan woman with diffuse scleredema had no systemic symptoms and negative serologies for underlying autoimmune disease. An abnormal band in the gamma region was present on immunofixation. She improved with chemotherapy for her underlying immunoglobulin A-κ myeloma.

First-Line Therapies

- Identify and treat underlying disease **D**
- Conservative management **D**

Scleredema: a review of 33 cases. Venencie PY, Powell FC, Su D, et al. *J Am Acad Dermatol* 1984; 11: 128–34.

Systemic corticosteroids, methotrexate, and D-penicillamine demonstrated no effect on the course of scleredema. Both diabetic and non-diabetic patients were studied. Some patients in both groups suffered from mild complications such as dysphagia and electrocardiogram (ECG) changes, but scleredema is generally a mild disease that poses no threat to overall health.

Fulminans in dermatology: a call to action: a recommendation for consideration of the term scleredema fulminans. Sommer LL, Heymann WR. *J Clin Aesthet Dermatol* 2014; 7: 42–5.

A 43-year-old man with an 11-year history of human immunodeficiency virus presented with a 3-month history of abrupt-onset progressive neck, shoulder, and back swelling shortly after diagnosis with type 2 diabetes. This case demonstrates the rapid onset that can occur in this chronic disease.

Second-Line Therapies

- Narrowband UVB phototherapy **E**
- UVA1 phototherapy **D**
- Electron beam therapy **E**
- Bath-PUVA and cream-PUVA **E**
- Physical therapy **E**
- Tamoxifen **E**
- High-dose penicillin **E**
- Ciclosporin **E**
- Extracorporeal photopheresis **E**
- Chemotherapy (melphalan) **E**
- Frequency-modulated electromagnetic neural stimulation **E**
- Allopurinol **E**
- Intravenous immunoglobulin **E**
- Tranilast **E**

Scleredema adultorum treated with narrow-band ultraviolet B phototherapy. Xiao T, Yang Z, He C, et al. *J Dermatol* 2007; 34: 270–2.

A 56-year-old Chinese man treated with NB-UVB (initial dose of 0.2 J/cm², three times weekly, increased by 25% per treatment for a total of 54 exposures [33.8 J/cm² dose]) improved significantly after the first 10 treatments. Beneficial effects were still evident 14 months after discontinuation. NB-UVB phototherapy has shorter irradiation times (no need for protective glasses after treatment) and reduced risk of photocarcinogenesis when compared with PUVA.

UVA1 phototherapy for cutaneous diseases: an experience of 92 cases in the United States. Tuchinda C, Kerr H, Taylor C, et al. *Photodermatol Photoimmunol Photomed* 2006; 22: 247–53.

Six patients with scleredema were treated with UVA1 phototherapy (five received low-dose regimens and one a medium-dose regimen). Moderate-to-good responses occurred in four of five

patients. UVA1 phototherapy should be considered in recalcitrant scleredema.

Scleredema diabeticorum case series: successful treatment with UV-A1. Kroft EB, de Jong EM. *Arch Dermatol* 2008; 144: 947–8.

Three cases demonstrated substantial clinical improvement after UVA1 therapy. Two patients were treated with 35 J/cm² per session and the third patient with 60 J/cm² per session.

Scleredema treated with broad-band ultraviolet A phototherapy plus colchicine. Yüksek J, Sezer E, Köseoglu D, et al. *Photodermatol Photoimmunol Photomed* 2010; 26: 257–60.

A 23-year-old female with scleredema was treated with low-dose broadband UVA phototherapy 15 J/cm², three times weekly for 40 sessions (total cumulative dose of 600 J/cm²) and colchicine 1800 mg/day for 1 year. Histopathologic and clinical improvement were noted.

Scleredema of Buschke successfully treated with electron beam therapy. Tamburin LM, Pena JR, Meredith R. *Arch Dermatol* 1998; 134: 419–22.

A patient with scleredema and insulin-dependent diabetes mellitus experienced complete resolution of skin induration after receiving electron beam therapy twice weekly for 36 days. Prior treatment with topical, intralesional, and systemic corticosteroids had failed. This patient also suffered restrictive pulmonary disease thought to be secondary to scleredema, and marked improvement in pulmonary function tests were noted after electron beam therapy. This treatment should be considered in patients with persistent disease and systemic complications.

Paraproteinemia-associated scleredema treated successfully with intravenous immunoglobulin. Eastham AB, Femia AN, Velez NE, et al. *JAMA Dermatol* 2014; 150: 788–9.

A woman in her 40s with a 2-year history of progressive erythema and induration of the face, neck, and upper trunk denied recent infection or history of diabetes. Limitation in range of motion (ROM) and induration occurred after two cycles of intravenous immunoglobulin (IVIG) given monthly.

Bath-PUVA therapy in three patients with scleredema adultorum. Hager CM, Sobhi HA, Humzelmann N, et al. *J Am Acad Dermatol* 1998; 38: 240–2.

Bath-PUVA therapy (median of 59 treatments) produced substantial clinical improvement. Two patients had diabetes mellitus and one had no associated condition. Diabetic patients with scleredema tend to have long, unremitting courses without treatment.

Cream PUVA therapy for scleredema adultorum. Grundmann-Kollmann M, Ochsendorf F, Zollner TM, et al. *Br J Dermatol* 2000; 142: 1058–9.

Topical PUVA therapy (35 irradiations) produced marked clinical improvement and softening of the skin in a non-insulin-dependent diabetic patient with a 10-year history of scleredema. Topical PUVA therapy is easier to administer than bath-PUVA.

Ultrasonic massage and physical therapy for scleredema: improving activities of daily living. Bray SM, Varghese S, English JC 3rd. *Arch Dermatol* 2010; 146: 453–4.

A 42-year-old man with diabetes-associated scleredema was treated with hydroxychloroquine and PUVA without improvement. Physical therapy with ultrasonic massage, active ROM exercises, and flexibility exercises three times weekly was initiated.

Ultrasonic massage therapy was performed using a Dynatron 709 series machine with the following parameters: 100%, 1 MHz, and 1.5 W/cm² for 10 min per session. Objective improvement in 9 of 10 ROM parameters was noted after 1 year of physical therapy.

Treatment of scleredema diabeticorum with tamoxifen. Alsaedi SH, Lee P. *J Rheumatol* 2010; 37: 2636–7.

A 61-year-old woman with diabetic scleredema was treated with tamoxifen 20 mg twice daily after failing methotrexate and D-penicillamine. Her symptoms improved after 2 months, and clinical softening of the skin on her back and improved shoulder flexibility occurred after 48 months. A 54-year-old female with diabetic scleredema treated with tamoxifen 20 mg twice daily demonstrated similar improvement, perhaps due to tamoxifen's antifibrotic effects.

Persistent scleredema of Buschke in a diabetic: improvement with high-dose penicillin. Krasagakis K, Hettmannsperger U, Trautmann C, et al. *Br J Dermatol* 1996; 134: 597–8.

High-dose (3 × 10⁶ IU daily) intravenous penicillin for 7 days led to a reduction in severity of scleredema perhaps due to its antifibrotic actions. This may explain why other antibiotics such as erythromycin are ineffective.

Cyclosporine in scleredema. Mattheou-Vakali G, Ioannides D, Thomas T, et al. *J Am Acad Dermatol* 1996; 35: 990–1.

Ciclosporin at a dose of 5 mg/kg daily for 5 weeks completely cleared postinfectious scleredema in two patients. Of course, resolution of their signs and symptoms may have occurred without treatment.

Scleredema associated with paraproteinemia treated by extracorporeal photopheresis. Stables GI, Taylor PC, Highet AS. *Br J Dermatol* 2000; 142: 781–3.

Significant improvement in skin lesions followed treatment with extracorporeal photopheresis. Reduction of treatment frequency, from two to one per month, led to worsening of the scleredema, suggesting that improvement was due to therapy rather than spontaneous resolution. This treatment should be considered since scleredema associated with paraproteinemia usually has a progressive, unremitting course.

Beneficial effect of aggressive low-density lipoprotein apheresis in a familial hypercholesterolemic patient with severe diabetic scleredema. Koga N. *Ther Apher* 2001; 5: 506–12.

A 59-year-old woman with diabetic scleredema treated with weekly low-density lipoprotein apheresis for 3 years had significant improvement in clinical parameters and histopathology when her lipid levels normalized.

Treatment with chemotherapy of scleredema associated with IgA myeloma. Santos-Juanes J, Osuna CG, Iglesias JR, et al. *Int J Dermatol* 2001; 40: 720–1.

A 70-year-old woman with IgA myeloma and scleredema was treated with oral melphalan and prednisone over a 6-month period. Clinical evidence of softening of the indurated and taut skin was observed during treatment and for 1 year after treatment was completed. Similar cases were cited in which chemotherapy for myeloma resulted in significant improvement of associated scleredema.

Treatment of acquired reactive perforating collagenosis with allopurinol incidentally improves scleredema diabeticorum. Lee FY, Chiu HY, Chiu HC. *J Am Acad Dermatol* 2011; 65: e115–7.

A 51-year-old man presented with acquired reactive perforating collagenosis associated with diabetes and scleredema of the upper back for over 20 years. Allopurinol 100 mg a day for 14 months proved effective for both conditions. Allopurinol is thought to improve endothelial function by reducing vascular oxidative stress.

Improvement in clinical symptoms of scleredema diabeticorum by frequency-modulated electromagnetic neural stimulation: a case report. Gandolfi A, Pontara A, Di Terlizzi G, et al. *Diabetes Care* 2014; 37: e233–4.

Scleredema associated with type 1 diabetes was treated with frequency-modulated electromagnetic neural stimulation (FREMS), transcutaneous electrotherapy, a therapy commonly used for diabetic neuropathy. Two series of 10–15 sessions of FREMS at 3-month intervals over 15 months led to improvement in both mobility and the Barthel Index of activities of daily living. No histologic improvement was identified after treatment.

Buschke's scleredema successfully treated extracorporeal photopheresis. Dezoteux F, Bourges M, Lionet A, et al. *La Revue de Medecine Interne* 2018; 39: 360–3.

Treatment with extracorporeal photopheresis twice monthly for 2 months demonstrated clinical improvement in a 50-year-old patient with scleredema. This was maintained as treatments were spread apart.

Successful treatment of scleredema diabeticorum with tranilast: three case reports. Sun M, Yang F, Hou M. *Diabetes Care* 2018; 41: e40–1.

Tranilast is an antiallergic, antiinflammatory medication that suppresses expression of the type I collagen and basal level of type I collagen in human dermal fibroblasts. All patients showed progressive normalization of skin softness and improved thickness on ultrasonography after oral administration of 0.3 g/day for 3 months.

Scleroderma (systemic sclerosis)

Gabriela A. Cobos, Ruth Ann Vleugels



Systemic sclerosis (SSc), sometimes referred to as *scleroderma*, is a rare, multisystem disease characterized by cutaneous sclerosis, auto-antibody production, and vascular abnormalities, often leading to visceral disease. It can affect any organ system, particularly the skin, gastrointestinal tract, kidney, heart, and lungs. Patients typically present with cutaneous sclerosis or Raynaud phenomenon (RP). The degree of skin involvement defines the clinical subset of the disease. Diffuse cutaneous SSc (dcSSc) involves the skin proximal to the neck, elbows, or knees, whereas involvement distal to these sites is known as *limited cutaneous SSc* (lcSSc). A small subset of patients known as *systemic sclerosis sine scleroderma* have no detectable skin involvement but have other clinical features along with autoantibodies specific to SSc. In some cases, older patients with late-onset disease and anti-RNA polymerase III antibodies may present with systemic sclerosis as a paraneoplastic phenomenon. Localized scleroderma, or morphea, is a distinct condition, with differing prognosis and treatment.

MANAGEMENT STRATEGY

Prognosis differs between lcSSc and dcSSc and is largely influenced by the degree of visceral involvement. Notably, patients with both lcSSc and dcSSc need to be evaluated for systemic disease. To date, there is no treatment that has proven uniformly effective in modifying disease course; however, increasing data supports the use of various therapeutic agents in SSc. Treatment should be tailored for each patient, taking into consideration disease subset, severity, and organ involvement.

In most cases, cutaneous lesions and RP precede systemic involvement. The face and hands are typically involved, with patients reporting increased skin stiffness/rigidity and skin displaying a characteristic shiny appearance. Patients should be counseled on gentle skin care practices. *Topical tretinoin* may improve perioral radial furrows and facial tightening. *Hyaluronidase* treatment may improve microstomia. *Antihistamines* may help itch; however, severe pruritus may require systemic therapy. *Calcinosis cutis* may require surgical removal, and *intralesional sodium thiosulfate* is occasionally justified.

For the treatment of RP, vasodilators such as *nifedipine* reduce vasospasm and improve peripheral blood flow. *Losartan* has been found to be effective in reducing the severity and frequency of attacks of RP. Phosphodiesterase type 5 (PDE-5) inhibitors, selective serotonin reuptake inhibitors (SSRIs), pentoxifylline, and α -blockers are other treatment options. Digital ulcers are a frequent problem in SSc and may become infected. Recalcitrant ulcers may respond to *sildenafil*. *Endothelin receptor antagonists* may improve digital perfusion. *Palmar sympathectomy* and *botulinum toxin* may be valuable. *Parenteral prostacyclin* analogs also improve the severity and frequency of RP.

Both *psoralens and ultraviolet A (PUVA) photochemotherapy* and *ultraviolet A1 (UVA1) phototherapy* have been reported to improve skin thickness. Most SSc experts currently use *mycophenolate* at doses of 2–3 g/day as first-line therapy as it has demonstrated benefit in both skin and lung involvement and has a favorable risk profile. *Cyclophosphamide* (1–2 mg/kg/day) can reduce cutaneous sclerosis and prevent development of lung fibrosis. *Pulsed therapy with cyclophosphamide* is effective and possibly safer. Both *low-dose prednisolone* and *methotrexate* 15–25 mg/week have been shown to reduce skin thickness scores. However, corticosteroids at doses >15 mg/day is a risk factor for the development of scleroderma renal crisis (SRC). *Ciclosporin* 3–4 mg/kg/day may improve skin induration but has no effect on internal organ involvement.

Various biologics (*rituximab*, *infliximab*, *basiliximab*, *imatinib*) have been investigated with varying success. *Stem cell transplantation* shows efficacy in progressive dcSSc with a poor prognosis, but has significant treatment-related morbidity and mortality. Patient selection is critical and must take into account the degree of organ involvement.

Respiratory involvement develops in roughly 60%–80% of SSc patients, with interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) being the most frequent types. *Iloprost* infusions have been shown to reduce PAH. *Angiotensin-converting enzyme (ACE) inhibitors* are particularly effective in the treatment of SRC. *Proton pump inhibitors* treat esophageal disease. *Prokinetic dopamine agonists* may help dysphagia and reflux. Intermittent broad-spectrum antibiotics may diminish bacterial overgrowth and blind loop syndrome.

Although SSc carries a high case-specific mortality, there have been significant advances in the management of skin, renal, and pulmonary complications. The identification of novel signaling pathways and mediators that are altered in SSc and contribute to tissue damage allows for their selective targeting. This in turn opens the door for therapeutic strategies using novel compounds or innovative ways of using already approved drugs.

Specific Investigations

- Skin biopsy (if clinical exam is uncertain) – skin exam classically shows distal sclerosis, nailfold capillary changes, Raynaud
- Nailfold capillaroscopy
- The modified Rodnan skin score (mRSS) is used in clinical research protocols
- Renal function tests, including urinalysis
- Blood pressure
- Antinuclear, anticentromere, anti-Scl-70, and anti-RNA polymerase III antibodies
- Pulmonary function tests with single breath diffusion capacity for carbon monoxide (DLCO)
- High resolution computed tomography with interstitial lung disease protocol
- Echocardiography, cardiac catheterization
- Consider paraneoplastic disease and evaluation

Antinuclear antibody negative systemic sclerosis. Salazar GA, Assassi S, Wigley F, et al. *Semin Arthritis Rheum* 2015; 44: 680–6.

The majority (90%–95%) of patients with SSc have antinuclear antibodies (ANA). ANA-negative SSc disproportionately affects males and tends to have less vasculopathy (decreased PAH, digital ulcers, telangiectasias) and possibly more frequent lower gastrointestinal involvement.

Evidence-based guidelines for the use of immunologic tests: anticentromere, Scl-70, and nucleolar antibodies. Reveille JD, Solomon D. *Arthritis Rheum* 2003; 49: 399–412.

Anti-Scl-70 and anticentromere (ACA) antibodies are very useful in distinguishing SSc patients from healthy controls, patients with other connective tissue diseases, and unaffected family members. Among SSc patients, antiScl-70 positivity is associated with higher risk for diffuse cutaneous involvement and radiographic pulmonary fibrosis while ACA positivity is more likely to have limited skin involvement and less likely to have radiographic pulmonary fibrosis.

Once a patient is determined as being antiScl-70 or ACA-positive or negative, there is no justification for serial determinations.

Cancer and scleroderma: a paraneoplastic disease with implications for malignancy screening. Shah AA, Casciola-Rosen L. *Curr Opin Rheumatol* 2015; 27: 563–70.

Studies have demonstrated that SSc patients with anti-RNA polymerase III antibodies have a significantly increased risk of cancer within a few years of disease onset. Epidemiologic data demonstrate that patients developing SSc at older ages also have a short cancer-scleroderma interval, suggestive of paraneoplastic disease.

First-Line Therapies: Raynaud

• Nifedipine	A
• Sildenafil	A
• Iloprost	B
• Losartan	B

Calcium channel blockers for primary and secondary Raynaud's phenomenon. Rirash F, Tingey P, Harding S, et al. *Cochrane Database Syst Rev* 2017; 12.

Calcium channel blockers led to a relative reduction of 44% in frequency of Raynaud episodes compared with placebo and also decreased pain and severity of attacks.

Efficacy of sildenafil on ischaemic digital ulcer healing in systemic sclerosis: the placebo controlled SEDUCE study. Hachulla E, Hatron P-Y, Carpentier P, et al. *Ann Rheum Dis* 2016; 75: 1009–15.

This prospective, randomized, double-blind, placebo-controlled study of 83 SSc patients showed sildenafil to significantly reduce the number of digital ulcers by week 8 compared with the placebo group, reflecting a higher healing rate in the sildenafil group.

Prospective, open-label, uncontrolled pilot study to study safety and efficacy of sildenafil in systemic sclerosis-related pulmonary artery hypertension and cutaneous vascular complications. Kumar U, Sankalp G, Sreenivas V, et al. *Rheumatol Int* 2013; 33: 1047–52.

A prospective, open-label, uncontrolled pilot study in 17 patients with scleroderma and PAH treated with sildenafil showed statistically significant improvement in 6-min walk test, World Health Organization (WHO) class of dyspnea, severity of RP, and mean pulmonary artery pressure (mPAP) from their pretreatment values. Additionally, there was no occurrence of new digital infarcts or ulcers, and existing ulcers showed signs of healing.

Iloprost for the treatment of systemic sclerosis. Hachulla E, Launay D, Hatron P-Y. *Presse Med* 2008; 37: 831–9.

Intravenous iloprost, a stable analog of PGI₂, is effective in the treatment of SSc-RP, reducing the frequency and severity of attacks. It also appears useful for the treatment of digital ulcers and improves kidney vasospasm.

Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel-group, controlled trial. Dziadzio M, Denton CP, Smith R, et al. *Arthritis Rheum* 1999; 42: 2646–55.

In this trial, 25 patients with primary RP and 27 patients with SSc-RP were treated with either losartan or nifedipine. Losartan reduced the frequency and severity of RP and its clinical benefit was greater in patients with primary RP.

Second-Line Therapies: Raynaud

• Botulinum toxin	B
• Prazosin	B
• Fluoxetine	B

The therapeutic efficacy of botulinum toxin in treating scleroderma-associated Raynaud's phenomenon. Bello RJ, Cooney CM, Melamed E, et al. *Arthritis Rheumatol* 2017; 69: 1661–9.

Forty patients with SSc-RP received 50 units of botulinum toxin type A in one randomly selected hand compared with sterile saline in the opposite hand. Patient reported outcomes (hand function, cold, pain sensitivity scores) were better in the Botox-treated hand but did not reach statistical significance.

Therapeutic management of acral manifestations of systemic sclerosis. Meyer MF, Daigeler A, Lehnhardt M, et al. *Med Klin* 2007; 102: 209–18.

Calcium channel antagonists, α_1 -adrenergic blockade with prazosin, losartan (angiotensin II receptor inhibitor), fluoxetine (SSRI), and prostacyclin analogs have been beneficial in the treatment of SSc-RP.

First-Line Therapies: Cutaneous Sclerosis and Visceral Involvement

• Mycophenolate	A
• Methotrexate	A
• Cyclophosphamide	A
• PDE-5-inhibitors	A
• Intravenous immunoglobulin	B
• Rituximab	B
• ACE inhibitors	B

Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial disease: Scleroderma Lung Study II (SLS II), a double-blind, parallel group, randomized controlled trial. Tashkin DP, Roth MD, Clements PJ, et al. *Lancet Respir Med* 2016; 4(9): 708–19.

In total, 142 SSc patients with ILD were randomized to receive treatment with mycophenolate mofetil (MMF) for 2 years or cyclophosphamide (CYC) for 1 year. Both treatments resulted in significant improvement in lung function over the 2-year course of the study. Skin improvement, measured by a decrease in mRSS, was seen in most patients irrespective of treatment (73.6% subjects on CYC, 71.7% subjects on MMF). MMF was better tolerated and had less toxicity.

A prospective observational study of mycophenolate mofetil treatment in progressive diffuse cutaneous systemic sclerosis of recent onset. Mendoza FA, Nagle SJ, Lee JB, et al. *J Rheumatol* 2012; 39: 1241–7.

Twenty-five treatment naïve patients with recent onset (less than 24 months) dcSSc received MMF as the only disease-modifying therapy. Patients experienced improvement in skin involvement (significant decrease in mRSS and body surface area) after an average of 18 months of therapy. Pulmonary function tests remained stable throughout the study. Skin biopsies from three patients showed histopathological improvement and decreased expression of fibrosis-related genes.

Treatment outcome in early diffuse cutaneous systemic sclerosis: the European Scleroderma Observational Study (ESOS). Herrick AL, Pan X, Peytrignet S, et al. *Ann Rheum Dis* 2017; 76: 1207–18.

A prospective, observational cohort study of early dcSSc (onset of skin thickening within 3 years) evaluated outcomes in 326 patients treated with one of four protocols: methotrexate (MTX), mycophenolate mofetil (MMF), cyclophosphamide (CYC), or 'no immunosuppressant' over a 2-year period. There were statistically significant reductions in mRSS at 12 months in all groups: −4.0 (−5.2 to −2.7) units for MTX, −4.1 (−5.3 to −2.9) for MMF, −3.3 (−4.9 to −1.7) for CYC, and −2.2 (−4.0 to −0.3) for no immunosuppressant (p value for between-group differences = 0.346). There were no statistically significant differences in survival between protocols before ($p = 0.389$) or after weighting ($p = 0.440$), but survival was poorest in the no immunosuppressant group (84.0%) at 24 months.

A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. Pope JE, Bellamy N, Seibold JR, et al. *Arthritis Rheum* 2001; 44: 1351–8.

In this double-blind trial (DBT), 71 patients with early dcSSc (onset <3 years) were randomized to 12-month treatment of methotrexate versus placebo. There were no statistically significant differences in skin scores [mRSS and University of California Los Angeles (UCLA) skin score], but there was a trend in favor of MTX.

Shifting our thinking about uncommon disease trials: the case of methotrexate in scleroderma. Johnson SR, Feldman BM, Pope JE, et al. *J Rheumatol* 2009; 36: 323–9.

Data from the above randomized controlled trial (RCT), led by Pope et al., was reanalyzed using Bayesian models and a beneficial effect of MTX over placebo on skin findings was confirmed. This analysis showed that the probability that MTX improves mRSS and UCLA skin score were 94% and 96%, respectively.

Cyclophosphamide versus placebo in scleroderma lung disease. Tashkin DP, Elashoff R, Clements PJ, et al. *N Engl J Med* 2006; 25: 2655–66.

In this DBT, 158 patients with SSc and ILD were randomized to receive oral cyclophosphamide (≤ 2 mg per kg) or placebo for 1 year and followed for one additional year. The subjects in the CYC group had significant improvement in skin thickening (measured by mRSS). Improvement was greater in patients with dcSSc compared to lcSSc. Additionally, the course of forced vital capacity, which was the primary outcome, adjusted at 1 year, was significantly better in the CYC group and was maintained through 24 months.

However, due to the risks of CYC toxicity, the medication should be reserved for patients with refractory and/or rapidly progressing cutaneous sclerosis in the presence of SSc-related ILD.

Efficacy and safety of intravenous cyclophosphamide pulse therapy with oral prednisolone in the treatment of interstitial lung disease with systemic sclerosis: 4-year follow-up. Tochimoto A, Kawaguchi Y, Hara M, et al. *Mod Rheumatol* 2011; 21: 296–301.

This open-label study of pulsed cyclophosphamide (0.4 g/m^2) with oral prednisolone concluded that the regimen was effective in producing improvement in ILD and skin disease, but that relapse was common, occurring in five of 13 patients, so maintenance therapy should be considered.

Sildenafil for pulmonary arterial hypertension associated with connective tissue disease. Badesch DB, Hill NS, Burgess G, et al. *J Rheumatol* 2007; 34: 2417–22.

The SUPER-1 trial was a 12-week, double-blind study of 278 patients with PAH who were randomized to oral placebo or sildenafil. In this post hoc subgroup analysis of 84 patients with PAH associated with connective tissue disease (45% with SSc), the 6-min walk distance (6MWD), WHO functional class, pulmonary artery pressure, and pulmonary vascular resistance were improved in the sildenafil group.

A randomized, double-blind, placebo-controlled trial: intravenous immunoglobulin treatment in patients with diffuse cutaneous systemic sclerosis. Takehar K, Ihn H, Sato S. *Clin Exp Rheumatol* 2013; 31: 151–6.

A randomized, double-blind, placebo-controlled trial of 63 patients with dcSSc showed no significant difference in skin scores between groups treated with intravenous immunoglobulin (IVIG) (400 mg/kg/day for 5 consecutive days) or placebo at 12 weeks. However, after a second course of IVIG, there was a significant improvement in mRSS in the IVIG group at 60 weeks.

IVIG may be an effective therapy for refractory, active diffuse cutaneous scleroderma. Poelman CL, Hummers LK, Wigley FM, et al. *J Rheumatol* 2015; 42: 236–42.

A retrospective study of 30 patients with refractory, active dcSSc treated with adjunctive IVIG (2 g/kg/month) demonstrated progressive improvement in skin induration, measured by reduction in mRSS, with maximal effect observed at 24 months.

Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. Jordan S, Distler JH, Maurer B, et al. *Ann Rheum Dis* 2015; 74: 1188–94.

A large, multicenter, nested case-control study of 63 SSc patients showed significant improvement in skin sclerosis (decrease in

mean mRSS) in the rituximab (RTX)-treated group compared with the RTX-untreated group. Additionally, there was prevention of worsening lung fibrosis in the RTX-treated group.

A multicenter, open-label, comparative study of B cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. Daoussis D, Melissaropoulos K, Sakellaropoulos G, et al. *Semin Arthritis Rheum* 2017; 46: 625–63.

In this study, 33 SSc patients treated with two or more cycles of RTX (each cycle consisted of four infusions of 375 mg of RTX per m² of body surface area (BSA) once weekly and repeated every 6 months) were compared with 18 SSc patients on conventional therapy (MTX, azathioprine, or MMF). Both cohorts had improvement in skin thickening (lower mRSS), but the RTX cohort had enhanced resolution of skin sclerosis. Additionally, the RTX cohort had a significant improvement in pulmonary function.

Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. Daoussis D, Liossis SN, Tsamandas AC, et al. *Rheumatology* 2010; 49: 271–80.

Eight patients with SSc-associated ILD were randomized to receive RTX in addition to standard therapy (prednisone, CYC, MMF) vs. standard therapy alone. At 12 months, the eight patients in the RTX group had significantly improved forced vital capacity and DLCO compared with the six subjects receiving standard therapy alone.

Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. Steen VD, Costantino JP, Shapiro AP, et al. *Ann Intern Med* 1990; 113: 352–7.

Patients with SSc who develop hypertension should be treated with an ACE inhibitor. Improved survival and successful discontinuation of dialysis are possible when ACE inhibitors are used to treat scleroderma-related renal crisis.

Second-Line Therapies: Cutaneous Sclerosis and Visceral Involvement

• Nintedanib	A
• Bosentan	A
• Prostacyclin analog	A
• Ambrisentan and tadalafil combination	B
• Tocilizumab	B
• Imatinib	B
• Systemic corticosteroids	B

Nintedanib for systemic sclerosis-associated interstitial lung disease. Distler O, Highland KB, Gahlemann M, et al. *N Engl J Med* 2019; 380: 2518–28.

In this double-blind, placebo-controlled trial, 576 subjects with SSc-ILD were randomly assigned to receive nintedanib, a tyrosine kinase inhibitor, 150 mg twice daily or placebo. The annual rate of decline in forced vital capacity was lower in the nintedanib group. No significant difference was noted in the mRSS between groups.

Bosentan therapy for pulmonary arterial hypertension. Rubin LJ, Badesch DB, Barst RJ, et al. *N Engl J Med* 2002; 346: 896–903.

In this randomized control trial of patients with PAH, the dual endothelin receptor antagonist bosentan improved exercise capacity. On

subgroup analysis, SSc patients with PAH had a modest increase in their 6MWD, although less than subjects with idiopathic PAH, and had delayed progression to clinical worsening compared with the placebo group.

Prostacyclin for pulmonary hypertension in adults. Paramothayan NS, Lasserson TJ, Wells AU, et al. *Cochrane Database Syst Rev* 2005; 2: CD002994.

Intravenous prostacyclin, in addition to conventional therapy at tolerable doses optimized by titration, can confer some short-term benefits (up to 12 weeks of treatment) in exercise capacity, New York Heart Association (NYHA) functional class, and cardiopulmonary hemodynamics. There is also some evidence that patients with more severe disease, based on NYHA functional class, showed a greater response to treatment.

Ambrisentan and tadalafil up-front combination therapy in scleroderma-associated pulmonary arterial hypertension. Hassoun PM, Zamanian RT, Damico R, et al. *Am J Respir Crit Care Med* 2015; 192: 1102–10.

A prospective, open-label, trial of 24 patients with SSc-associated PAH demonstrated combination therapy with ambrisentan (an endothelin-1 receptor antagonist) and tadalafil (a phosphodiesterase type 5 inhibitor) resulted in improved 6MWD, pulmonary vascular resistance, and right ventricular structure and function.

Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis: results from the open-label period of a phase II randomized controlled trial (faSScinate). Khanna D, Denton CP, Lin CJF, et al. *Ann Rheum Dis* 2018; 77: 212–20.

In the 48-week double-blind trial, 87 SSc patients were randomized to receive tocilizumab or placebo. The tocilizumab group had a clinically significant decline in mRSS, although not statistically significant, compared with placebo. In the subsequent open-label period, 70.5% of patients originally in the placebo group transitioned to tocilizumab and 69.8% of patients in the tocilizumab group continued with weekly tocilizumab treatment. Skin score improvement and pulmonary function stabilization were noted in both groups. A phase III study with a larger sample size is currently underway.

Imatinib mesylate (Gleevec) in the treatment of diffuse cutaneous systemic sclerosis: results of a 1-year, phase IIa, single-arm, open-label clinical trial. Spiera RF, Gordon JK, Mersten JN, et al. *Ann Rheum Dis* 2011; 70: 1003–9.

Twenty-four of 30 patients showed an improved mRSS of more than 20% after 12 months of 400 mg daily of imatinib. Forced vital capacity improved and pulmonary diffusing capacity remained stable. Unfortunately, adverse events were common, although 97.6% were mild-to-moderate (grade 1 or 2).

Treatment of early diffuse cutaneous systemic sclerosis patients in Japan by low-dose corticosteroids for skin involvement. Takehara K. *Clin Exp Rheumatol* 2004; 22: S87–9.

Twenty-three patients with early dcSSc were treated with low-dose corticosteroid therapy (initial dose of 20 mg/day of prednisolone) tapered by 2.5 mg/day every 2–6 months until reaching maintenance dose of 2.5–10 mg/day. Sixty-nine percent of patients had at least a 50% reduction in their mRSS. Notably, none of the patients had renal crisis during therapy.

Of note, several studies have suggested an association between steroid use and higher risk of SRC. Thus, patients need to be monitored very closely when on these medications and the lowest effective dose should be used.

Third-Line Therapies: Cutaneous Sclerosis and Visceral Involvement

- Autologous non-myeloablative hemopoietic stem cell transplantation (HSTC) **B**
- Extracorporeal photochemotherapy **B**
- Ultraviolet A (UVA) **C**
- Kidney transplantation **C**
- Cyclosporin **C**
- Retinoic acid **C**

Myeloablative autologous stem-cell transplantation for severe scleroderma. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, et al. *N Engl J Med* 2018; 378: 35–47.

In this randomized trial, 75 severe SSc patients received either myeloablative autologous HSCT or 12 monthly cyclophosphamide infusions. Global rank composite scores comprising pre-defined hierarchy of outcomes (with rankings from highest to lowest: death, event-free survival, forced vital capacity, scores on the Health Assessment Questionnaire Disability Index, and Rodnan score) favored transplantation over cyclophosphamide (67% of 1404 pairwise comparisons favored transplant while 33% favored cyclophosphamide). The transplant-related mortality was 3% at 54 months and 6% at 72 months, as compared with 0% in the cyclophosphamide group; 9% of transplant patients had initiated disease-modifying antirheumatic drugs by 24 months.

A randomized, double-blind, placebo-controlled trial of photopheresis in systemic sclerosis. Knobler RM, French LE, Kim Y, et al. *J Am Acad Dermatol* 2006; 54: 793–9.

Sixty-four patients with SSc of less than 2 years' duration were randomized to receive either monthly active or sham

photopheresis treatment for 12 months. Although the active treatment group had statistically significant improvement in skin scores compared to baseline, there was no significant difference between treatment arms.

Different low doses of broad-band UVA in the treatment of morphea and systemic sclerosis. El-Mofty M, Mostafa W, El-Darouty M, et al. *Photodermatol Photoimmunol Photomed* 2004; 20: 148–56.

UVA phototherapy has been shown to be effective in SSc, but its use is restricted by limited availability.

Kidney transplantation for systemic sclerosis improves survival and may modulate disease activity. Gibney EM, Parikh CR, Jani A, et al. *Am J Transplant* 2004; 4: 2027–31.

Survival was significantly prolonged in the 142 SSc patients who received transplant, with a 3-year survival of 79.5% compared with 54.6% in those who did not receive transplant. Early graft loss was common with 33% of all graft losses (21/66) occurring within 90 days of transplantation.

Cyclosporine in systemic sclerosis. Clements PJ, Lachenbruch PA, Sterz M, et al. *Arthritis Rheum* 1993; 36: 75–83.

Cyclosporin may improve skin induration but has no effect on internal organ involvement. Additionally, its use is precluded in SSc given its high incidence of nephrotoxicity.

Retinoic acid for treatment of systemic sclerosis and morphea: a literature review. Thomas RM, Worswick S, Aleshin M. *Dermatol Ther* 2017; 30: e12455.

Case reports and case series suggest skin improvement in patients with SSc treated with various retinoids.

Sebaceous gland hyperplasia

Shyam B. Verma, Uwe Wollina



Sebaceous gland hyperplasia (SGH) represents the most common sebaceous tumor. It is a benign proliferation of sebaceous glands. Neonatal SGH is seen in about 60% of newborns but is self-limited, requiring no treatment.

Senile SGH primarily affects the elderly and is a symptom of exogenous (ultraviolet [UV]-induced) facial aging. In most cases lesions appear as tiny, dome-shaped, umbilicated, isolated papules, whitish or yellowish in color. Diffuse, presenile SGH can be induced by drugs such as ciclosporin A, systemic corticosteroids, and tacrolimus. Naevoid SGH is a benign hamartoma characterized by multiple, asymptomatic yellowish to skin-colored papules on the face. The face is most commonly affected but areolar and genital distribution have also been observed.

Specific Investigations

They are usually not necessary; biopsy may be considered in cases of diagnostic uncertainty.

MANAGEMENT STRATEGY

SGH is a benign condition that may negatively affect self-esteem and well-being. SGH may be in the differential diagnosis of other dermatoses including cutaneous malignancies. In clinically ill-defined cases, histopathological confirmation is recommended. In most cases the diagnosis is made clinically.

Treatment of sebaceous gland hyperplasia: a review of the literature. Hussein L, Perrett C. *J Dermatolog Treat* 2020; 1–33. <https://doi.org/10.1080/09546634.2020.1720582> [Epub ahead of print].

Effectiveness does not depend on the technique itself but instead on the number of lesions, financial cost, psychological factors, skin phototype, and age.

First-Line Therapies for Senile SGH

• Cryotherapy	B
• Laser therapy	B
• Electrodissection	C
• Low-dose isotretinoin	B

Evaluation of the efficacy of cryosurgery in patients with sebaceous hyperplasia of the face. Atas H, Gönül M. *J Cutan Med Surg* 2017; 21: 202–6.

Cryotherapy with liquid nitrogen six times every other week achieved excellent response rates in 71.4% for males and 61.8% for females ($n = 40$). Hyperpigmentation was seen in <1%.

Treatment of sebaceous hyperplasia by laser modalities: a review of the literature and presentation of our experience with erbium-doped yttrium aluminium garnet (Er:YAG). Liu A, Taylor MB, Sotoodian B. *J Drugs Dermatol* 2020; 19(5): 547–52.

Different laser types are used for sebaceous hyperplasia. Short-pulsed dye laser (PDL) produces faster results than long PDL. CO₂ laser is very effective without recurrence, but significant adverse effects have been reported, including scarring and pigmentary changes. Diode 1450-nm laser has been described to produce good (75%) clinical improvement and lesion shrinkage ranging between 50% to >75% without lasting adverse effects. The erbium-doped yttrium aluminum garnet laser achieves significant cosmetic outcomes with a low recurrence rate and minimal adverse effects.

Surgical pearl: intralesional electrodesiccation of sebaceous hyperplasia. Bader RS, Scarborough DA. *J Am Acad Dermatol* 2000; 42: 127–8.

The authors describe a nice technique for intralesional electrodesiccation using a fine epilating needle. They report no recurrence in more than 30 lesions followed up to 7 months.

Sebaceous hyperplasia: systemic treatment with isotretinoin. Tagliolatto S, de Oliveira Santos Neto O, Alchorne MM, et al. *An Bras Dermatol* 2015; 90: 211–5.

In an open trial with 20 patients, sebaceous hyperplasia was treated by oral isotretinoin at a dosage of 1 mg/kg/day for 8 weeks. The average number of sebaceous hyperplasia lesions before treatment was 24 per patient and declined to two per patient. Two years after the end of the treatment, the average number of sebaceous hyperplasia lesions was four per patient. There were no severe adverse events.

Second-Line Therapies

• Photodynamic therapy	C
• Erbium:YAG laser	D
• CO ₂ laser	D
• Diode laser 1420nm	D
• Diode laser 1720nm	E
• Pulsed dye laser	E

Treatment of sebaceous hyperplasia with a novel 1720-nm laser. Winstanley D, Blalock T, Houghton N, et al. *J Drugs Dermatol* 2012; 11: 1323–6.

A series of three treatments with a 1720 nm diode laser achieved rapid resolution of lesions in four patients with minimal damage to surrounding tissues. At 3 months posttreatment, there was nearly complete clearance without residual scarring. However, higher patient numbers and long-term follow-up are needed to confirm these observations.

Treatment of sebaceous gland hyperplasia by photodynamic therapy with 5-aminolevulinic acid and a blue light source or intense pulsed light source. Gold MH, Bradshaw VL, Boring MM, et al. *J Drugs Dermatol* 2004; 3: S6–9.

In an open randomized trial, 12 patients with SGH received PDT with 5-aminolevulinic acid (ALA) topically applied with a 30- to 60-minute drug incubation period. Patients received either 405–420 nm blue light for 15 minutes or intense pulsed light (IPL) 500–1200 nm with a 550 nm cut-off filter once per month for 4 consecutive months. A greater than 50% reduction lesion count was achieved in both treatment arms without recurrence during the treatment and follow-up periods of 12 months. Adverse effects were transient erythema and blisters, which resolved without sequelae.

Third-Line Therapies

• CO ₂ laser and curettage	B
• CO ₂ laser and ALA-PDT	D
• Nanosecond pulsed electric field	B

Combination of CO₂ laser therapy and curettage for sebaceous gland hyperplasia. Kavoussi H, Rezaei M, Azimi M, et al. *Acta Dermatovenerol Alp Pannonica Adriat* 2019; 28: 11–4.

In an interventional study of 46 patients, lesions were treated with a CO₂ laser, and then the shrunken lesions were removed

with a fine, sharp curette. The mean time of repair was 11.5 ± 1.9 days. A fair cosmetic outcome was seen in 76.1% of cases, with better results reported for females (with less severe lesions) and for skin types II and III.

Light and laser therapies for the treatment of sebaceous gland hyperplasia: a review of the literature. Simmons BJ, Griffith RD, Falto-Aizpurua LA, et al. *International League of Dermatological Societies, European Dermatology Forum. J Eur Acad Dermatol Venereol* 2015; 29: 2080–7.

The combination of 10,600 nm CO₂ laser ablation or diode laser and subsequent PDT with aminolevulinic acid seems to achieve higher response rates than laser or PDT alone.

Laser-assisted photodynamic therapy: two novel protocols for enhanced treatment results. Stevenson ML, Karen JK, Hale EK. *J Drugs Dermatol* 2017; 16: 329–31.

In this protocol, topical 20% ALA solution is applied to the face and allowed to incubate for 2 hours at 25 °C. After that, ALA is activated with red light (633 nm) for 5 minutes and 51 seconds providing a dose of 37 J/cm². The individual sebaceous hyperplasia lesions are then treated with a 595 nm PDL with a 10 mm spot size, fluence of 7.5 J/cm², and a pulse duration of 10 milliseconds. This combination allows the treatment of otherwise recalcitrant lesions.

Safety and efficacy of nanosecond pulsed electric field treatment of sebaceous gland hyperplasia. Munavalli GS, Zelickson BD, Selim MM, et al. *Dermatol Surg* 2020; 46(6): 803–9.

Nanosecond pulsed electric field is a new non-thermal technology that involves delivery of ultrashort pulses of electrical energy. In a clinical trial with 72 patients, a clearance rate of 99.6% was achieved.

Seborrheic eczema

Gaurav K. Dhawan, Ian H. Coulson



Seborrheic eczema (seborrheic dermatitis) is a chronic relapsing dermatitis affecting between 3% and 10% of adults, becoming more prevalent with age. It accounts for up to 3.5% of dermatology specialist outpatient consultations. It is more common in patients with Parkinson disease, HIV, AIDS, and alcohol dependency.

The signs and symptoms comprise erythema, greasy scaling, pruritus, burning, and dryness in a typical distribution pattern affecting the scalp and the face (particularly the nasolabial folds, eyebrows, and ears). Blepharoconjunctivitis may occur alone or in conjunction with skin lesions.

Seborrheic eczema can also affect infants up to the age of 3–4 months in the diaper area.

Although the etiology has yet to be fully elucidated, important factors are *Malassezia* yeasts, immune status, and individual susceptibility.

MANAGEMENT STRATEGY

Seborrheic eczema responds to a variety of immunosuppressive and antifungal therapies, but there is no cure.

Seborrheic eczema of the face is dry and flaky, so soap avoidance and substitution with a *light emollient cleanser* will help. Facial and flexural disease responds to *mild topical corticosteroids*, alone or in combination with a variety of *topical antipityrosporal agents* such as *miconazole*, *ketoconazole*, *bifonazole*, *itraconazole*, or *ciclopiroxolamine*. An ointment containing *lithium gluconate/succinate* may also be helpful.

Studies have demonstrated short-term efficacy with the topical calcineurin inhibitors *tacrolimus* and *pimecrolimus*. *Terbinafine cream* and *metronidazole gel* may also be beneficial, whereas resistant cases may respond to short courses of *oral itraconazole* or *terbinafine*.

Scalp seborrheic dermatitis can be helped with *topical ketoconazole*, *zinc pyrithione*, *selenium sulfide*, *corticosteroid* and *tar shampoos*, or a *propylene glycol* preparation formulated for scalp use. Severe cases with marked hyperkeratosis or pityriasis amiantacea may require topical keratolytics such as *salicylic acid ointment* or *coconut compound ointment*.

Specific Investigations

- Dermoscopy
- Tests for HIV infection
- Zinc levels

In neonates and children, consider acrodermatitis enteropathica or transient neonatal zinc deficiency, which can mimic recalcitrant seborrheic dermatitis. A similar eruption in parenterally fed adults also can occur due to zinc deficiency.

Dermoscopy can be useful in differentiating scalp psoriasis from seborrheic dermatitis. Kim GW, Jung HJ, Ko HC, et al. *Br J Dermatol* 2011; 164: 652–6.

Dermoscopy features on the scalp include arborizing vessels and comma vessels.

This may be of value as a means of differentiating from scalp psoriasis. These findings appear to have been replicated in several later studies.

New insights into HIV-1-primary skin disorders. Cedeno-Laurent F, Gómez-Flores M, Mendez N, et al. *Int AIDS Soc* 2011; 24: 14–5.

This article reports seborrheic dermatitis in up to 40% of patients with HIV with worsening severity as lymphocyte counts decline. Incidence in AIDS patients is up to 80%.

Seborrheic dermatitis and risk of future Parkinson's disease (PD). Tanner C, Albers K, Goldman S, et al. *Neurology* 2012; 78 (Meeting Abstracts 1): S42.001.

This nested case-control study included 2651 PD cases and 13,255 controls. Seborrheic eczema was associated with increased risk of PD (OR = 1.69, 95% CI 1.36, 2.1; $p < 0.001$). PD risk was also increased when seborrheic dermatitis was diagnosed 5 or more years before (2.1% cases, 1.4% controls, OR = 1.42, 95% CI 1.05, 1.93; $p = 0.024$).

Cutaneous changes in chronic alcoholics. Rao GS. *Indian J Dermatol Venereol Leprol* 2004; 70: 79–81.

In this study of 200 alcoholic patients attending for alcohol detoxification, seborrheic dermatitis was the second most common skin disorder (11.5% of cases).

NON-SCALP DISEASE

First-Line Therapies

• Topical ketoconazole	A
• Mild-to-moderate topical corticosteroids	A
• Emollients and soap substitutes	D

Ketoconazole 2% cream versus hydrocortisone 1% cream in the treatment of seborrheic dermatitis. A double-blind

comparative study. Stratigos JD, Antoniou C, Katsambas A, et al. *J Am Acad Dermatol* 1988; 19: 850–3.

In this double-blind study, 72 patients were treated daily for 4 weeks with either ketoconazole 2% cream or hydrocortisone 1% cream; 80.5% of the ketoconazole group showed a significant improvement in all symptoms compared with 94.4% of the hydrocortisone group. There was no significant difference in relapse rates.

Topical antifungals for seborrheic dermatitis. Okokon EO, Verbeek JH, Ruotsalainen JH, et al. *Cochrane Database Syst Rev* 2015; 5: CD008138.

This review included 51 studies with a total of 9052 participants. Eight trials compared use of topical 2% ketoconazole with placebo or vehicle. Active treatment was associated with a 31% lower risk of failure of clearance. Six trials compared topical ketoconazole with topical steroids. Remission rates were similar (RR 1.17, 95% CI 0.58–1.64), but occurrence of side effects was 44% lower in the ketoconazole group. Quality of data was limited by study duration and heterogeneity between studies.

Second-Line Therapies

• Lithium succinate/lithium gluconate	A
• Ciclopirox olamine cream	A
• Topical calcineurin inhibitors	A
• Topical azoles (miconazole/clotrimazole)	A

Lithium gluconate 8% vs. ketoconazole 2% in the treatment of seborrheic dermatitis: a multicenter, randomized study. Dreno B, Chosidow O, Revuz J, et al. *Br J Dermatol* 2003; 148: 1230–6.

This randomized, noninferiority study compared 8% lithium gluconate twice daily for 8 weeks with ketoconazole 2% twice weekly for 4 weeks, then once weekly for a further 4 weeks, in moderate-to-severe seborrheic dermatitis. Two hundred and sixty-nine patients were treated, and complete response was achieved in 52.0% and 30.1%, respectively.

Randomized, placebo-controlled, double-blind study on clinical efficacy of ciclopirox olamine 1% cream in facial seborrheic dermatitis. Dupuy P, Maurette C, Amoric JC, et al. *Br J Dermatol* 2001; 144: 1033–7.

One hundred and twenty-nine patients were randomized to receive either 1% ciclopirox olamine cream twice daily for 28 days, followed by once-daily application for a further 28 days, or placebo. At 8 weeks, 63% of patients in the ciclopirox olamine group achieved clearance of their test lesions versus 34% of placebo patients ($p < 0.007$).

An open, randomized, prospective, comparative study of topical pimecrolimus 1% cream and topical ketoconazole 2% cream in the treatment of seborrheic dermatitis. Koc E, Arca E, Kose O, et al. *J Dermatolog Treat* 2009; 20: 4–9.

In this open-label, randomized comparison study, 48 patients received either pimecrolimus 1% cream or ketoconazole 2% cream twice daily for 6 weeks. At 12 weeks both groups achieved statistically significant reductions in clinical severity scores, with an average decrease of 86.2% and 86.1%, respectively ($p < 0.05$). There was no significant difference between the two groups.

Single-blind, randomized controlled trial evaluating the treatment of facial seborrheic dermatitis with hydrocortisone

1% ointment compared with tacrolimus 0.1% ointment in adults. Papp KA, Papp A, Dahmer B, et al. *J Am Acad Dermatol* 2012; 67: e11–5.

Thirty patients received either hydrocortisone 1% cream or tacrolimus 0.1% ointment twice daily to symptomatic areas for 12 weeks. Both groups showed improvement in clinical severity, with patients using tacrolimus needing fewer applications of treatment.

Proactive treatment of adult facial seborrheic dermatitis with 0.1% tacrolimus ointment: randomized, double-blind, vehicle-controlled, multicenter trial. Kim TW, Mun JH, Jwa SW, et al. *Acta Derm Venereol* 2013; 93: 557–61.

In this double-blind, placebo-controlled trial, 75 patients used tacrolimus 0.1% ointment twice daily to stabilize their facial seborrheic dermatitis. They were then randomized to use tacrolimus 0.1% once a week, twice a week, or vehicle twice a week, for 10 weeks. Both treatment groups showed significant improvements in erythema, scaling, and pruritus compared with baseline ($p < 0.001$) with lower recurrence rates compared with vehicle ($p < 0.005$).

Third-Line Therapies

• Oral terbinafine	A
• Oral itraconazole	B
• Metronidazole gel	B
• Phototherapy	C
• Topical terbinafine	C

Oral terbinafine in the treatment of multisite seborrheic dermatitis: a multicenter, double-blind placebo-controlled study. Vena GA, Micala G, Santoianni P, et al. *Int J Immunopharmacol* 2005; 18: 745–53.

One hundred and seventy-four patients with seborrheic dermatitis were randomized to receive either terbinafine 250 mg once daily or placebo for 6 weeks. Terbinafine was statistically more effective at achieving 50% improvement than placebo in nonexposed sites (70% vs. 45%) and in achieving patient satisfaction (66% vs. 40%). There was no statistical difference in patients with lesions on exposed sites.

Efficacy of oral itraconazole in the treatment and relapse prevention of moderate to severe seborrheic dermatitis: a randomized, placebo-controlled trial. Ghodsi SZ, Abbas Z, Abedeni R. *Am J Clin Dermatol* 2015; 16: 431–7.

In this double-blind, placebo-controlled trial, 68 patients with moderate/severe seborrheic eczema received itraconazole 200 mg once daily or placebo daily for 1 week and then for the first 2 days of the month for 3 months. The treatment group showed a more significant clinical improvement ($p < 0.023$) and lower relapse rates compared with placebo ($p = 0.003$) with response rates of 93.8%, 87.5%, and 93.1% at the end of 2 weeks, 1 month, and 4 months.

Metronidazole 0.75% gel vs. ketoconazole 2% cream in the treatment of facial seborrheic dermatitis: a randomized, double blind study. Seckin D, Gurbuz O, Akin O. *J Eur Acad Dermatol Venereol* 2007; 21: 345–50.

Sixty patients with facial seborrheic dermatitis used either 0.75% metronidazole gel (with ketoconazole cream as vehicle) or 2% ketoconazole cream (with metronidazole gel as vehicle) for 4 weeks. Around 80% improvement was noted in both groups, with no statistical difference.

Narrow-band ultraviolet B (TL-01) phototherapy is an effective and safe treatment option for patients with severe seborrheic dermatitis. Pirkhammer D, Seeber A, Honigsman H, et al. *Br J Dermatol* 2000; 143: 964–8.

Eighteen patients were treated three times weekly until complete clearance or to a maximum of 8 weeks. Six showed complete clearance and 12 showed marked improvement.

Efficiency of terbinafine 1% cream in comparison with ketoconazole 2% cream and placebo in patients with facial seborrheic dermatitis. Azimi H, Golfaroushan F, Jaberian M, et al. *J Dermatolog Treat* 2013 [Epub ahead of print].

Ninety patients were randomized to use terbinafine 1% cream, ketoconazole 2% cream, or vehicle twice daily for 4 weeks. Both treatment groups showed a significant improvement in clinical severity scores compared with vehicle ($p = 0.003$). No significant difference was found between the two active treatments ($p > 0.05$).

SCALP DISEASE

First-Line Therapies

• Ketoconazole shampoo	A
• Ciclopirox shampoo	A
• Zinc pyrithione shampoo	A

Topical antiinflammatory agents for seborrheic dermatitis of the face or scalp. Kastarinen H, Oksanen T, Okokon EO, et al. *Cochrane Database Syst Rev* 2014; 5: CD009446.

Successful treatment and prophylaxis of scalp seborrheic dermatitis and dandruff with 2% ketoconazole shampoo: results of a multicenter, double-blind, placebo-controlled trial. Peter RU, Richarz-Barthauer U. *Br J Dermatol* 1995; 132: 441–5.

Five hundred seventy-five patients with moderate-to-severe scalp seborrheic dermatitis and dandruff were treated with ketoconazole 2% shampoo twice weekly for 2 months, producing clearance in 88%. Three hundred twelve responders were then randomized to active treatment or placebo once weekly. There were fewer relapses in the ketoconazole prophylactic treatment group after 6 months (47% vs. 19%).

Treatment and prophylaxis of seborrheic dermatitis of the scalp with antipityrosporal 1% ciclopirox shampoo. Shuster S, Meynadier J, Kerl H, et al. *Arch Dermatol* 2005; 141: 47–52.

In this double-blind, vehicle-control trial, 949 patients received ciclopirox 1% shampoo either twice or once weekly or vehicle. After 4 weeks responders were randomized for maintenance therapy with one of the three regimens for a further 12 weeks. At 4 weeks both ciclopirox regimens were statistically more effective than placebo (response rates 57.9% vs. 45.4% vs. 31.6%). During the maintenance phase relapse rates were significantly lower for both active regimens compared with placebo (14.9% vs. 22.1% vs. 35.5%).

A multicenter randomized trial of ketoconazole 2% and zinc pyrithione 1% shampoos in severe dandruff and seborrheic dermatitis. Piérard-Franchimont C, Goffin V, Decroix J, et al. *Skin Pharmacol Appl Skin Physiol* 2002; 15: 434–41.

In this 4-week, open-label, randomized trial, 331 patients with either seborrheic dermatitis or dandruff were randomized to

either twice-weekly ketoconazole 2% shampoo or at least twice-weekly zinc pyrithione 1% shampoo. Both groups showed clinical benefit with reductions in dandruff severity of 73% and 61%, respectively.

Second-Line Therapies

• Propylene glycol lotion	A
• Potent/superpotent topical corticosteroids	A
• Miconazole	A
• Selenium sulfide shampoo	C

Propylene glycol in the treatment of seborrheic dermatitis of the scalp: a double-blind study. Faergemann J. *Cutis* 1988; 42: 69–71.

Thirty-nine patients with scalp seborrheic dermatitis were treated in a double-blind, controlled study with 15% propylene glycol in a base of 50% ethanol and 35% water or vehicle alone; 89% in the group treated with propylene glycol showed healing, compared with 32% in the control group.

A randomized, double-blind, placebo-controlled trial of ketoconazole 2% shampoo versus selenium sulfide 2.5% shampoo in the treatment of moderate to severe dandruff. Danby FW, Maddin WS, Margeson LJ, et al. *J Am Acad Dermatol* 1993; 29: 1008–12.

A total of 236 patients were included in the study. Both medicated shampoos were statistically better than placebo in treating scaling and itching. However, ketoconazole was superior to selenium shampoo.

Seborrheic dermatitis and *Pityrosporum orbiculare*: treatment of seborrheic dermatitis of the scalp with miconazole-hydrocortisone (Daktacort), miconazole and hydrocortisone. Faergemann J. *Br J Dermatol* 1986; 114: 695–700.

In this double-blind, randomized, controlled study, 70 patients received 2% miconazole base and 1% hydrocortisone (Daktacort), 2% miconazole base, or 1% hydrocortisone daily for 3 weeks. The drugs were incorporated into a solution of 60% ethyl alcohol, 10% propylene glycol, and purified water. After 3 weeks responders moved to maintenance therapy with the same agent for a further 3 weeks. Non-responders continued with daily application. All three groups showed reduced organism culture and clinical improvement with 82.6%, 65.2%, and 29.1% deemed clear in each group.

Multicenter, double-blind, parallel group study investigating the noninferiority of efficacy and safety of a 2% miconazole nitrate shampoo in comparison with a 2% ketoconazole shampoo in the treatment of seborrheic dermatitis of the scalp. Buechner SA. *J Dermatolog Treat* 2014; 25: 226–31.

In this randomized, double-blind, comparative, parallel-group, multicenter study, 274 patients used either miconazole nitrate 2% shampoo or ketoconazole 2% shampoo twice weekly for 4 weeks. Miconazole was found to be non-inferior to ketoconazole.

Efficacy of betamethasone valerate 0.1% thermophobic foam in seborrheic dermatitis of the scalp: an open-label, multicenter, prospective trial on 180 patients. Milani M, Antonio Di Molfetta S, et al. *Curr Med Res Opin* 2003; 19: 342–5.

In this open-label trial, 180 patients were treated with 2g of betamethasone 17-valerate 0.1% foam daily for 15 days and then

every other day for 15 days. At 4 weeks there was a statistically significant clinical improvement. Eighty-five percent of patients preferred the betamethasone foam to previous treatments.

Efficacious and safe management of moderate to severe scalp seborrhoeic dermatitis using clobetasol propionate shampoo 0.05% combined with ketoconazole shampoo 2%: a randomized, controlled study. Ortonne JP, Nikkels AF, Reich K, et al. Br J Dermatol 2011; 165: 171–6.

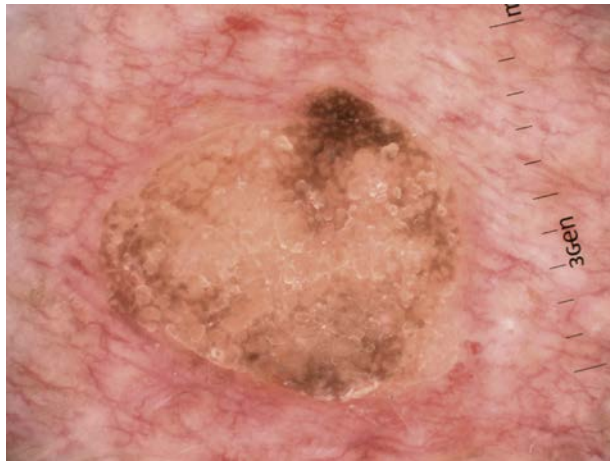
This investigator-blind, randomized, controlled trial had four arms of treatment: ketoconazole 2% shampoo twice weekly; clobetasol propionate 0.05% shampoo twice weekly; alternating

ketoconazole and clobetasol twice weekly; or ketoconazole four times weekly alternating with clobetasol twice weekly for 4 weeks. This was followed by a 4-week maintenance phase where all patients received weekly ketoconazole and a further 4-week follow-up phase. In total, 326 patients were included. All groups demonstrated clinical improvement, and all three clobetasol-containing regimens were significantly more effective than ketoconazole alone. Of these the twice weekly alternating clobetasol and ketoconazole regimen was the most effective.

The authors would like to stress that potent and superpotent steroids may not be considered suitable for long-term use.

Seborrheic keratosis

Shyam B. Verma, Uwe Wollina



Seborrheic keratosis (SK) is the most common human skin tumor. It is a benign lesion that increases in incidence with age. Areas of predilection are the face and trunk, and they follow Langer lines. There are several variants of SK-like hyperkeratotic, acanthotic, reticular, clonal, irritated, verrucous, and melanoacanthoma type. Dermatitis papulosa nigra is a variant in Fitzpatrick skin type 3–6 with multiple, tiny, hyperpigmented papules that usually occur on the face. They are usually asymptomatic. Diagnosis is primarily clinical but dermoscopy is useful in differentiating SK from mimickers such as melanoma or squamous cell carcinoma. Rapid eruption of multiple SKs is thought to be a paraneoplastic phenomenon and is known as ‘Leser-Trélat sign’.

MANAGEMENT STRATEGY

Removal of SK is often requested due to aesthetic concerns. The other main indication is when it is considered in a differential diagnosis of a cutaneous neoplasia.

Cryotherapy is a low-cost treatment but may cause pigmentary changes, especially in individuals with dark skin. It is less suitable for larger lesions and multiple lesions. **Electrodessication or cautery** are other options for multiple smaller lesions, but hyperpigmentation is a possible complication.

Curettage and shave excision may be used in particular for thicker lesions and in case of possible differential diagnoses, since they allow histopathologic examination. **Complete excision** is warranted in less common cases of possible collision tumors.

First-Line Therapies

• Cryotherapy	B
• Cautery	B
• Electrodessication	B

Specific Investigation

- Dermoscopy can be helpful in differentiation of SK from other cutaneous lesions
- In multiple eruptive SK consider the sign of Leser-Trélat and investigate for underlying malignancy

Effectiveness of cryosurgery vs curettage in the treatment of seborrheic keratoses. Wood LD, Stucki JK, Hollenbeak CS, et al. JAMA Dermatol 2013; 149: 108–9.

Twenty-five adult patients were randomized to curettage or cryotherapy with liquid nitrogen. At week 6, 60% preferred cryotherapy while 36% preferred curettage. Pain perception was not statistically different. However, leftover lesions and hypopigmentations occurred more often with cryotherapy.

Second-Line Therapies

Ablative lasers offer a rapid and effective treatment in particular in case of multiple SK. Healing time is shorter than with curettage of electrodesiccation.

Second-Line Therapies

• CO ₂ laser (10,600 nm)	C
• Erbium:YAG laser (2940 nm)	B
• Diode laser (532 nm)	B
• Fractional thulium fiber laser (1927 nm)	C

Treatment of dermatosis papulosa nigra using a carbon dioxide laser. Furukawa F, Mizawa M, Shimizu T. J Cosmet Dermatol 2020 Jan. <https://doi.org/10.1111/jocd.13309> [Epub ahead of print].

Three female Japanese patients suffering from dermatosis papulosa nigra were treated by a CO₂ laser with a computerized scanner (8–10 W; pulse duration, 0.05–seconds; rest duration, 0.36 seconds; laser spot size, 1.2 mm) for 5–10 months. All lesions could be removed without scar formation in all cases. The treated lesions did not relapse for more than 1 year.

Erbium-YAG laser therapy – analysis of more than 1,200 treatments. Wollina U. Global Dermatol 2016; 3: 268–72.

With the 2940-nm erbium:YAG laser, 240 patients were treated for SK, 83% with multiple lesions. In most cases a single laser session was effective to remove the lesions completely. Adverse effects were rarely seen, such as pigmentary changes. Scars were not induced.

Effectiveness of erbium:YAG laser and cryosurgery in seborrheic keratoses: randomized, prospective intraindividual comparison study. Gurel MS, Aral BB. J Dermatolog Treat 2015; 26: 477–80.

The study was carried out on 42 patients with SK. Lesions with a similar size and location on the same patient were matched. In the same session, half of the lesions were treated with cryotherapy, while the other half were treated with erbium:YAG laser. After a single treatment, complete healing was detected in 100% of lesions treated with erbium:YAG lasers, while the healing rate was 68% in the cryotherapy group. In the erbium:YAG laser-treated group, hyperpigmentation was significantly lower, and more erythema developed than in the cryotherapy group.

532-nm diode laser treatment of seborrheic keratoses with color enhancement. Culbertson GR. *Dermatol Surg* 2008; 34: 525–8.

Laser ablation with 532-nm laser and color enhancement using a red marker or ferric subsulfate was used in 326 patients who presented with 1567 SKs. Complete clearance occurred in 93% of lesions. The remaining 7% of SKs required a second round of laser treatment for incomplete ablation. There were no cases of hyperpigmentation or hypertrophic scar formation of the skin, but hypopigmentation was observed in 6% of patients and was associated with old, chronic, or recalcitrant lesions.

Treatment of macular seborrheic keratoses using a novel 1927-nm fractional thulium fiber laser. Polder KD, Mithani A, Harrison A, et al. *Dermatol Surg* 2012; 38: 1025–31.

A fractionated, non-ablative 1927-nm thulium fiber laser was used for the treatment of macular SK in non-facial areas in six patients. Patients received three treatments at 3- to 4-week intervals. Patients were treated at settings of 10–20 mJ with 30–55% surface area coverage and four to eight passes at each session. At baseline, average global SK count was 43.2 ± 27.3 . At 1-month follow-up, 20.7 ± 16.6 lesions remained. At 6-month follow-up, 14.7 ± 18.6 lesions remained, respectively. A decrease in thickness and SK counts within the 5×5 cm square was also observed. Moderate erythema and mild edema were noted after treatment.

Third-Line Therapies

In recent years new topical modalities have been developed to treat SK.

Third-Line Therapies

• Eskata 40% (w/w) topical hydrogen peroxide	A
• Nitrizinc Complex solution	B
• Artemether 3% solution	C

Safety and efficacy of hydrogen peroxide topical solution, 40% (w/w), in patients with seborrheic keratoses: results from 2 identical, randomized, double-blind, placebo-controlled, phase 3 studies (A-101-SEBK-301/302). Baumann LS, Blauvelt A, Draeos ZD, et al. *J Am Acad Dermatol* 2018; 79: 869–7.

Safety and efficacy of 40% hydrogen peroxide topical solution (HP40) versus vehicle for the treatment of SKs was investigated in 937 patients with four SKs each. Patients were randomized 1:1 to HP40 or vehicle. At each visit, SKs were graded using the Physician's Lesion Assessment (PLA) scale (0, clear; 1, nearly clear; 2, ≤ 1 mm thick; and 3, > 1 mm thick). After one treatment, SKs with a PLA score higher than 0 were retreated 3 weeks later. At day 106, significantly more patients treated with HP40 than with vehicle

achieved a PLA score of 0 on all four SKs (study 1: 4% vs. 0%; study 2: 8% vs. 0%) and on three of four SKs (study 1: 13% vs. 0%; study 2: 23% vs. 0%). A higher mean per-patient percentage of SKs was clear (study 1: 25% vs. 2%; study 2, 34% vs. 1%) and clear or nearly clear (study 1: 47% vs. 10%; study 2: 54% vs. 5%) with HP40 than with vehicle. Local skin reactions were largely mild and resolved by day 106.

Anatomic site-specific treatment response with 40% hydrogen peroxide (w/w) topical formulation for raised seborrheic keratoses: pooled analysis of data from two phase 3 studies. Smith SR, Xu S, Estes E, et al. *J Drugs Dermatol* 2018; 17: 1092–8.

Up to two treatments with topical 40% (w/w) hydrogen peroxide topical solution (HP40) were allowed in two randomized, double-blind, vehicle (VEH)-controlled clinical trials, including 937 patients, each with four target SKs ($n = 3748$ SKs), with at least one on the face and one on the trunk or extremities. Treatment response was greater with HP40 versus VEH regardless of anatomic location of the SK. Clear or near-clear SKs with HP40 was observed in 65% of facial SKs (vs. 10% VEH), 46% of truncal SKs (vs. 5% VEH), and 38% of extremity SKs (vs. 9% VEH). Facial SKs were more likely to be clear or near clear after a single treatment (43%), versus SKs on the trunk (31%) or extremities (14%). The most common immediate reactions with HP40 were erythema, stinging, and edema.

A novel Nitrizinc Complex® solution for topical treatment of seborrheic keratosis: an interventional clinical study. Tribó MJ, Aladren S, Garre A, et al. *Eur J Dermatol* 2019; 29: 203–8.

Nitrizinc Complex topical solution for treatment of SK was used for one to two topical applications. Thirty-two SK patients with a total of 59 lesions were treated. Six months after treatment, complete clearance was observed in 80% of the lesions (72% of the patients), while 93.3% of the lesions showed at least 50% reduction. Treatment ended with 100% cosmetic benefit as no scars or dyschromia were observed in the treated areas. Subjective treatment and cosmetic satisfaction were high. Discomfort, such as pain and itching/burning sensations, was minimal. No relapse cases have been observed at 12 months after treatment.

Artemether for topical use in patients with seborrheic keratosis. Härtel A, Jung T, Sift Carter R. *Br J Dermatol* 2018; 179: 1225–6.

The artemisinin derivate artemether (approved for malaria) was used in a topical 3% gel formulation in 11 patients with five SKs twice daily for 8 weeks in an open trial with a follow-up until week 12. At week 8, 31% of lesions improved; at week 12, 64% improved. Complete or almost complete clearance was achieved in 18% at week 12. Adverse events were mild pruritus, burning, or erythema.

Sporotrichosis

Mahreen Ameen, Wanda Sonia Robles



Sporotrichosis is a deep, cutaneous fungal infection caused by several species of *Sporothrix* of which the most common is *S. schenckii*, a rapidly growing dimorphic saprophytic fungus found in soil and plant matter. It can affect both humans and animals and is prevalent worldwide, but is more common in the Tropics. Sporadic zoonotic transmission (most commonly with cats) is now also well recognized. Cutaneous lesions develop following traumatic inoculation of *S. schenckii*. Infection is therefore more common in some occupations, such as horticulturists, carpenters, and miners; 15% of cases occur in children less than 10 years of age. The initial lesion appears at the site of injury as an erythematous, ulcerated, or verrucous nodule. Lesions can be localized and are known as fixed-type sporotrichosis. The more common presentation is the lymphocutaneous form, where there is nodular lymphangitic spread. Pulmonary and disseminated infection following inhalation is uncommon. It is a risk in the immunocompromised and an emerging problem in those with advanced HIV infection. Infection is usually sporadic, but outbreaks may occur due to contaminated soil and wood.

MANAGEMENT STRATEGY

Although there have been cases describing the spontaneous remission of sporotrichosis, it is common practice to treat the disease. Treatment includes localized physical therapies, saturated solution of potassium iodide (SSKI), azoles, terbinafine, and amphotericin B. Historically, uncomplicated lymphangitic and fixed forms of sporotrichosis have been treated with high-dose SSKI initiated with five drops three times daily and increased as tolerated to 10–50 drops three times daily (equivalent to 250 mg to 1 g three times daily). Treatment is continued for 3–4 weeks after clinical cure. The mechanism of action of potassium iodide is not known but it is highly effective, with reported cure rates ranging from 80% to 100%. It is also inexpensive, and is first-line treatment for sporotrichosis in most developing countries. However, it is inconvenient to administer and side effects are common,

although not serious, and include metallic taste, nausea, abdominal pain, and salivary gland enlargement.

Itraconazole is first-line therapy in countries where it is affordable. It should be initiated at a loading dose of 200 mg three times daily for 3 days, followed by 100–400 mg daily, depending on disease severity. It may be administered continuously or intermittently (pulse). Cure rates for cutaneous and lymphocutaneous infection are high, generally 90%–100%. Terbinafine (250–1000 mg daily) produces similar efficacy. Fluconazole (400–800 mg daily) therapy gives response rates of 63%–71% and therefore is recommended for second-line therapy only. Ketoconazole is ineffective for the treatment of sporotrichosis. Drug therapies are sometimes combined in order to increase efficacy. There are limited case reports of the use of physical therapies, which have been used either alone or in combination with drug therapy. These include thermotherapy (using infrared wavelengths to heat tissues to 42–43°C), photodynamic therapy, laser (Nd:YAG), cryotherapy, and electrosurgery. Physical therapies may have a useful role as monotherapy in those for whom systemic therapies are contraindicated.

There are no clinical trials to guide therapy for disseminated or meningeal sporotrichosis, which can occur with immunosuppression. Based on case reports, parenteral amphotericin B (AmB) is the preferred treatment (AmB deoxycholate 0.7 mg/kg daily, or as a lipid formulation 3.0–5.0 mg/kg daily). A lipid formulation of AmB is recommended for meningeal infection. Following AmB induction therapy, itraconazole (200 mg twice daily) is given as maintenance therapy.

Clinical Practice Guidelines for the Management of Sporotrichosis: 2007 Update by the Infectious Diseases Society of America. Kauffman CA, Bustamante B, Chapman SW, et al. Clin Infect Dis 2007; 45(10): 1255–65.

For cutaneous and lymphocutaneous infection in developed countries, first-line recommended therapy is with itraconazole 200 mg daily, which is continued for 2–4 weeks after all lesions have resolved. Usually a 3–6 month course of treatment is recommended. Patients who fail to respond can be given either high-dose itraconazole 200 mg twice daily, terbinafine 500 mg twice daily, or saturated solution of potassium iodide (SSKI initiated at a dose of five drops three times daily and increased as tolerated to 40–50 drops thrice daily). Children can be treated with the same drugs at a dose of 6–10 mg/kg for itraconazole (maximum 400 mg daily) and a maximum of one drop/kg of SSKI. Fluconazole should only be used in patients who cannot tolerate any of these treatments. Thermotherapy can be used for fixed lesions in those in whom oral therapy is contraindicated, such as pregnant women. Amphotericin B is recommended first-line therapy for severe pulmonary or osteoarticular infection, and disseminated and meningeal sporotrichosis. After initial response, itraconazole is recommended as stepdown therapy and should be given to complete a total of at least 12 months of therapy. Amp B is also the drug of choice for severe infection in pregnancy.

Future updated guidelines will need to incorporate recent data demonstrating the efficacy of lower doses of itraconazole and terbinafine for sporotrichosis.

Specific Investigations

- Culture
- Histology
- Serology for HIV infection (where relevant)

Direct microscopy of infected material is futile because the infective organisms are scarce in tissue. Culture is the most sensitive means of diagnosis, and is characteristically rapid, with growth usually seen within 1 week in 90% of cases. In the remaining 10% it may take up to 4 weeks to achieve a positive result on Sabouraud agar culture. The diagnosis is confirmed by demonstrating dimorphism, or conversion to the yeast phase. Suitable material for culture may include lesion swab, aspirate, or biopsy. Histopathology reveals a mixed granulomatous and pyogenic inflammatory response with pseudoepitheliomatous hyperplasia. The fungus is sometimes visualized with periodic acid–Schiff staining and is associated with extracellular *Sporothrix* asteroid bodies, consisting of yeast surrounded by radiating eosinophilic spicules. There is only limited data for polymerase chain reaction, and it requires further clinical validation.

Immunity and treatment of sporotrichosis. Garcia Carnero LC, Lozoya Perez NE, Gonzalez Hernandez SE, et al. *J Fungi* (Basel) 2018; 4(3): 100.

Given the limitations of current drug therapies and the acquisition of antifungal drug resistance, this review discusses passive and active immunological responses as a topic of growing interest in the development of a potential anti-*Sporothrix* vaccine

Sporotrichosis in immunocompromised hosts. Queiroz-Telles F, Bucchini R, et al. *J Fungi* (Basel) 2019; 11(5): 8.

This reviews the presentation of opportunistic sporotrichosis in several different immunosuppressive states including diabetes, alcoholism, transplantation, hematological malignancies, HIV, and iatrogenic immunosuppression. It discusses how higher doses of antifungals and more prolonged courses are usually required. *Therapy was generally started with amphotericin formulations, which were switched to itraconazole after the initial improvement.*

The impact of sporotrichosis in HIV-infected patients: a systematic review. Moreira JAS, Freitas DF, et al. *Infection* 2015; 43(3): 267–76.

This is a systematic review of reported cases of HIV-associated sporotrichosis found via PubMed (1984–2013). A total of 39 papers were included, and 58 patients' data analyzed; 56.9% of cases were from Brazil and 31% from the US. The median CD4 cell count was 97 cells/mm³. The most common clinical forms were disseminated and disseminated cutaneous affecting 56.9% and 17.5% of patients, respectively. Mortality was 30% and significantly higher in those with central nervous system involvement and death.

In this group of patients, AmB was usually the drug of choice and itraconazole was used as maintenance therapy.

Potassium iodide in dermatology: a 19th century drug for the 21st century: uses, pharmacology, adverse effects, and contraindications. Sterling JB, Heymann WR. *J Am Acad Dermatol* 2000; 43: 691–7.

This article reviews the pharmacology and adverse effects of potassium iodide as a therapeutic agent. It discusses contraindications to its use, which include a history of thyroid or kidney disease, and pregnancy.

First-Line Therapies

• Itraconazole	A
• Terbinafine	A
• Potassium iodide	B
• Amphotericin B	E (for disseminated sporotrichosis)

Treatment of cutaneous sporotrichosis with itraconazole: study of 645 patients. de Lima Barros MB, Schubach AO, de Vasconcellos Carvalhaes de Oliveira R, et al. *Clin Infect Dis* 2011; 52(12): e200–6.

This is the largest study of sporotrichosis (68.1% with lymphocutaneous form and 23.1% with fixed form) treated with itraconazole 50–400 mg/day. There was a 94.6% cure rate in the 619 patients who completed treatment (547 with 100 mg/day, 59 with 200–400 mg/day, and four children with 50 mg/day). Treatment was given until cure and the median treatment duration was 12 weeks (range 2–64 weeks). Lymphocutaneous and disseminated forms required approximately 2 weeks longer to achieve cure than the fixed form. The most frequent clinical adverse effect was nausea, and 12.4% required further courses of treatment because of relapse. These were mainly those treated with the lower dose of 100 mg/day. One patient, despite dose escalation of itraconazole to 400 mg/day, failed and was cured only after switching to potassium iodide.

This study demonstrated that 100 mg daily dose is highly effective in the vast majority of patients with fixed or lymphocutaneous disease, although it was sometimes associated with a higher risk of relapse. This is important as it makes itraconazole a more affordable option in resource-poor regions. This report has also demonstrated that potassium iodide can be more efficacious than itraconazole although there have been no comparative studies.

Efficacy and safety of itraconazole pulses vs. continuous regimen in cutaneous sporotrichosis. Song Y, Zhong SX, Yao L, et al. *J Eur Acad Dermatol Venereol* 2011; 25(3): 302–5.

This randomized controlled trial comparing pulse itraconazole 200 mg twice daily for one week every month ($n=25$, mean course of treatment 2.65 ± 0.81 pulses) with continuous itraconazole 100 mg twice daily ($n=25$, mean course of treatment 2.8 ± 2.33 months) demonstrated cure rates at 48 weeks of 81.8% and 95.8%, respectively. Side effects in the pulse therapy and continuous therapy groups were 4.5% vs. 16.7%, respectively.

Pulse therapy has the advantages of lower cost and fewer adverse effects, although this small trial demonstrates higher efficacy with the continuous itraconazole regimen.

Cutaneous sporotrichosis in Himachal Pradesh, India. Mahajan VK, Sharma NL, Sharma RC, et al. *Mycoses* 2005; 48(1): 25–31.

This article describes 103 cases of the lymphocutaneous and fixed cutaneous varieties of sporotrichosis during the period 1990–2002. Potassium iodide was used as first-line treatment, and in 93% of patients healing of lesions occurred in 4–32 weeks (average 8.7 weeks) without significant side effects. Itraconazole was used in 12 patients, and was also highly effective.

This study demonstrates that the efficacy of potassium iodide is comparable to itraconazole.

Sporotrichosis in childhood: clinical and therapeutic experience in 25 patients. Bonifaz A, Saúl A, Paredes-Solis V, et al. *Pediatr Dermatol* 2007; 24(4): 369–72.

The mean age of this cohort of affected children was 9.3 years. Two-thirds were affected with the lymphocutaneous form, and the upper limbs and face were most commonly affected. Nineteen children were cured clinically and mycologically with potassium iodide, three with itraconazole, and one with heat therapy.

Comparative evaluation of the efficacy and safety of two doses of terbinafine (500 and 1000 mg/day) in the treatment of cutaneous or lymphocutaneous sporotrichosis. Chapman SW, Pappas P, Kauffmann C, et al. *Mycoses* 2004; 47: 62–8.

This was a multicenter, randomized, double-blind trial evaluating the safety and efficacy of oral terbinafine for the treatment of cutaneous and lymphocutaneous sporotrichosis. Patients were treated with either 500 mg daily ($n=28$) or 1000 mg daily ($n=35$) for a maximum period of 24 weeks. Cure was significantly higher in the higher dose treatment group (87% vs. 52%, $p=0.004$) with no relapses 24 weeks after treatment cessation. By contrast, there were six relapses in the lower dose group.

Terbinafine has fungicidal activity and therefore continuing treatment beyond mycological cure may not be required, although studies have yet to demonstrate this.

Terbinafine (250 mg/day): an effective and safe treatment of cutaneous sporotrichosis. Francesconi G, Valle AC, Passos S, Reis R, Galhardo MC. J Eur Acad Dermatol Venereol 2009; 23(11): 1273–6.

Of 50 cases of sporotrichosis treated with terbinafine 250 mg daily, 96% ($n=48$) were cured after a mean treatment period of 14 weeks with no recurrence after a mean follow-up period of 37 weeks. One patient discontinued drug therapy because of the development of a skin rash.

This study demonstrates that standard doses of terbinafine have adequate efficacy and that sporotrichosis does not generally require high-dose terbinafine therapy. The authors also point out that one of the advantages of terbinafine is that it has fewer drug–drug interactions than itraconazole.

Comparative study of 250 mg/day terbinafine and 100 mg/day itraconazole for the treatment of cutaneous sporotrichosis. Francesconi G, Francesconi do Valle AC, Passos SL, et al. Mycopathologia 2011; 171(5): 349–54.

Itraconazole 100 mg daily and terbinafine 250 mg given to 249 and 55 patients, respectively, with culture-proven sporotrichosis demonstrated almost equal cure rates in both group of 92%–93% within a similar mean period (11.5–11.8 weeks). Adverse effects were equally frequent with both drugs occurring in approximately 7% of those treated and were generally mild except in two patients receiving itraconazole who had to discontinue treatment.

This study provides further evidence for the efficacy of lower doses of itraconazole or terbinafine therapy. It also demonstrates that terbinafine is perhaps better tolerated.

Report of 73 cases of cutaneous sporotrichosis in Mexico. Estrada-Castañón R, Chávez-López G, Guadalupe Estrada-Chávez G, et al. An Bra Dermatol 2018; 93(6): 907–9.

All patients in this recent study were treated with potassium iodide: children 1–3 g/daily and adults 3–6 g/daily for 2 months. Treatment was extended for a further month if there were still active lesions. Almost 90% had fixed cutaneous or lymphocutaneous sporotrichosis. Children under 15 years of age comprised 50% of the cases. All confirmed cases were of *S. schenckii*. Treatment was well tolerated with minimal side effects, which were mostly gastric intolerance and taste disturbances. Long-term follow-up was possible in 74% of patients, and they all demonstrated clinical and mycological cure.

The authors of this valuable study state that potassium iodide is their first-line option for treatment of rural communities as it is easy to transport and prepare, and is low cost. This study demonstrates its high efficacy and tolerability.

Second-Line Therapy

- Fluconazole

B

A Pan-American 5-year study of fluconazole therapy for deep mycoses in the immunocompetent host. Pan-American Study Group. Diaz M, Negroni R, Montero-Gei F, et al. Clin Infect Dis 1992; 14 Suppl 1: S68–76.

An open-label multicenter trial of fluconazole administered at a dose of 200–400 mg daily to 19 patients with sporotrichosis produced a 63% cure rate. The vast majority of patients required a 400 mg daily dose. Treatment was well tolerated.

Treatment of lymphocutaneous and visceral sporotrichosis with fluconazole. Kauffman CA, Pappas PG, McKinsey DS, et al. Clin Infect Dis 1996; 22: 46–50.

This clinical trial involved 14 patients with lymphocutaneous infection and 16 with osteoarticular or visceral sporotrichosis. Eleven of the 30 patients had previously been treated with other forms of antifungal therapy without success. Most patients were treated with fluconazole 400 mg/day. Four patients received fluconazole 200 mg/day and another four received 800 mg/day. Results show that 71% of patients (10/14) with lymphocutaneous sporotrichosis were cured. However, only 31% (5/16) with osteoarticular or visceral sporotrichosis responded to treatment.

This paper concluded that fluconazole is only modestly effective for the treatment of sporotrichosis, and perhaps should be considered second-line therapy in patients who are unable to take itraconazole.

Third-Line Therapies

- Thermotherapy D
- Cryotherapy D

Hyperthermic treatment of sporotrichosis: experimental use of infrared and far infrared rays. Hiruma M, Kawada A, Noguchi H, Ishibashi A, Conti Díaz IA. Mycoses 1992; 35(11–12): 293–9.

Pocket warmers and infrared and far infrared rays were used to treat 14 cases of sporotrichosis: seven in children and seven in adults. Daily applications of heat were applied to the lesions and the devices warmed tissues to 42 °C–43 °C. All lesions treated with pocket warmers were facial lesions in children. Infrared and far infrared rays generated more heat than pocket warmers allowing the length of a single treatment to be reduced by three-quarters to only a single 15-min treatment daily. The overall cure rate was 71%.

The efficacy for this form of treatment has not been satisfactorily evaluated. However, it has an important role in the treatment of infection in those who are unable to take systemic therapy.

Cryosurgery as adjuvant therapy in cutaneous sporotrichosis. Ferreira CP, Galhardo MC, Valle AC, et al. Infect Dis 2011; 15(2): 181–3.

Nine patients with one or two lesions of sporotrichosis that persisted, despite completing drug therapy with either itraconazole, potassium iodide, or terbinafine, were then treated with cryotherapy given monthly as two cycles of 15 seconds with a halo of 5 mm. The patients required 1–4 cryotherapy sessions to achieve cure.

The study has demonstrated the efficacy of cryotherapy and its ability to speed up disease resolution. By acting as an adjunctive therapy, it has the potential to decrease the duration of chemotherapy.

Squamous cell carcinoma

Sreya Talasila, Bassel H. Mahmoud,
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Cutaneous squamous cell carcinoma (cSCC) originates from keratinizing cells of the epidermis or its appendages. Most commonly it presents as an erythematous papule or nodule with scale and crust, but it may also be ulcerated, hyperpigmented, or surmounted by a cutaneous horn.

Squamous cell carcinoma (SCC) is not only the second most common type of skin cancer, but also the second most common malignancy of any kind in the United States. Incidence varies geographically, with higher rates at lower latitudes. The lifetime risk for SCC is increasing worldwide, escalating 50%–300% in the last three decades. Cumulative ultraviolet light (UVL) exposure is the most common cause of SCC of the skin, which explains why the majority of SCCs occur on the head, neck, and extremities – areas of maximum

sun exposure. Depletion of atmospheric ozone and longer life expectancy contribute to larger cumulative exposures. Other risk factors include use of tanning beds, chemical carcinogens, and immunosuppressive drug therapy; chronic scarring; chronic dermatoses such as epidermolysis bullosa; human papilloma virus (HPV) infection; and genodermatoses such as xeroderma pigmentosum. A person with one SCC is at high risk for developing more SCCs as well as other skin cancers, including basal cell carcinoma (BCC) and melanoma.

MANAGEMENT STRATEGY

The importance of prevention by educating everyone from an early age about this hazard of solar UV exposure cannot be overemphasized.

The goals of treatment of primary cutaneous SCC are to completely remove the tumor, to minimize the risk of metastasis and recurrence, to restore normal function after treatment, and to provide the best possible cosmetic outcome. Preoperative workup includes history of prior treatment, clinical size of the lesion, and an accurate histopathologic diagnosis. Physical examination should include regional lymph node palpation. A shave biopsy is generally sufficient for epidermal and deep dermal inspection, but punch biopsy to subcutaneous fat or an incisional or excisional biopsy may provide additional information. For reasons of prognostication, the pathology report should comment on depth of tumor invasion, histologic differentiation, and the presence or absence of sclerosis, single cell infiltration, and neurotropism. Additional laboratory and imaging studies are not generally helpful, although they may be performed when an aggressive high-risk tumor is suspected.

Staging is important to identify high-risk tumors (Table 229.1). The Brigham and Women's Hospital (BWH) staging classification is commonly used for cutaneous SCC. It identifies the high-risk factors (HRF) as (1) tumors greater than 2 cm in diameter; (2) histological recognition of poor differentiation or (3) perineural inflammation; and (4) tumor invasion beyond fat.

Advanced cutaneous SCC accounts for 5% of all cases of SCC but up to 60% of disease-related deaths. Immunosuppression also increases risk, notably in transplant recipients.

When choosing therapy, the main consideration is the cure rate; however, every patient should be assessed individually regarding site and size of the lesion, functional and cosmetic implications of treatment, the patient's general medical condition, ability to return for additional treatment, and the patient's preferences.

Mohs micrographic surgery (MMS) provides the best long-term cure rate and is the treatment of choice for large lesions in critical sites, as well as for high-risk and recurrent SCC, because of its unique method of margin control as well as its tissue-sparing benefits. In this technique, marginal, normal-appearing skin is removed as a thin, tangential layer around and under the clinically apparent tumor, precisely oriented, horizontally sectioned, and immediately processed as a frozen section for histologic

Table 229.1

BWH stage	Number of HRF	% 10-yr local recurrence	% 10-yr nodal metastasis	% 10-yr disease specific death
T1	0	0.9	0.2	0
T2a	1	9.8	5.2	1.2
T2b	2–3	28.4	23.8	17.4
T3	4 or bone invasion	84.2	62.1	94.8

BWH, Brigham and Women's Hospital; HRF, high-risk factors

evaluation. Specimens are then removed where the margins were positive and processed, with repeated excision until all margins are histologically clear. Based on the appropriate use criteria developed by the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery, and American Society for Mohs Surgery, MMS is appropriate for all SCCs in the high-risk and intermediate-risk areas; for SCCs 11 mm in diameter or greater in any site; for SCCs in situ in areas of chronic inflammation, osteomyelitis, prior radiation, or scar; for locally recurrent and incompletely excised SCCs; and for all SCCs in immunosuppressed patients or in patients with genetic syndromes. MMS is also indicated in SCC with aggressive histologic features and those with perineural or perivascular invasion.

Standard surgical excision may be performed for well-circumscribed tumors with diameters less than 2 cm that do not occur on the ears, lips, eyelids, nose, or scalp and do not invade the fat. Surgical margins of 4–6 mm are usually adequate to achieve a 95% chance of a cure. Lesions with diameters of 2 cm or greater in low-risk locations may be excised with 10-mm margins, but tissue rearrangement should not be performed until there is pathologic verification of tumor-free margins.

Electrodesiccation and curettage (ED&C) is considered for the treatment of low-risk, well-differentiated primary SCC and SCC in situ <1 cm in diameter. It involves a sequence of three curette scrapings and electrodesiccations. A margin of 3–4 mm around the tumor should be included in the treatment area to ensure complete removal of the tumor. Treated lesions often require several weeks to heal and may leave a white atrophic or hypertrophic scar that can be cosmetically unappealing. Cosmetically sensitive areas, convex surfaces, and skin prone to keloid formation or poor wound healing should be avoided. Cure rates are highly technique dependent but range from 80% to 95%. The main disadvantage of destructive therapy is that there is no tissue obtained for histologic analysis.

Cryosurgery is another destructive technique that can be considered for small (<1 cm), low-risk SCC and SCC in situ with cure rates similar to treatment by ED&C if performed properly. Cryosurgery destroys a tumor if it is frozen to –60 °C, achievable with timed stages or the use of thermocouples. It leaves a wound that may blister and drain but otherwise heals without complication to a porcelain-white atrophic scar. It has the advantage of being fast, simple, and inexpensive, but the success of the procedure is very much operator dependent.

Photodynamic therapy (PDT) involves the application of a photosensitizing agent onto the skin followed by irradiation with a light source. It is approved by the Food and Drug Administration (FDA) for the treatment of actinic keratoses, but other studies using different treatment regimens have documented some success for the treatment of non-melanoma skin cancers. PDT is not recommended for treatment of invasive SCC.

Radiation therapy as a primary treatment modality for SCC is best reserved for those situations in which surgical risk is not acceptable. Because of the potential long-term sequelae, it is not advisable in patients under 60 years old. Treatment is given sequentially over several weeks. Complications include hypopigmentation, telangiectasia, loss of adnexae, radiation dermatitis, and the appearance of a new primary tumor 10–20 years later. Radiation therapy is also recommended as adjuvant therapy for SCC with substantial perineural involvement, especially when the involved nerves are 0.1 mm or greater in caliber. Brachytherapy has recently been widely used because of the ability to deliver energy at a high-dose rate, leading to fewer patient visits.

Other options may be useful for specific patients. *Topical therapy* with *imiquimod* or *5-fluorouracil (5-FU) cream* has a low cure rate and is therefore reserved mainly for patients with SCC in situ,

especially in the setting of a large number of lesions. Some patients with many lesions, particularly on the legs, may be successfully treated with *intralesional methotrexate*, *5-FU*, *bleomycin*, or *interferon (IFN)*. For patients with many lesions who are immunosuppressed, systemic therapy with *retinoids* or *IFN* may be tried, but the results are mixed and there is usually only suppression of growth, not cure.

Systemic treatment for SCC includes *chemotherapy* for metastatic disease. *Cisplatin* has been used alone or in combination with *5-FU*, *methotrexate*, *bleomycin*, or *doxorubicin*. Epidermal growth factor receptor inhibitors, including *cetuximab* and *gefitinib*, have been used off-label to treat metastatic SCC because of the overexpression of epidermal growth factor (EGFR) in some tumors. Many of these are approved for head and neck SCC (HNSCC), but it is misleading to extrapolate data from HNSCC to apply it to advanced cSCC.

Patients with a history of SCC need continued lifelong cutaneous surveillance to monitor for tumor recurrence and metastasis, as well as for new developing lesions, as they are at higher risk of another skin cancer even within 5 years of the first tumor.

Specific Investigations

- Biopsy
- Staging
- Radiologic examination (PET, MRI, computed tomography (CT), ultrasound) if high-risk tumor
- Sentinel lymph node biopsy (controversial) may be considered for very high-risk tumors

Negative predictive value of biopsy margins in keratinocyte carcinoma: a literature review. Purnell JC, Duncan JR, Stratton MS, et al. *Dermatol Surg* 2020; 46: 525–9.

Pathologists may include commentary on margin status on dermatology biopsies of keratinocyte carcinoma. A review showed that of 221 specimens with negative-reported histologic margins, 55 cases had residual tumors on subsequent analysis, translating to a negative predictive value of 75.1% for all keratinocyte carcinomas, 87.2% for SCC, and 72.5% for BCC. Thus, negative histologic margin status on shave biopsy is a poor predictor of complete tumor removal.

Measuring the depth of perineural invasion in cutaneous squamous cell carcinoma: implications on biopsy technique. Tang JC, Seung-David LK, Stratman EJ. *Dermatol Surg* 2018; 44: 1170–3.

Accurate staging of cSCC depends on identification of high-risk features. The greatest chance of detecting perineural invasion by biopsy is using a technique that yields a specimen at least 3–4 mm deep.

Performance of the American Joint Committee on Cancer Staging Manual, 8th edition vs the Brigham and Women's Hospital Tumor Classification System for cutaneous squamous cell carcinoma. Ruiz ES, Karia PS, Besaw R, et al. *JAMA Dermatol* 2019; 155: 819–25.

BWH staging criteria had higher specificity and positive predictive value for identifying cases at risk for metastasis and death. It should be used when identifying patients to recommend for routine nodal staging or consideration of adjuvant therapy.

The role of imaging in the management of patients with non-melanoma skin cancer: when is imaging necessary? Humphreys TR, Shah K, Wysong A, et al. *J Am Acad Dermatol* 2017; 76: 591–607.

Preoperative imaging studies may be indicated in high-risk SCC. CT is performed when bony invasion is suspected. High-risk ocular tumors can also be defined by orbital CT. MRI is modality of choice for imaging disease spread in soft tissue or for identifying perineural involvement. Both CT and MRI are used to evaluate lymph nodes in the head and neck and offer similar sensitivity and specificity.

Nodal staging of high risk cutaneous squamous cell carcinoma. Fox M, Brown M, Golda N, et al. *J Am Acad Dermatol* 2019; 81: 548–57.

Early nodal disease is usually curable and therefore this workgroup on high-risk SCC suggests nodal staging for patients with BWH stage T2b and T3. Preoperative nodal staging with ultrasonography may be more useful than CT or MRI. Sentinel lymph node biopsy can also be considered if imaging is negative.

Sentinel lymph node biopsy for high-thickness cutaneous squamous cell carcinoma. Kofler L, Kofler K, Schulz C, et al. *Arch Dermatol Res* 2020.

Of 720 patients with high-risk SCC, 101 had completed sentinel lymph node biopsy (SLNB) and the rest were assigned observation status. In both groups, 11% of patients had lymph node metastasis in the course of their disease. The rate of distant metastasis and tumor-specific deaths were also not statistically significant. SLNB can be carried out to determine lymph node status; however, it did not provide any benefit in this study.

First-Line Therapies

• Mohs micrographic surgery	B
• Standard excision	B
• Curettage and electrodesiccation	B
• Cryosurgery	B
• Radiation therapy	B

Mohs surgery for squamous cell carcinoma. Belkin D, Carucci JA. *Dermatol Clin* 2011; 29: 161–74.

MMS provides the highest cure rates for both primary and recurrent tumors. The 5-year recurrence rates for primary tumors of the skin were 7.9% for non-Mohs modalities and 3.1% for MMS. For primary SCC of the lip, 5-year recurrence rates were 10.5% for non-Mohs modalities and 2.3% for MMS. For primary SCC of the ear, 5-year recurrence rates were 18.7% for non-Mohs modalities and 5.3% for MMS.

Outcomes in intermediate-risk squamous cell carcinomas treated with Mohs micrographic surgery compared with wide local excision. Xiong DD, Beal BT, Varra V, et al. *J Am Acad Dermatol* 2020; 82: 1195–204.

BWH stage T2a (single high-risk feature) SCC had significantly higher risk of local recurrence after wide local excision when compared with MMS (4% vs. 1.2%). In this study, immunocompromised state also increased likelihood of local recurrence. Poor outcomes overall were associated with wide local excision, high-risk location, and poor histologic differentiation.

Surgical margins for excision of primary squamous cell carcinoma. Brodland DG, Zitelli JA. *J Am Acad Dermatol* 1992; 27: 241–8.

Based on a prospective study of subclinical microscopic tumor extension, it was recommended that minimal margins of 4 mm be taken around clinical borders of SCC. Margins of at least 6 mm

were proposed for tumors ≥ 2 cm, histologic grade ≥ 2 , with invasion of subcutaneous tissue, and/or location in high-risk areas.

Tumor recurrence five years after treatment of cutaneous basal cell carcinoma and squamous cell carcinoma. Chren MM, Linos E, Torres JS, et al. *J Invest Dermatol* 2013; 133: 1188–96.

Prospective cohort study of consecutive patients from a university practice and a Veterans Affairs Medical Center shows common treatments for non-melanoma skin cancers were at least 95% effective. While SCC is not specifically separated in many of their calculations, they note that destruction is recommended only for tumors at low risk of recurrence. Readers of this paper will be reminded of the importance of making the appropriate choice of treatment option for each lesion as well as continued surveillance for recurrence.

Patient-reported outcomes of electrodesiccation & curettage for treatment of non-melanoma skin cancer. Galles E, Parvataneni R, Stuart SE, et al. *J Am Acad Dermatol* 2014; 71: 1026–8.

Patients treated with ED&C are more bothered by the treatment site 1 year after treatment than patients who underwent excision or MMS.

Office-based radiation therapy for cutaneous carcinoma: evaluation of 710 treatments. Hernandez-Machin B, Borrego L, Gil-Garcia M, et al. *Int J Dermatol* 2007; 46: 453–9.

A retrospective study of 604 BCCs and 106 SCCs irradiated between 1971 and 1996 revealed cure rates for SCC of 92.7% at 5 years and 78.6% at 15 years, suggesting that radiation therapy is an effective first option in many cases.

Guidelines of care for the management of cutaneous squamous cell carcinoma. Workgroup; Invited Reviewers. *J Am Acad Dermatol* 2018; 78: 560–78.

Comprehensive guidelines for the management of cSCC based on evidence in the literature with extended bibliography. Among other recommendations, they note that most important is a treatment plan that considers recurrence rate, preservation of function, patient expectations, and potential adverse effects. Low-risk primary cSCC treatments can be treated by excision with 4–6 mm margins, electrodesiccation and curettage, and cryotherapy, while high-risk cSCC warrants treatment with MMS. This group states that radiation therapy can be considered for primary treatment when tumors are low risk with the understanding the cure rate may be lower. There is insufficient evidence to make a recommendation on laser therapies or electronic surface brachytherapy.

Second-Line Therapies

• Topical imiquimod	B
• Topical 5-fluorouracil	B
• Photodynamic therapy	B
• Intralesional interferon- α	B
• Intralesional methotrexate	D
• Intralesional 5-fluorouracil	B
• Electrochemotherapy with bleomycin	B
• Intralesional bleomycin	E

Note: resolution of SCC after intralesional HPV vaccination has been reported; however, there is no guideline rating for use of this therapy. The HPV vaccine may have therapeutic utility in patients where SCC are HPV related such as in the transplant population.

Imiquimod 5% cream monotherapy for cutaneous squamous cell carcinoma in situ (Bowen's disease): a randomized, double-blind, placebo-controlled trial. Patel GK, Goodwin R, Chawla M, et al. *J Am Acad Dermatol* 2006; 54: 1025–32.

In total, 31 patients with biopsy-proven SCC in situ were randomized to placebo vs. imiquimod 5% cream daily for 16 weeks. Results showed 73% resolution at 28 weeks with imiquimod, 0% with placebo.

Present and future perspectives of photodynamic therapy for cutaneous squamous cell carcinoma. Keyal U, Bhatta AK, Zhang G, et al. *J Am Acad Dermatol* 2019; 80: 765–73.

Good results of PDT for SCC are mainly seen in case reports of SCC in situ or microinvasive SCC. This article reviews the literature and also discusses enhancement with pretreatment by medications, laser therapy, and microneedling.

Intralesional 5-fluorouracil (FU) as a treatment for nonmelanoma skin cancer: a review. Metterle L, Nelson C, Patel N. *J Am Acad Dermatol* 2016; 74: 552–7.

This literature review found 12 studies with dosing and efficacy information. For SCC, keratoacanthoma (KA) type, there were 68 tumors, treated 2/day to 1–2/week, 2–34 treatments (average was 6 treatments if the patient with 34 treatments was not included in the calculation). The dose used was 50 mg/mL FU with a clinically observed efficacy of 97%. For other SCC, there were 27 tumors, treated once weekly for 6–8 treatments. The dose ranged from 30 to 50 mg/cc. Average follow-up at 4 months found a reported efficacy of 98% based on repeat biopsy.

Intralesional chemotherapy for nonmelanoma skin cancer: a practical review. Kirby JS, Miller CJ. *J Am Acad Dermatol* 2010; 63: 689–702.

A review article with guidelines for the treatment of SCC, KA, and BCC with the most widely available intralesional agents (methotrexate, 5-FU, bleomycin, and IFN).

Third-Line Therapies

- Systemic retinoids **B**
- Chemotherapy **B**

Randomized controlled trial of acitretin versus placebo in patients at high-risk for basal cell or squamous cell carcinoma of the skin (North Central Cancer Treatment Group Study 969251). Kadakia KC, Barton DL, Loprinzi CL, et al. *Cancer* 2012; 15: 2128–37.

A 2-year treatment period did not reduce rate of new primary NMSCs in high risk but non-transplantation patients. Placebo group had significantly fewer adverse skin reactions.

Use of topical and systemic retinoids in solid organ transplant recipients: update and review of the current literature. Herold M, Good AJ, Nielson CB, et al. *Dermatol Surg* 2019; 45: 1442–9.

A systematic review of the literature in order to grade recommendation for retinoid therapy. Acitretin achieved a Grade A recommendation for prophylaxis of non-melanoma skin cancers and treatment and prophylaxis of actinic keratosis in solid organ transplant patients.

Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single arm trial.

Migden MR, Khushalani NI, Chang ALS, et al. *Lancet Oncol* 2020; 21: 294–305.

A total of 78 patients pooled from 25 sites received cemiplimab therapy for locally advanced cSCC that could not otherwise be treated. Results showed that 13% of patients had complete response and 31% had a partial response; 44% of patients had Grade 3–4 treatment-emergent adverse events, including one death with aspiration pneumonia.

Level of Evidence for Management of Metastatic SCC

- Adjuvant therapy **B**
- Epidermal growth factor inhibitors **B**
- PD-1 checkpoint inhibitors **B**
- Multidisciplinary consultation **A**
- Palliative care **A**

Evaluation of the utility of localized adjuvant radiation for node-negative primary cutaneous squamous cell carcinoma with clear histologic margins. Ruiz ES, Koyfman SA, Que SKT, et al. *J Am Acad Dermatol* 2019; 19: 32431–4.

Adjuvant radiation does not improve outcomes of treatment of cSCC compared with surgical monotherapy due to an overall low baseline risk of recurrence. However, adjuvant radiation therapy is recommended for named nerve invasion and large caliber nerve invasion of three or more nerves.

Surgery and salvage radiation limited field irradiation for control of cutaneous squamous cell carcinoma with microscopic residual disease. Ruiz ES, Koyfman SA, Kass J, et al. *JAMA Dermatol* 2019; 155: 1193–5.

Salvage radiation therapy for positive histologic margins after surgical therapy of cSCC result in a progression rate of greater than 80%. Radiation therapy can aid in local control of tumors when histologically negative margins cannot be achieved, but overall disease control is limited. Aggressive surgical clearance to achieve negative margins is recommended for cSCC whenever possible.

PD-1 and PD-L1 inhibitors in the treatment of non-melanoma skin cancer: a systematic review. Choi FD, Kraus CN, Elsensohn AN, et al. *J Am Acad Dermatol* 2019; 82: 440–59.

PD-1 and PD-L1 inhibitors have efficacy in treatment of SCC. One trial of cemiplimab 3 mg/kg every 2 weeks in 59 patients with metastatic cSCC showed 7% complete remission, 41% partial remission, and 5% disease progression. Another trial of cemiplimab of patients with metastatic or locally advanced SCC described 50% partial remission and 12% disease progression. In September 2018, cemiplimab was granted FDA approval for metastatic or locally advanced cSCC and is the only FDA-approved agent for treatment of advanced cSCC. Nivolumab used at a dose of 3 mg/kg or 200 mg every 2 weeks over 8–78 weeks in seven cases showed 6–19.5 months progression-free survival. Complete remission was noted in a case of invasive, poorly differentiated, recurrent cSCC treated with nivolumab and weekly cetuximab. Progression-free survival was 28–48 weeks. Pembrolizumab in one trial used at 200 mg every 3 weeks for up to 2 years in 19 patients with unresectable chemotherapy naive cSCC showed 5% complete remission, 37% partial remission, 16% stable disease, and 42% disease progression, with a median progression-free survival of 28 weeks. The differences in severity of cSCC may account for the range of response rates seen with different inhibitors. Currently there are numerous active clinical trials for treatment of SCC with PD-1 and PD-L1 inhibitors.

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Staphylococcal scalded skin syndrome

Emma Rowland, Dimitra Koch, Saleem M. Taibjee



Staphylococcal scalded skin syndrome (SSSS) is a highly contagious, blistering condition triggered by exfoliative, toxin-producing *Staphylococcus aureus*, most commonly affecting neonates and children under the age of 6 years. It rarely presents in adults, although the incidence in adults appears to be increasing, usually in association with renal failure, immunocompromise, and possibly non-steroidal antiinflammatory drugs (NSAIDs). SSSS can develop after viral illnesses such as respiratory tract infections and varicella and after skin-penetrating procedures such as heel prick and vitamin K injections in neonates, intraarticular injections, and peritoneal dialysis.

The estimated incidence in Western countries ranges from 0.56 to 2.51 cases/year/million inhabitants with a reported seasonal peak in summer/autumn, although this link has been disputed. In healthy infants, mortality is uncommon, with reported rates up to 3%, contrasting with up to 50%–60% in adults with comorbidity. Death occurs due to complications such as pneumonia, hypovolemia, electrolyte imbalance, and sepsis.

SSSS is caused by hematogenous spread of exfoliative toxin (ET), mainly ET-A and/or B, produced by *S. aureus*, including methicillin-sensitive (MSSA), methicillin-resistant (MRSA), and multidrug resistant strains. Approximately 5% of all *S. aureus* produce ET. ET-producing MRSA strains appear more prevalent in Japan. ETs are serine proteases specifically cleaving desmosomal protein desmoglein-1, disrupting keratinocyte adhesion in the superficial epidermis. Increased susceptibility may reflect impaired renal clearance of ET in neonates and adults with renal failure or low titers of ET-specific antibodies in immunocompromised individuals.

Clinical features include a prodrome of malaise, irritability, and fever. Skin manifestations develop within 24 to 48 hours. Tender erythema is followed by superficial, flaccid blistering, most pronounced in flexural and periorificial areas, sparing mucosal surfaces, and ranging from localized blisters to widespread

exfoliation. This leads to impaired thermoregulation and fluid balance and susceptibility to sepsis and secondary infection. The Nikolsky sign is positive. With successful treatment SSSS resolves over 10–14 days. Bullae rupture leaving denuded skin, followed by reepithelialization without scarring.

The causative organism cannot usually be cultured from affected skin because this is a circulating toxin-mediated process. The infection may be acquired by skin-to-skin contact from another individual with either a symptomatic infection or one who is an asymptomatic carrier. It may be possible to culture ET-producing *S. aureus* from extracutaneous sites, most commonly the nasopharynx, but also the rectum, conjunctiva, urinary tract, umbilicus, and blood. Polymerase chain reaction (PCR) or random amplified polymorphic DNA analysis may identify the toxin-encoding genes. Histology of affected skin typically shows a superficial subcorneal blister, absence of epidermal necrosis, and minimal inflammation. A frozen section of blister roof can confirm the superficial level of cleavage, facilitating a more rapid diagnosis.

The main differential diagnosis is the Stevens–Johnson syndrome–toxic epidermal necrolysis spectrum, in which distinguishing features include targetoid skin lesions, mucosal involvement, and subepidermal level of blistering with full-thickness epidermal necrosis. Additional differential diagnoses in infants include hereditary conditions such as epidermolysis bullosa, epidermolytic ichthyosis, and bullous mastocytosis.

MANAGEMENT STRATEGY

Treatment includes antibiotic therapy in combination with supportive measures addressing electrolyte and fluid balance, temperature regulation, nutrition, analgesia, and skin care. Bland emollients such as 50:50 white soft paraffin/liquid paraffin should be applied regularly to reduce friction and insensible fluid losses. Non-adherent dressings are used to cover denuded areas, with avoidance of adhesive tapes directly on skin. Systemic β -lactamase-resistant antibiotics are necessary to eradicate the causative *S. aureus* strain. Patients with extensive SSSS require intravenous antibiotics and in-hospital care provided by a multidisciplinary team experienced in delivering optimal skin care (e.g., on a burns unit). In view of the growing emergence of resistant ET-producing *S. aureus* strains, in particular MRSA and fusidic acid-resistant strains, antibiotic choice should be guided by local protocols/microbiology advice, which may be specifically targeted to cover MRSA in areas of high incidence. Clindamycin inhibits *S. aureus* toxin production and may be used in conjunction with the chosen treatment antibiotic, but is not recommended as monotherapy.

The spectrum of staphylococcal scalded skin syndrome: a case series in children. Mazori DR, Leonard A, Alexander JB, et al. Clin Exp Dermatol 2020; 45: 333–6.

The range of clinical presentations including mild and moderate variants of SSSS is described in four infants. A high level of suspicion for SSSS should be maintained in pediatric patients with any degree of periorificial, flexural, and/or acral desquamation, regardless of systemic toxicity. The presence of sterile lesions and some degree of exanthem helps differentiate even mild SSSS from bullous impetigo, which may progress to SSSS.

Epidemiology of staphylococcal scalded skin syndrome in US adults. Silverberg J. J Am Acad Dermatol 2018; 79: 774–6.

A retrospective study conducted using the US Nationwide Inpatient Sample database of adults admitted to hospital with a diagnosis of primary and secondary SSSS between 2008 and 2012,

indicating an incidence of 0.98 per million within this cohort. No seasonal variation was seen. The incidence appears to be increasing over time.

Staphylococcal-scalded skin syndrome: evaluation, diagnosis and management. Leung AKC, Barankin B, Leong KF. *World J Paediatr* 2018; 14: 116–20.

An up-to-date summary of SSSS, including epidemiology, pathophysiology, presentation, management, and treatment.

SSSS outbreaks on maternity and neonatal units are reported. Strict infection control measures are advisable, including patient isolation, barrier nursing, and scrupulous handwashing. Screening programs may identify *S. aureus* carriers among contacts, including healthcare workers. Colonized individuals require treatment with topical antiseptics (e.g., chlorhexidine) with nasal carriage eradicated by topical antibiotics such as mupirocin.

Nosocomial staphylococcal scalded skin syndrome caused by intraarticular injection. Emberger M, Koller J, Laimer M, et al. *J Eur Acad Dermatol Venereol* 2011; 25: 227–31.

Nosocomial outbreak of SSSS in three patients on NSAIDs who received intraarticular injections by an orthopedic surgeon with confirmed ET-producing *S. aureus* nasal colonization.

Nosocomial outbreak of staphylococcal scalded skin syndrome in neonates: epidemiologic investigation and control. El Helali N, Carbonne A, Naas T, et al. *J Hosp Infect* 2005; 61: 130–8.

SSSS outbreak affecting 13 neonates in a maternity unit; temporary removal from duty of a nurse with chronic hand dermatitis confirmed as a carrier of the causative ET-producing *S. aureus*. Infection control measures (patient isolation, barrier nursing, chlorhexidine handwashing, treatment of carriers with nasal mupirocin, and chlorhexidine showers) controlled the outbreak. All affected neonates were successfully treated with oxacillin.

Healthcare workers are an important potential source in outbreaks.

Specific Investigations

- Nose, throat, conjunctival, umbilical, rectal, and skin swabs for bacterial culture and sensitivities
- Culture from suspected site of primary infection
- Polymerase chain reaction (PCR) for rapid detection and characterization of SSSS-associated *S. aureus*
- Blood cultures
- Full blood count
- Serum urea, creatinine, and electrolytes
- Skin biopsy or frozen section of blister roof
- Dermoscopy
- Screening contacts for *S. aureus* carriage

Isolating *Staphylococcus aureus* from children with suspected staphylococcal scalded skin syndrome is not clinically useful. Ladhani S, Robbie S, Chapple DS, et al. *Pediatr Infect Dis J* 2003; 22: 284–6.

PCR for *ETA* and *ETB* genes and Western blotting confirmed ET-producing strains in only 17 of 54 (31%) isolates over a 4-year study period.

Failure to isolate ET-producing S. aureus from affected skin does not exclude the diagnosis of SSSS.

Staphylococcal scalded skin syndrome in an extremely low-birth-weight neonate: molecular characterization and rapid

detection by multiplex and real-time PCR of methicillin-resistant *Staphylococcus aureus*. Shi D, Ishii S, Sato T, et al. *Pediatr Int* 2011; 53: 211–7.

Multiplex and PCR assays were developed to target five virulence genes (*ETA*, *ETB*, *ETD*, *PVL*, *CNA*), aiming at rapid detection of SSSS-associated MRSA.

Adult case of staphylococcal scalded skin syndrome differentiated from toxic epidermal necrolysis with the aid of dermoscopy. Miyashita K, Ogawa K, Iioka H, et al. *J Dermatol* 2016; 43: 842–3.

Dermoscopy as a diagnostic tool was utilized to demonstrate superficial level of cleavage at a fresh exfoliation site; subcorneal detachment was subsequently confirmed histologically.

Nosocomial outbreak of staphylococcal scalded skin syndrome in neonates in England, December 2012 to March 2013. Paranthaman K, Bentley A, Milne LM, et al. *Euro Surveill* 2014; 19: 1–7.

A healthcare worker with chronic hand dermatitis was identified as the source of the outbreak after mass screening involving multisite swabbing and pooled, enrichment culture.

First-Line Therapy

- β -Lactamase-resistant penicillins (e.g., flucloxacillin, **D** oxacillin)

Antibiotic sensitivity and resistance patterns in pediatric staphylococcal scalded skin syndrome. Braunstein I, Wanat KA, Abuabara K, et al. *Pediatr Dermatol* 2014; 31: 305–8.

This retrospective study of 21 culture-confirmed SSSS cases at the Children's Hospital of Philadelphia between 2005 and 2011 reports 86% oxacillin-susceptible and 52% clindamycin-resistant SSSS cases.

Mild staphylococcal scalded skin syndrome: an underdiagnosed clinical disorder. Hubiche T, Bes M, Roudiere L, et al. *Br J Dermatol* 2012; 166: 213–5.

Five children, age range 7–48 months, with a mild form of SSSS devoid of systemic symptoms, were successfully treated with intravenous oxacillin (100 mg/kg daily); one patient had additional gentamicin.

Second-Line Therapy

- Glycopeptide antibiotic (e.g., vancomycin) **E**

Emergence of *Staphylococcus aureus* carrying multiple drug resistance genes on a plasmid encoding exfoliative toxin B. Hisatsune J, Hirakawa H, Yamaguchi T, et al. *Antimicrob Agents Chemother* 2013; 57: 6131–40.

ETB-producing *S. aureus*, including MRSA strains, causing impetigo/SSSS is more prevalent in Japan than in Western countries. Reports indicate a significant increase in strains resistant to β -lactams, erythromycin, and gentamicin in Japan.

Staphylococcal scalded skin syndrome in the course of lupus nephritis. Rydzewska-Rosolowska A, Brzosko S, Borawski J, et al. *Nephrology* 2008; 13: 265–6.

An adult with systemic lupus erythematosus, antiphospholipid syndrome, and chronic renal failure receiving pulsed

cyclophosphamide and prednisolone developed SSSS due to MRSA. She recovered with intravenous vancomycin therapy (750 mg every 48 hours).

A reduced vancomycin dosage is required in renal failure.

Staphylococcal scalded skin syndrome in an adult due to methicillin-resistant *Staphylococcus aureus*. Ito Y, Yoh MF, Toda K, et al. *J Infect Chemother* 2002; 8: 256–61.

An adult with diabetes mellitus and metastatic renal cell carcinoma who developed cholecystitis and SSSS due to ET-producing MRSA was successfully treated with a combination of intravenous vancomycin and teicoplanin and percutaneous transhepatic gallbladder drainage.

Third-Line Therapies

• Cephalosporins	D
• Aminoglycosides	D
• Pooled human immunoglobulin	E
• Fresh-frozen plasma	E
• Skin substitute dressings	E
• Plasma exchange	E

Staphylococcal scalded skin syndrome in neonates: an 8-year retrospective study in a single institution. Li MY, Wei GH, Qiu L. *Pediatr Dermatol* 2014; 31: 43–7.

Thirty-nine neonates were successfully treated at a southwest Chinese neonatal unit between 2004 and 2012 for clinically diagnosed SSSS. Four received a cephalosporin (50–100 mg/kg/day), two a β -lactam (50–100 mg/kg/day), 24 both cephalosporin and β -lactam (50–100 mg/kg/day), five vancomycin (20 mg/kg/day), and four gammaglobulin in addition to cephalosporin and β -lactam. Median days of hospitalization were longer for immunoglobulin therapy.

Staphylococcal scalded skin syndrome as a harbinger of late-onset staphylococcal septicemia in a premature infant of very low birth weight. Hütten M, Heimann K, Baron JM, et al. *Acta Derm Venereol* 2008; 88: 416–7.

A preterm (29 weeks' gestation), extremely low-birthweight (985 g) male infant developed SSSS (ET-A- and ET-B-producing MSSA strain) at 37 days with systemic symptoms and was successfully treated with intravenous cefuroxime (100 mg/kg) in an incubator with high air humidity, minimal handling, and 100% maintenance fluid plus the Parkland correction for a 15% epidermal loss.

Neonatal staphylococcal scalded skin syndrome: clinical and outbreak containment review. Neylon O, O'Connell NH, Slevin B, et al. *Eur J Pediatr* 2010; 169: 1503–9.

Five neonates were successfully treated for MSSA ET-A-mediated SSSS with flucloxacillin and gentamicin given intravenously for a mean of 5.8 days followed by a mean of 3.8 days of oral flucloxacillin.

Adult staphylococcus scalded skin syndrome in a peritoneal dialysis patient. Suzuki R, Iwasaki S, Ito Y, et al. *Clin Exp Nephrol* 2003; 7: 77–80.

An adult undergoing peritoneal dialysis developed acute peritonitis initially treated with intraperitoneal and intravenous vancomycin (0.5 g/day each, 1 g/day total). He subsequently developed SSSS with septic shock and was successfully treated with intravenous amikacin (100 mg/day) for 1 day followed by cefoperazone with sulbactam.

Staphylococcal scalded skin syndrome in an extremely premature neonate: a case report with a brief review of the literature. Kapoor V, Travadi J, Braye S. *J Pediatr Child Health* 2008; 44: 374–6.

A premature neonate with SSSS was successfully treated with intravenous flucloxacillin and a single dose of intravenous immunoglobulin 1 g/kg in view of transient low immunoglobulin G (IgG) levels.

Severe staphylococcal scalded skin syndrome in children. Blyth M, Estela C, Young ER. *Burns* 2008; 34: 98–103.

Four children with severe SSSS were successfully treated with a regimen including intravenous penicillinase-resistant penicillin and fresh-frozen plasma, postulated to possess antitoxin properties.

An innovative local treatment for staphylococcal scalded skin syndrome. Mueller E, Haim M, Petnehazy T, et al. *Eur J Clin Microbiol Infect Dis* 2010; 29: 893–7.

The benefits of a synthetic copolymer wound dressing (Suprathel, based on DL-lactic acid) are illustrated in a 14-month-old boy with whole-body skin denudation secondary to severe SSSS. The dressing reportedly relieves pain, prevents heat loss and secondary infection, and accelerates wound healing. It is transparent, allowing wound inspection without removal of the dressing, and is cost-effective.

Use of skin substitute dressings in the treatment of staphylococcal scalded skin syndrome in neonates and young infants. Baartmans MGA, Docter J, den Hollander JC, et al. *Neonatology* 2011; 100: 9–13.

The use of skin substitutes such as Omiderm, a water vapor-permeable polyurethane membrane, and Suprathel as valuable adjuvant treatments in severe SSSS is described in seven infants.

Optimal skin care with supportive topical treatments provided by an experienced multidisciplinary team is essential (e.g., on a burns unit).

Adult staphylococcal scalded skin syndrome successfully treated with plasma exchange. Kato T, Fujimoto N, Nakanishi G, et al. *Acta Derm Venereol* 2015; 95: 612–3.

A 68-year-old man with infective endocarditis and MRSA sepsis was initially treated with intravenous immunoglobulin, methylprednisolone, and daptomycin for presumed toxic epidermal necrolysis. The skin desquamation improved after plasma exchange therapy. SSSS was diagnosed retrospectively upon skin histology and bacterial culture results.

Steatocystoma multiplex

Rabindranath Nambi, Ian H. Coulson



Steatocystoma multiplex represents a benign hamartomatous malformation of the pilosebaceous unit. Although probably genetically heterogeneous, steatocystoma multiplex often demonstrates an autosomal-dominant pattern of inheritance. Some pedigrees have demonstrable keratin 17 abnormalities. Clinically, 2–15-mm firm, white, and skin-colored dermal cysts are seen on the trunk, proximal limbs, axilla, face, and scalp. Rare variants may be seen on vulva and palms. An oily white liquid can be expressed from many cysts. The adolescent age of onset suggests a hormonal basis. These are true sebaceous cysts: they contain sebum, and sebaceous gland lobules are present in their walls. Overlap with eruptive vellus hair cysts and an association with pachyonychia congenita type II have been reported. Some cases may be associated with persistent primary dentition.

MANAGEMENT STRATEGY

The cysts persist indefinitely. Although usually a minor cosmetic problem, they can be highly disfiguring. Paradoxically, those patients who would benefit most from treatment are sometimes regarded as being unsuitable for surgery because they have too many cysts to excise. The *surgical* technique described later is quick and can be used on large numbers of lesions in one session. It produces good cosmetic results.

Lesions can become inflamed due to rupture of the cyst wall, with leakage of the contents into the dermis, or because of secondary bacterial infection. Suppuration and scarring may follow. The

clinical picture then resembles cystic acne and is called *steatocystoma multiplex suppurativum*. Oral isotretinoin is an effective treatment for inflammatory lesions but not for non-inflamed cysts. This suggests it operates by a direct antiinflammatory effect rather than by reducing the sebum excretion rate. Alternatively, inflamed cysts can be treated with *incision and drainage*, *intralesional triamcinolone*, *tetracycline* 1 g/day, or *minocycline* 100–200 mg/day.

Topical treatment is largely ineffective because it does not penetrate to reach the cyst wall.

Specific Investigations

- Skin biopsy if diagnosis is in doubt
- Keratin gene testing

A novel mutation (p. Arg94Gly) of keratin 17 in a Chinese family with steatocystoma multiplex. Zang D, Zhou C, He M, et al. *Eur J Dermatol* 2011; 21: 142–4.

Steatocystoma multiplex, oligodontia and partial persistent primary dentition associated with a novel keratin 17 mutation. Gass JK, Wilson NJ, Smith FJ, et al. *Br J Dermatol* 2009; 161: 1396–8.

First-Line Therapies

Lesions not inflamed

- Surgical incision and extraction of cyst wall **D**

Inflamed lesions

- Isotretinoin **D**
- Antibiotics **E**
- Incision and drainage **E**

Steatocystoma multiplex suppurativum: treatment with isotretinoin. Schwartz JL, Goldsmith LA. *Cutis* 1984; 34: 149–53.

The treatment of steatocystoma multiplex suppurativum with isotretinoin. Statham BN, Cunliffe WJ. *Br J Dermatol* 1984; 111: 246.

Isotretinoin in the treatment of steatocystoma multiplex: a possible adverse reaction. Rosen BL, Broadkin RH. *Cutis* 1986; 115: 115–20.

Steatocystoma multiplex treated with isotretinoin: a delayed response. Mortiz DL, Silverman RA. *Cutis* 1988; 42: 437–9.

Treatment of steatocystoma multiplex and pseudofolliculitis barbae with isotretinoin. Friedman SJ. *Cutis* 1987; 39: 506–7.

Steatocystoma multiplex suppurativa: case report of a rare condition. Lima-Santana CNL, Pereira DN, Lisboa AP, et al. *An Bras Dermatol* 2016; 91(5 Suppl 1): 51–3.

These six papers report a total of seven patients treated with oral isotretinoin at a dose of approximately 1 mg/kg/day for about 20 weeks. Inflammation of cysts was greatly reduced. Non-inflammatory lesions were unaffected and in one patient appeared to increase in size and number. In one patient the dose was continued on a low dose of 30 mg daily for 12 months to maintain remission. One successfully treated patient relapsed 10

weeks after ceasing therapy, but other patients did not relapse during a follow-up period of up to 8 months.

Successful treatment of steatocystoma multiplex by simple surgery. Keefe M, Leppard BJ, Royle G. *Br J Dermatol* 1992; 127: 41–4.

Five generations with steatocystoma multiplex congenita: a treatment regimen. Pamoukian VN, Westreich M. *Plast Reconstr Surg* 1997; 99: 1142–6.

Surgical pearl: mini-incisions for the extraction of steatocystoma multiplex. Schmook T, Burg G, Hafner J. *J Am Acad Dermatol* 2001; 44: 1041–2.

A simple surgical technique for the treatment of steatocystoma multiplex. Kaya TI, Ikizoglu G, Kokturk A, et al. *Int J Dermatol* 2001; 40: 785–8.

Suggestion for the treatment of steatocystoma multiplex located exclusively on the face. Duzova AN, Senturk GB. *Int J Dermatol* 2004; 43: 60–2.

The vein hook successfully used for eradication of steatocystoma multiplex. Lee SJ, Choe YS, Park BC, et al. *Dermatol Surg* 2007; 33: 82–4.

Perforation and extirpation of steatocystoma multiplex. Madan V, August PJ. *Int J Dermatol* 2009; 48: 329–30.

These seven reports describe variants of a simple surgical technique for non-inflamed cysts. Local, regional, general, or no anesthesia is used, depending on the exact technique and the number of cysts being treated. In most cases, a 1- to 10-mm incision is made with a surgical blade, and the contents of the cyst are expressed; fine artery forceps are then passed through the opening to grasp the base of the cyst, which is pulled out. The incisions heal by secondary intention. Good cosmetic results and a very low recurrence rate are reported.

Excision of cysts and aspiration with an 18G needle have also been described.

Second-Line Therapies

• CO ₂ laser therapy	E
• Combination laser therapy	E

CO₂ laser therapy for steatocystoma multiplex. Krahenbuhl A, Eichmann A, Pfaltz M. *Dermatologica* 1991; 183: 294–6.
‘Fairly good’ results were reported.

1450-nm diode laser in combination with the 1550-nm fractionated erbium-doped fiber laser for the treatment of steatocystoma multiplex: a case report. Moody MN, Landau JM, Goldberg LH, et al. *Dermatol Surg* 2012; 38: 1104–6.

A single case report showing substantial clearance of chest and abdominal steatocystoma after two laser treatment sessions using two complementary lasers: a 1450-nm diode laser to target the abnormal sebaceous glands and a 1550-nm fractionated erbium-doped fiber laser to target the dermal cysts.

Carbon dioxide laser perforation and extirpation of steatocystoma multiplex. Bakkour W, Madan V. *Dermatol Surg* 2014; 40: 658–62.

A series of eight patients with multiple lesions treated by CO₂ laser puncturing of the cysts, followed by enucleation of the cyst contents with a Volkmann spoon. This resulted in high patient satisfaction and low recurrence rates, with minimal scarring.

Fractionated ablative carbon dioxide laser treatment of steatocystoma multiplex. Kassira S, Korta DZ, de Feraudy S, et al. *J Cosmet Laser Ther* 2016; 16: 1–12.

A 51-year-old woman with steatocystoma limited to the face who, after two treatments with a fractionated ablative carbon dioxide laser, remained free of cysts for 3 years.

Third-Line Therapies

• Cryotherapy	E
• Adalimumab	E

Treatment of lesions of steatocystoma multiplex and other epidermal cysts by cryosurgery. Notowicz A. *J Dermatol Surg Oncol* 1980; 6: 98–9.

Three or 4 days after cryotherapy, the necrotic skin overlying the cyst was removed and the intact cyst expressed through the opening.

Steatocystoma multiplex suppurativa associated with hidradenitis suppurativa successfully treated with adalimumab. Atzori L, Zanniello R, Pilloni L, et al. *J Eur Acad Dermatol Venereol* 2019; 33: 42–4.

Three patients who presented with a mixed clinical and histological picture of steatocystoma multiplex suppurativa and grade III hidradenitis were treated with a loading dose of adalimumab 160 mg, 80 mg at day 15, followed by 40 mg every week. Patients rapidly responded and had no new lesions at 18 months. Having failed previous treatments, this was an impressive response in both hidradenitis suppurativa and steatocystoma multiplex suppurativa lesions. The improvement in non-inflammatory lesions was unexpected and maintained at 18 months.

Stoma care

Calum C. Lyon



Stomas are artificial openings created to maintain proper drainage from internal structures. The most common are colostomies, ileostomies, and urostomies (ileal conduits), formed as either a temporary or a permanent measure. They are ideally produced electively, having been correctly sited by a stoma nurse specialist, but may be created under emergency conditions. Even with the best of preventative measures, dermatologic problems will occur in over 50% of patients at some time. These are mostly irritant reactions to body fluids, particularly in the higher-output stomas (ileostomy and urostomy), but a range of common skin disorders, infections, or any dermatosis exacerbated by trauma or irritation may also be seen (Table 232.e1 online).

MANAGEMENT STRATEGY

Although all irritant reactions share similar histological features, the clinical appearance depends on the type of stoma and the source of irritation. Ileostomies have a high output with a pH of nearly seven containing degradative enzymes and irritant bile acids, so severe dermatitis and erosions may be seen. Irritated colostomies generally have a milder dermatitis, often due to occlusion, but sizable

hypergranulating polyps and acanthomas can occur where there are leaks or irritation from ill-fitting appliances. Urostomy dermatitis may also be erosive because of the high output and ileal mucus production, predisposing to leaks. The pH may be higher than that of healthy skin, especially in the presence of urea-splitting bacteria and this can rapidly worsen skin irritation. Chronic papillomatous dermatitis is a distinct eruption comprising aggregating hyperplastic papulonodules that usually affects leaking urostomies. It responds to appliance modifications and acidification of the urine.

Input from an expert stoma nurse is essential when managing irritant reactions. They can advise on the most appropriate appliance so that mechanical trauma to the skin or stoma and exposure of normal skin to effluent can be avoided. Patients anxious to avoid leaks, smells, etc., sometimes wear bags too tightly or change them excessively, frequently resulting in skin damage and irritation. The stoma nurse specialist is trained to identify and resolve such issues.

It is appropriate to treat symptomatic irritant inflammation with antiinflammatory preparations such as *topical corticosteroids*, *tacrolimus*, or *pimecrolimus*. The choice of vehicle is very important, as oily creams, etc., will prevent proper adhesion and cause leaks. Products useful on peristomal skin include a range of foams, lotions, and gels formulated for scalp, ear, or eye disorders, and corticosteroid asthma inhalers. *Fludrocortide tape*, an occlusive corticosteroid therapy, can be particularly useful for smaller affected areas because the stoma device can be applied over the tape. Leaks and inflammation are sometimes inevitable despite appliance changes. It may be necessary to use topical antiinflammatories intermittently, with care taken to avoid steroid atrophy. Hypergranulation can be treated with silver nitrate, cryotherapy, or cautery ± shave or curettage.

Allergic contact dermatitis is rare, as ostomy manufacturers strive to minimize allergens in their products. When it occurs, it is mostly due to perfumed deodorizers and excipients in topical products (e.g., biocides in wet wipes). Usage tests are particularly helpful in identifying the offending product, even if patch testing fails to identify the precise allergen. Treatment is as for irritant reactions.

Skin infection is not uncommon in the moist and warm environment under a stoma bag, especially folliculitis in those who shave their abdomens. All rashes should be swabbed for culture and sensitivity, because bacterial infection can present as a non-specific dermatitis under occlusion, and preexisting rashes can become secondarily infected. Treatment involves careful hygiene and the use of specific antimicrobials.

Preexisting skin diseases that particularly affect stomas are psoriasis, seborrheic dermatitis, cutaneous Crohn disease, pyoderma gangrenosum, lichen sclerosus, and eczema.

Specific Investigations

- Skin biopsy
- Wound culture
- Patch testing and usage test

The spectrum of skin disorders in abdominal stoma patients. Lyon CC, Smith AJ, Griffiths CEM, et al. *Br J Dermatol* 2000; 143: 1248–60.

This large cohort study documented the many different types of skin disorders that can occur around a stoma. Initial evaluations for patients presenting with inflammation include a bacterial swab, because infections are relatively common and easy to treat. Allergic contact hypersensitivity is rare but should be suspected in any patient with persistent disease that is unresponsive to treatment. A biopsy should be performed for any peristomal skin disorder with ulceration or a papular component if the diagnosis is in question.

This is a comprehensive review discussing the various different pathologies that can occur with a stoma, and how to evaluate them.

A prospective audit of stomas – analysis of risk factors and complications and their management. Arumugam PJ, Bevan L, Macdonald L, et al. *Colorectal Dis* 2003; 5: 49–52.

Healthy peristomal skin is dependent on good surgical technique, with more problems being associated with short stomas (ileostomies <20 mm and colostomies <5 mm) and after emergency procedures. Body mass index (BMI) and diabetes are significantly associated with skin problems. Bleeding hypergranulation is more common in colostomies. Careful postoperative stoma nurse follow-up helps prevent skin problems.

The relevance of patch testing in peristomal dermatitis. Al-Niaimi F, Beck M, Almaani N, et al. *Br J Dermatol* 2012; 167: 103–9.

A subset of 149 patients from a cohort of 850 were patch-tested to a comprehensive series of potential allergens. Only seven of these had reactions of current relevance and most of these were to common fragrances and preservatives in stoma accessories rather than pouching systems.

First-Line Therapies

• Change/modify appliance	D
• Absorbent powders	D
• Antibiotics	D
• Topical corticosteroids	B

Dermatologic considerations of stoma care. Rothstein MS. *J Am Acad Dermatol* 1986; 15: 411–32.

Ill-fitting devices can cause stoma and skin irritation. The chemical irritation caused from the stomal effluent, mechanical irritation, and contact dermatitis can all be alleviated by replacing the stoma device at the earliest sign of irritation. Additionally, careful drying of the skin after washing and the use of absorbent powders at the time of device changes will alleviate irritation caused by intertrigo and ill-fitting devices.

Peristomal dermatoses: a novel indication for topical steroid lotions. Lyon CC, Smith AJ, Griffiths CEM, et al. *J Am Acad Dermatol* 2000; 43: 679–82.

This large clinical study demonstrated the benefits of treating inflammatory peristomal skin diseases at the time of device changes with topical corticosteroids formulated in an aqueous alcohol lotion. This formulation was found advantageous because it did not interfere with adhesion of the ostomy bag to the skin.

Beclometasone inhaler used to treat pyoderma gangrenosum. Chriba M, Skellett AM, Levell NJ. *Clin Exp Dermatol* 2010; 35(3): 337–8.

Treating peristomal pyoderma gangrenosum with topical crushed prednisone: a report of three cases. DeMartyn LE, Faller NA, Miller L. *Ostomy Wound Manage* 2014; 60(6): 50–4.

There is no ideal topical preparation applicable to stomas that is available 'off the shelf'. Lotions containing oils should be avoided and the patient should be warned that gel preparations containing propylene glycol should be left to dry for 10 minutes before placing their bag. Alcoholic scalp lotions can sting when applied to broken skin and can be applied to the bag directly and left to dry before fitting. Some patients, particularly those with longer stomas, are able to use creams or ointments applied to the peristomal skin for 30–60 min during which time the patient is inactive, and a stoma bag

is held in place over the stoma using a waist belt. The greasy medicament can then be cleaned from the skin and a bag applied normally. The potency of the steroid is increased under occlusion. Continuous daily treatment should be for no more than 4 weeks and thereafter no more than three times per week to avoid skin atrophy, but topical therapies are applied only as often as the device is changed.

Peristomal psoriasis. Marshall C, Woodmansey S, Lyon CC. *Clin Exp Dermatol* 2017; 42(3): 282–6.

Peristomal psoriasis accounts for approximately 5% of skin problems in a large cohort of stoma patients. Half of these had associated inflammatory bowel disease and most had psoriasis elsewhere. In most cases changing the appliance for a mostly hydrocolloid wafer and/or using intermittent topical steroid controlled the problem. Phototherapy or systemic treatment was required in 20% of cases.

Peristomal pyoderma gangrenosum: 12-year experience in a single tertiary referral centre. Toh JWT, Young CJ, Rickard M, et al. *ANZ J Surg* 2018; 88(10): E693–7.

Peristomal pyoderma gangrenosum affected approximately 10% of all stoma cases in a large series. The majority settled with topical medical treatment over a period of therapy up to 9 months. Recurrences were rare.

Second-Line Therapies

• Sucralfate	C
• Tacrolimus ointment or pimecrolimus cream	E
• Intralesional corticosteroids	C
• Surgical debridement and repair	D

Topical sucralfate in the management of peristomal skin disease: an open study. Lyon CC, Stapelton M, Smith AJ, et al. *Clin Exp Dermatol* 2000; 25: 584–8.

The authors demonstrated the ability of sucralfate to help treat peristomal erosions. Sucralfate is a basic aluminum salt of sucrose octasulfate that polymerizes in acidic environments, providing a viscous barrier on mucosal surfaces. Sucralfate was effective for erosions and irritation caused by either feces or urine. However, it was ineffective for peristomal pyoderma gangrenosum.

Peristomal pyoderma gangrenosum. Keltz M, Lebwohl M, Bishop S. *J Am Acad Dermatol* 1992; 27: 360–4.

A patient with peristomal pyoderma gangrenosum is described who responded well to intralesional corticosteroids. Intralesional triamcinolone acetonide 10 mg/cc was injected around the ulcer at 2-week intervals until reepithelialization.

The amount injected is determined by the size of the ulcer, and the frequency of injection can be adjusted depending on response. This article also discusses the difficulties in diagnosing peristomal pyoderma gangrenosum.

Risk factors and treatment outcomes of peristomal pyoderma gangrenosum in patients with inflammatory bowel disease. Wang J, Prenner J, Wang W, et al. *Aliment Pharmacol Ther* 2020; 51: 1365–72.

Female sex, raised BMI, and stoma bag waist belts were associated with increased risk of developing peristomal pyoderma gangrenosum (PPG). Most PPG cases resolved after treatment with the highest rates of complete resolution seen with anti-TNF agents and surgical intervention unlike for some other studies looking at all cases, not just those associated with inflammatory bowel disease.

Peristomal lichen sclerosis (LS): the role of occlusion and urine exposure? Al-Niaimi F, Lyon C. Br J Dermatol 2013; 168(3): 643–6.

Nine of 12 patients required intralesional corticosteroids to achieve complete resolution of active LS.

Topical tacrolimus in the management of peristomal pyoderma gangrenosum. Lyon CC, Stapelton M, Smith AJ, et al. J Dermatol Treat 2001; 12: 13–7.

Topical tacrolimus (0.3% in carmellose sodium paste) in conjunction with other treatments was found to rapidly heal pyoderma gangrenosum.

Third-Line Therapies	
• Botulinum toxin	C
• Oral dapsone	E
• Ciclosporin	D
• Tumor necrosis factor-blocking drugs	E
• Collagen injections	E
• Lipectomy/fat transfer	E
• Stoma revision surgery	E

Paraileostomy recontouring by collagen sealant injection: a novel approach to one aspect of ileostomy morbidity.

Report of a case. Smith GH, Skipworth RJ, Terrace JD, et al. Dis Colon Rectum 2007; 50: 1719–23.

Peristomal dermal deformity, such as skin creasing, impairs appliance placement. A dermal contour defect was successfully treated with intradermal injections of collagen.

Botulinum neurotoxin A is an effective treatment for irritant dermatitis caused by ostomy leaks in patients with retractile stomas. Bhoyrul B, Ondhia D, Lyon C. Br J Dermatol 2019; 181(3): 629–31.

Botulinum toxin A injection into stoma muscle will effectively prevent leaks in retractile ileostomies or urostomies that shorten spasmodically. It will not make a fixed, short stoma longer. This includes all colostomies so that patient selection is important.

Autologous fat grafting as a novel approach to parastomal soft-tissue volume deficiencies. Wu RC, et al. Plast Reconstr Surg Glob Open 2014; 2: e123.

Suction lipectomy or autologous fat grafting can correct leakage from ill-fitting appliances by smoothing the skin contours, thereby allowing for better adhesion.

Table 232.e1 Peristomal skin disorders according to primary source

Source of skin problems	Examples	Effects on skin
Appliance (pouch)	Chronic occlusion (common) Potential allergens or irritants (very rare) in appliances such as adhesives and tackifiers	Damage to skin barrier function resulting in dermatitis
Accessories: (1) pastes (fillers); (2) wet cleansing wipes; (3) deodorizing sprays; (4) skin barrier wipes/lotions; (5) adhesive removers	Irritant contact dermatitis (ICD) Allergic contact dermatitis (ACD)	ICD, e.g., alcohol in pastes and wipes, karaya (powder and pastes) ACD, especially fragrances or preservatives
Stoma effluent where there are leaks	Urine, especially if infection is present, which raises pH (urea-splitting bacteria) Stool, particularly where the constituency is more liquid, or volume produced is high. More proximal stomas will produce larger volume with greater enzymic content and higher pH. <i>Measures to thicken the stool should be considered including diet advice and antimotility drugs, e.g., loperamide</i>	Irritant reactions including dermatitis, granulomas, and chronic papillomatous dermatitis
Stoma	Type: loop stomas are associated with more skin complications Structural integrity: short, buried, or prolapsed stomas are more prone to leaks	As above
Skin	Genetic problems (rare), e.g., ichthyotic or bullous disorders Common, acquired disorders such as eczema or psoriasis can present atypically under occlusion. Rarer disorders may be more frequent than expected because of the population affected, e.g., pemphigoid in older patients with colostomies and pyoderma gangrenosum in young adults with ileostomies for inflammatory bowel disease	Any inflammatory or scaly skin disease may impair bag adhesion and cause leaks that precipitate irritant reactions that in turn can worsen the primary skin problem
Infections	Dermatophyte, <i>Candida</i> , and viral infections present typically. Bacterial infections may mimic or secondarily affect common disorders such as eczema	Eroded dermatitis, folliculitis, and occasionally ulceration

Striae

Ezra Hazan, Hooman Khorasani



Striae distensae (SD), or stretch marks, are common skin lesions that are medically benign but may lead to cosmetic and psychological morbidity. SD are dermal scars that commonly result from stretching of the skin in susceptible individuals. They commonly appear symmetrically in skin tension lines on the abdomen, breasts, hips, and buttocks. Striae are common in teenagers undergoing their growth spurts and in overweight individuals as well as in pregnancy, which are termed striae gravidarum. Striae rubra (SR) represent early striae which are linear, red-to-violaceous patches or plaques that may be pruritic. Gradually, they become white, atrophic, linear, depressed patches, which are referred to as striae alba (SA). Extensive striae that are deeper and wider may be seen with long-term systemic corticosteroid use or Cushing syndrome. Striae are likely the result of a combination of factors, including genetic predisposition, mechanical stress (e.g., growth spurt, bodybuilding, pregnancy), and hormones (e.g., systemic glucocorticosteroids, excessive potent topical steroids). SD are considered permanent, although some fading may occur, especially in adolescent striae. Histologically, early striae show dermal edema with perivascular lymphocytes and, over time, epidermal and dermal atrophy develops.

MANAGEMENT STRATEGY

Treatments ranging from topical therapies to lasers and light-based devices have been investigated to improve SD. No treatment can completely eradicate SD, but an improvement in cosmetic appearance can be gained. Treatments aimed at increasing collagen production, decreasing redness in SR, and/or improving pigmentation in SA are the most utilized.

The goal of treatment is an acceptable aesthetic improvement, making realistic patient expectations essential. Currently, there is no 'gold standard' treatment, but a combination approach with earlier intervention may yield the best results.

Several studies have shown that *topical tretinoin* improves the appearance of striae. There are some conflicting reports, however. *Centella asiatica* appears better used as a prophylactic in a trial with pregnant women but has been combined with other ingredients like *onion extract*, *hyaluronic acid*, and *silicone*, showing variable results.

Other therapies, including *chemical peels*, *microdermabrasion*, *platelet-rich plasma (PRP)*, and *microneedling* (also known as *percutaneous collagen induction therapy*), have shown promising results. The authors are skeptical of lighter peels because they do not have sufficient dermal penetration.

Lasers can be more aggressive but do not necessarily improve efficacy. Caution about downtime and side effects like postinflammatory hyperpigmentation (PIH) must be taken when using certain devices. Both *ablative* and *non-ablative fractional lasers* have produced favorable results. *Radiofrequency devices* are gaining popularity and results are encouraging.

Vascular devices, including the 585-nm pulsed dye laser (PDL), neodymium-doped yttrium aluminum garnet (Nd:YAG), and intense pulsed light (IPL), have shown efficacy primarily in improving the redness of SR. UV light and xenon-chloride excimer laser have been used to stimulate pigmentation in SA with results that appear to be transient.

Specific Investigations

- Thorough history (weight changes, steroid use) and physical examination
- Skin biopsy (not generally necessary)
- Serum adrenocorticotrophic hormone, 24-hour urine free cortisol, plasma cortisol (if there's concern for Cushing syndrome)

The diagnosis and cause of striae are usually straightforward to elucidate. When the lesions are particularly severe and the cause is unknown, laboratory testing to exclude Cushing syndrome is advised. Occasionally, striae may be confused with linear focal elastosis, which are striae-like, asymptomatic, slightly palpable, yellow bands commonly found on the lower back of older adults. Hypermobile Ehlers-Danlos syndrome (hEDS) and Marfan syndrome are two important conditions to be aware of. Marfan syndrome presents with unusually distributed striae in a tall, young patient, and early diagnosis can help prevent fatal aortic aneurysm rupture. In hEDS, patients present with easy bruising, soft skin, and joint laxity, but unexplained striae may aid in the diagnosis.

First-Line Therapy

- Observation

E

Observation is the route that most people choose, especially in mild cases. Given the lack of reliable therapeutic modalities, their associated costs, and potential side effects, observation may be warranted in selected cases. Specifically, adolescent striae that appear after growth spurts may become less conspicuous over time. However, for most patients seeking improvement, observation is not recommended.

Adolescent striae. Ammar NM, Roa B, Schwartz RA, et al. *Cutis* 2000; 65: 69–70.

Second-Line Therapies

• Topical tretinoin	A
• Non-ablative fractional photothermolysis	A
• Ablative fractional photothermolysis	A
• Microneedling	B
• RF microneedling	B
• Poly-L lactic acid	E

Topical tretinoin (retinoic acid) improves early stretch marks. Kang S, Kim KJ, Griffiths CE, et al. *Arch Dermatol* 1996; 132(5): 519.

This double-blind, randomized, vehicle-controlled trial studied 22 patients who used either 0.1% tretinoin nightly ($n=10$) or vehicle ($n=12$) for 6 months. After 2 and 6 months of treatment, striae were significantly improved in the treatment group. At 6 months, mean length and width decreased in the treatment group, whereas they increased in the control group.

Treatment of striae distensae with nonablative fractional laser versus ablative CO₂ fractional laser: a randomized controlled trial. Yang YJ, Lee GY. *Ann Dermatol* 2011; 23: 481–9.

Twenty-four patients with abdominal SA were enrolled in a randomized, double-blind, split study. They were treated with 1550-nm fractional Er:glass laser (pulse energy [PE] of 50 mJ, spot density of 100 spots/cm², scan area of 5×10 mm) and ablative fractional CO₂ laser resurfacing (PE 40–50 mJ, spot density 75–100 spots/cm², scan area of 8×8 mm). Each half of the lesion was treated three times at 4-week intervals. Pain, PIH, and crusting were seen in both treatments but worse on the CO₂ side. Although no significant differences were seen between the two groups, clinical improvement was seen in 91% of patients. Patients reported 82% improvement with the non-ablative vs. 91% improvement with the ablative.

Treatment of striae distensae with fractional photothermolysis. Bak H, Kim BJ, Lee WJ, et al. *Dermatol Surg* 2009; 35: 1215–20.

In total, 22 Asian women were treated with two laser treatments (Fraxel SR1500) separated by 4 weeks at PE 30 mJ, density level of 6, and eight passes. Comparing pretreatment and 1-month posttreatment photos, six of 22 (27%) demonstrated marked improvement while the remaining 16 showed mild improvement. Outcomes were better in patients with white rather than red striae.

Treatment of striae distensae using an ablative 10,600-nm carbon dioxide fractional laser: a retrospective review of 27 participants. Lee SE, Kim JH, Lee SJ, et al. *Dermatol Surg* 2010; 36: 1683–90.

In this review, 27 women with striae were treated with one session of fractional CO₂ Ultrapulse Encore System's DeepFx mode at PE of 10 mJ and density of 2 (10% coverage) with spot diameter of 1–10 mm. Three months after treatment, 7.4% had grade 4 clinical improvement, 51.9% grade 3, 33.3% grade 2, and 7.4% grade 1. None of the participants showed PIH or worsening.

Microneedling treatment of striae distensae in light and dark skin with long-term follow-up. Alster TS, Li MK. *Dermatol Surg* 2020; 46: 459–64.

In this study, 25 consecutive patients with skin types I–V were treated for 1–3 sessions with a handheld microneedling device. The sessions were spaced 4 weeks apart and directed at SD on various body parts. All striae improved at least 50% after an average of 1.8 treatments, with 28% demonstrating greater than 75% improvement after an average of 2.5 treatments. No differences were noted in response with different skin phototypes and no depigmentation was noted.

Treatment of striae distensae with needling therapy versus CO₂ fractional laser. Khater MH, Khattab FM, Abdelhaleem MR. *J Cosmet Laser Ther* 2016; 28: 1–5.

One group of 10 female patients with striae were treated with a microneedle dermaroller (1.5 mm depth), and another 10 were treated with fractional CO₂ (spot diameter 1–10 mm according to lesion width, PE 100 watts, repetition rate of 20 Hz) monthly for three sessions. Nine of the 10 needle-treated patients showed some clinical improvement, whereas only five of the 10 CO₂-treated patients showed clinical improvement. The microneedling patients were significantly more satisfied.

An efficacy and safety of nanofractional radiofrequency for the treatment of striae alba. Pongsrihadulchai N, Chalermchai T, Ophaswongse S, et al. *K Cosmet Dermatol* 2017; 16(1): 84–90.

Thirty-three patients with skin types III–IV were treated for SA with three sessions at 4-week intervals with a nanofractional radiofrequency device (Venus Viva TM, Toronto, Canada). This study was assessor-blind and uncontrolled. From baseline to 4 weeks after the last treatment, total surface area was reduced from 6.41 to 2.55 cm² ($p < 0.001$); length and width were significantly reduced as well. PIH was noted in six patients.

Poly-L lactic acid for minimally invasive gluteal augmentation. Lin MJ, Dubin DP, Khorasani H. *Dermatol Surg* 2020; 46: 386–94.

In this case series, two patients were treated with poly-L lactic acid (Sculptra; Galderma, Lausanne, Switzerland) for gluteal augmentation. One patient received three monthly treatments with four vials and the other received two monthly treatments with three vials; 30-mL dilution was used for each vial. Anecdotally, the authors report improved gluteal rejuvenation with improvement in striae.

Third-Line Therapies

• 70% glycolic acid lotion	A
• Onion extract and <i>Centella asiatica</i> in a hyaluronic acid emollient	B
• Long-pulsed Nd:YAG laser	B
• Pulsed dye laser	B
• Intense pulsed light	B
• Radiofrequency device and PDL	B
• Platelet-rich plasma	B
• Platelet-rich plasma and microdermabrasion	B
• Excimer laser	C

A superficial texture analysis of 70% glycolic acid topical therapy and striae distensae. Mazzarello V, Farace F, Ena P, et al. *Plast Reconstr Surg* 2012; 129(3): 589e–90e.

A double-blind, controlled bilateral comparison study on 40 patients with SD. They applied 70% glycolic acid lotion (Neo-Strata Company, Inc., Princeton, United States) vs. placebo for 1–2 minutes on a monthly basis for six treatments. A significant

decrease in furrow width was noted after 6 months. Analysis was performed using a silicone replica where casts were analyzed by scanning electron microscopy and imaging software.

Evaluation of an onion extract, *Centella asiatica* and hyaluronic acid cream in the appearance of striae rubra. Draelos ZD, Gold MH, Kaur M, et al. *Skinmed* 2010; 8(2): 80–6.

A randomized, controlled, investigator-blinded study of 52 women with SR on their thighs applied an onion extract cream (Mederma for Stretch Marks, Merz Pharmaceuticals, LLC, Greensboro, United States) twice daily to one thigh and nothing to the other thigh for 12 weeks. There was a statistically significant improvement in overall appearance between the treated and untreated thighs at week 12. Change in size was not a studied end point. This was a company sponsored trial.

Comparison of the effectiveness of two fluences using long-pulsed Nd:YAG laser in the treatment of striae distensae. Histologic and morphometric evaluation. Elsaie ML, Hussein MS, Tawfik AA, et al. *Lasers Med Sci* 2016; 31(9): 1845–53.

Forty-five patients with skin types III–V were treated with two fluences (75 and 100 J/cm²) of a long-pulsed 1064-nm Nd:YAG laser for four sessions at 3-week intervals. A 15-ms pulse duration (PD) and 5-mm spot size (SS) were used. Comparing pretreatment and 3-month posttreatment photographs, there was statistically significant improvement in length and width of all striae. There was no statistical difference between the two fluences, but SR improved more with the 75 J/cm² and SA improved more with the 100 J/cm². Only 2.2% developed hyperpigmentation.

Treatment of striae rubra and striae alba with 585-nm pulsed-dye laser. Jimenez GP, Flores F, Berman B, et al. *Dermatol Surg* 2003; 29(4): 362–5.

Twenty patients (skin types II–VI) with SR (9) and SA (11) were treated with two sessions of 585-nm PDL (Cynosure 585 VLS, Chelmsford, United States), separated by 6 weeks. Striae were randomly selected for treatment and untreated control. Parameters included 10-mm SS with 10% overlap and 3.0 J/cm² (PD was not listed). There was no significant difference in the treated vs. control striae. Four of nine SR had a change in color (one which was considered complete), whereas all SA had no color change.

A comparative study of the effectiveness of intense pulsed light wavelengths (650 nm vs 590 nm) in the treatment of striae distensae. Al-Dhalimi MA, Abo Nasyria AA. *J Cosmet Laser Ther* 2013; 15(3): 120–5.

Twenty patients with SR and skin types III–IV were treated with an IPL device for five sessions at 2-week intervals. 590- and 650-nm filters were used to treat opposite sides. Fluences ranged from 13 to 15.5 J/cm². Two months posttreatment, there was significant reduction in length and width with both wavelengths. The 590-nm wavelength achieved greater patient satisfaction scores and better reduction in erythema.

Efficacy of pulsed dye laser versus intense pulsed light in the treatment of striae distensae. Shokeir H, El Bedewi A, Sayed S, et al. *Dermatol Surg* 2014; 40: 632–40.

Sixteen patients with SR and four with SA underwent treatment with PDL and IPL to different sides of their bodies. There were five treatments at 4-week intervals using 595-nm PDL (Cynosure, Chelmsford, United States) with 10-mm SS, 0.5 ms PD, energy density of 2.5 J/cm², and Fluorescence IPL (Medical Bio Care, Gothenburg, Sweden) using 565-nm, 10×20 mm SS, 50–70 ms PD, and energy density of 17.5 J/cm². Striae width was decreased and skin texture was improved after with both devices. SR gave a superior response with either PDL or IPL compared with SA.

Radiofrequency and 585-nm pulsed dye laser treatment of striae distensae: a report of 37 Asian patients. Suh DH, Chang KY, Son HC, et al. *Dermatol Surg* 2007; 33: 29–34.

Thirty-seven patients with abdominal SD were treated with one session of radiofrequency (Thermage Cool TC; Thermage Inc., Hayward, United States) using 53–97 J/cm² and with a 585-nm PDL device (V-star; Cynosure, Bedford, United States) using 3.0 J/cm², 0.5 ms PD, and 10-mm SS followed by two more session of PDL at 4-week intervals. At the 12-week follow-up, 89.2% showed 'good' or 'very good' improvement.

Platelet-rich plasma versus tretinoin in treatment of striae distensae: a comparative study. Gamil HD, Ibrahim SA, Ebrahim HM, et al. *Dermatol Surg* 2018; 44: 697–704.

Thirty patients with skin phototypes III–V with symmetric SD were enrolled in this randomized split design, evaluator-blinded study. One side was treated with double-spun PRP monthly for three sessions and the other with 0.05% tretinoin cream nightly. A KA-1000-80-2B low-speed centrifuge machine was used. The PRP side showed improvement in 86.6% of patients vs. 60% for tretinoin ($p < 0.015$). SR responded more than SA in both groups. Patient satisfaction was 90% with PRP vs. 60% with tretinoin, and 90% reported pain with PRP and 10% reported mild itching with tretinoin.

Comparison between the efficacy and safety of platelet-rich plasma vs. microdermabrasion in the treatment of striae distensae: clinical and histopathological study. Ibrahim ZA, El-Tatawy RA, El-Samongy MA, et al. *J Cosmet Dermatol* 2015; 14: 336–46.

Sixty-eight patients with SR and SA were randomly assigned to three treatment groups: intradermal injection of PRP alone, microdermabrasion (deep clean, EME-Italy) alone, or combination. Patients were treated every 2 weeks for a maximum of six sessions or until patient satisfaction was achieved. Clinical improvement based on before-and-after photographs was rated by two dermatologists. PRP was more effective than microdermabrasion, but the combination showed more rapid results than either treatment alone.

The 308-nm excimer laser in the darkening of the white lines of striae alba. Ostovari N, Saadat N, Nasiri S, et al. *J Dermatolog Treat* 2010; 21: 229–31.

Ten subjects were treated using an excimer laser on the white lines of striae. Dose was titrated up to an erythematous response for a maximum of 10 weekly sessions or until full repigmentation was achieved. Based on before-and-after photos, repigmentation was poor (0%–25%) or moderate (26%–50%) in 80% of patients.

Subacute cutaneous lupus erythematosus

Jan P. Dutz



Subacute cutaneous lupus erythematosus (SCLE) is a non-scarring, photosensitive variant of cutaneous lupus erythematosus (CLE). Patients can have annular or papulosquamous plaques or a morphologic combination that is characteristically in a sun-exposed distribution. Although SCLE does not scar, it can result in significant dyspigmentation.

MANAGEMENT STRATEGY

SCLE can be diagnosed clinically but should be confirmed with skin biopsy. The patient should have a careful history, physical examination, and laboratory studies directed at uncovering systemic manifestations of systemic lupus erythematosus (SLE). Historical details that could help uncover exacerbating factors or that could affect therapeutic choice should be obtained. There are few double-blind, placebo-controlled trials of drugs used in the treatment of SCLE. The goals of management are to treat current lesions and symptoms and to prevent lesion formation. This is done through a combination of patient education, sun protection, and topical and systemic therapies. Two excellent recent therapeutic reviews have been published.

S2k Guide for the treatment of cutaneous lupus erythematosus – guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). Kuhn A, Aberer E, Bata-Csörgö, et al. *J Eur Acad Dermatol Venereol* 2017; 31: 389–404.

Consensus guidelines on the treatment of patients with CLE by a European group of experts developed in 2014 including a treatment algorithm based on an extensive literature review.

Management of cutaneous manifestations of lupus erythematosus: a systematic review. Fairley JK, Oon S, Saracino AM, et al. *Semin Arthritis Rheum* 2020; 50: 95–127.

A systematic review of clinical trials and observational studies including five or more patients assessing the management of CLE.

The cornerstone of treatment of CLE includes using the safest drugs possible to achieve disease control. The most common therapies utilized include *photoprotection*, *topical corticosteroids*, *calcineurin inhibitors*, and oral *antimalarials*. Although systemic corticosteroids can be effective, steroid-sparing systemic agents (e.g., *methotrexate*, *mycophenolate mofetil*, *retinoids*, or *dapsone*) are preferred to avoid corticosteroid-associated side effects. CLE can affect quality of life. In addition to increased disease control, cosmetic agents used to camouflage lesions or dyspigmentation are important adjuncts.

SCLE can have numerous associations that need to be addressed, including more recalcitrant disease in the setting of tobacco use and a potential risk for neonatal lupus during pregnancy.

Up to 50% of patients with SCLE meet four or more of the criteria of the American College of Rheumatology for classification of SLE. However, they do so by fulfilling the criteria involving skin lesions, photosensitivity, and positive serologies. As a result, those classified as SLE typically only have mild systemic symptoms with major end organ damage occurring in <10%.

Up to 30% of SCLE is induced or exacerbated by a medication. Over 100 different agents have been reported, including anti-hypertensive agents, statins, antifungals, tumor necrosis factor inhibitors, antiepileptics, and proton pump inhibitors. A complete list of the patient's medications will assist in the exclusion of drug-induced SCLE. In the setting of treatment for cancer, SCLE can occur as a result of chemotherapy exposure, radiation exposure, or as a paraneoplastic syndrome itself.

There are controversial data regarding whether tobacco affects the effectiveness of antimalarial agents. However, multiple studies have reported that cigarette smokers have more severe disease and that a subset of these patients is more refractory to therapies. Hence, patients should be counseled on smoking cessation for the benefit of their skin as well as the increased risk of cardiovascular disease with SLE and possibly CLE.

Specific Investigations

- Ro/SSA antibody
- Exclude systemic disease
- Medication review
- Smoking status

First-Line Therapies

Local therapy

• Cosmetics	E
• Sunscreens, protective clothing, and sun avoidance	A
• High-potency corticosteroids	B
• Topical tacrolimus or pimecrolimus	A

Systemic therapy

• Antimalarials (hydroxychloroquine, chloroquine, ± the addition of quinacrine)	A

Photoprotective effects of a broad-spectrum sunscreen in ultraviolet-induced cutaneous lupus erythematosus: a randomized, vehicle-controlled, double-blind study. Kuhn A, Gensch K, Haust M, et al. *J Am Acad Dermatol* 2010; 64: 37–48.

Of the 16 CLE patients who had positive provocation study results to ultraviolet A (UVA) or UVB, 88% developed CLE lesions in the vehicle control area, whereas none developed lesions in the broad-spectrum, SPF 60, sunscreen-applied areas.

Discoid lupus erythematosus. Diagnostic features and evaluation of topical corticosteroid therapy. Roenigk HH Jr, Martin JS, Eichorn P, Gilliam JN. *Cutis* 1980; 25: 281–5.

Despite the longstanding use of high-potency topical corticosteroids as first-line therapy, this is the only randomized controlled trial examining the efficacy in CLE.

Efficacy of tacrolimus 0.1% ointment in cutaneous lupus erythematosus: a multicenter, randomized, double-blind, vehicle-controlled trial. Kuhn A, Gensch K, Haust M, et al. *J Am Acad Dermatol* 2011; 65: 54–64.

Significant improvement in all end points was noted in all CLE subtypes in a study of 30 patients after 4 and 8 weeks. The four patients with SCLE in this study improved, but this was not statistically significant compared with placebo.

Treatment of cutaneous lupus erythematosus with acitretin and hydroxychloroquine. Ruzicka T, Sommerburg C, Goerz G, et al. *Br J Dermatol* 1992; 127: 513–8.

In this multicenter, randomized controlled trial, 50% of patients treated with hydroxychloroquine (HCQ) improved at 8 weeks.

Low blood concentrations of hydroxychloroquine in patients with refractory cutaneous lupus erythematosus: a French multicenter prospective study. Francés C, Cosnes A, Duhaut P, et al. *Arch Dermatol* 2012; 148: 479–84.

In this study of 300 patients with CLE, blood HCQ concentrations greater than 755 ng/mL were associated with a better clinical efficacy.

Monitoring hydroxychloroquine (HCQ) blood concentrations may be an alternative to the use of a fixed dose of HCQ or to prescribing based on the patient's weight.

The effect of increasing the dose of hydroxychloroquine (HCQ) in patients with refractory cutaneous lupus erythematosus (CLE): an open-label prospective pilot study. Chasset E, Arnaud L, Costedoat-Chalumeau N, et al. *J Am Acad Dermatol* 2016; 74: 693–9.

Of 34 patients (11 with SCLE) who did not respond clinically to weight-based HCQ after 3 months, with HCQ blood level <750 ng/mL, increasing the dose to 600 mg/day resulted in clinical response in 26/34 (81%) of patients. This clinical response corresponded to HCQ levels of >750 ng/mL. Among responders, the daily dose of HCQ could be decreased to 400 mg/day in 73% of responders, with one-third of responders having sustained cutaneous improvement despite dose reduction, but the remaining two-thirds of the responders experiencing a relapse of CLE.

In patients on weight-based HCQ without response, one could attempt a short-term dose increase of HCQ if low HCQ blood levels are present, with the goal of reducing the dose. The former may increase the likelihood of eye toxicity if therapy at higher doses is prolonged. This study also suggests one might consider checking HCQ levels in recalcitrant patients.

Response to antimalarial agents in cutaneous lupus erythematosus: a prospective analysis. Chang AY, Piette EW, Foering KP, et al. *Arch Dermatol* 2011; 147: 1261–7.

Of 11 patients started on HCQ, 55% were responders. Of 15 patients who were non-responders to HCQ monotherapy, 67% gained response with the addition of quinacrine, as measured via cutaneous lupus erythematosus disease area and severity index (CLASI).

This report demonstrates the efficacy of combination therapy. The authors use the same algorithmic clinical approach to antimalarial treatment as outlined in this study. HCQ was dosed at 200–400 mg/day, and chloroquine was dosed at 250 mg/day for 5–7 days per week, both determined by ideal body weight. Quinacrine was dosed at 100 mg/day. If first-line HCQ treatment fails after 3–6 months, we add quinacrine. If HCQ–quinacrine treatment fails after 3–6 months (or the patient does not have access to a compounding pharmacy for quinacrine), we replace HCQ with chloroquine (± quinacrine). Of note, HCQ is first line due to less eye toxicity than chloroquine (but it is also less efficacious). Quinacrine is a great adjunct to either HCQ or chloroquine, as it does not add to eye toxicity. Use of the HCQ and chloroquine combination is contraindicated due to compounded eye toxicity. Quinacrine must be compounded, and chloroquine is becoming much harder to obtain.

Second-Line Therapies

Immunosuppressive agents

• Mycophenolate mofetil, enteric-coated mycophenolate sodium (mycophenolic acid)	B
• Methotrexate	D

Immunomodulators

• Oral retinoids	B
• Thalidomide, lenalidomide	B, C
• Dapsone	D

Mycophenolate sodium for subacute cutaneous lupus erythematosus resistant to standard therapy. Kreuter A, Tomi NS, Weiner SM, et al. *Br J Dermatol* 2007; 156: 1321–7.

In this prospective, open-label pilot study, 10 patients with recalcitrant SCLE were treated with enteric-coated mycophenolate sodium as monotherapy. They had statistically significant reductions in CLASI after 3 months of treatment (1440 mg/day). No serious side effects were noted.

This is the equivalent of 1000 mg twice daily of mycophenolate mofetil (MMF). Table 3 is a good summary of MMF (1–3 g/day) and enteric-coated mycophenolate sodium (720–2160 mg/day) efficacy in treating SCLE in multiple case reports and small studies. Pisoni et al. (2005) is the only report of a lack of MMF response in seven SLE/CLE patients (one of which had SCLE); however, patients failed to respond to a median of 4 (range 2–10) different CLE drugs, and treatment efficacy was determined after only 2 months of MMF therapy in 3/7 patients.

Typically MMF in the treatment of CLE is done in combination with antimalarials and topical therapies, with the goal of tapering to the lowest-needed dose/therapies. Authors typically have good response with MMF in patients who fail first-line therapies.

Methotrexate treatment for refractory subacute cutaneous lupus erythematosus. Kuhn A, Specker C, Ruzicka T, et al. *J Am Acad Dermatol* 2002; 46: 600–3.

Contains a summary of retrospective studies and reports from the literature of treatment with methotrexate (MTX), including

19 CLE patients (8 SCLE patients), with doses ranging from 10 to 25 mg/week.

In patients who fail antimalarials, MTX orally or subcutaneously once weekly is an option.

Efficacy and safety of methotrexate in recalcitrant cutaneous lupus erythematosus: results of a retrospective study in 43 patients. Wenzel J, Brähler S, Bauer R, et al. *Br J Dermatol* 2005; 153: 157–62.

A retrospective analysis of 43 treatment-refractory CLE patients (15 SCLE) treated with methotrexate 15–25 mg weekly. Improvement of CLE occurred in nearly all patients (42/43). *This is a large number of patients with excellent improvement. This agent has not been as successful in the patients the authors have treated, often necessitating the addition of combined antimalarial therapy, or transitioning to MMF, when MTX therapy fails.*

Case series from the 1980s and 1990s have shown successful treatment of CLE (mainly generalized and palmoplantar discoid lupus erythematosus [DLE], but also a series including SCLE) with azathioprine 100–150 mg daily. However, recent evidence suggests that azathioprine strongly promotes mutagenic photosensitivity to UVA (O'Donovan et al. 2005) and cutaneous malignancy (Cho HG et al. 2018) and thus long-term therapy should be minimized or the drug should be used with strict photoprotection.

Treatment of cutaneous lupus erythematosus with acitretin and hydroxychloroquine. Ruzicka T, Sommerburg C, Goerz G, et al. *Br J Dermatol* 1992; 127: 513–8.

In this randomized, double-blind, multicenter study, overall improvement was noticed in 13/28 (46%) of patients treated with acitretin 50 mg/day. The median duration of treatment was 56.5 days. Low-dose acitretin may be added to the therapy of patients with CLE refractory to combination antimalarial therapy as this combination has shown efficacy in hypertrophic CLE (Green and Pasternak 2012).

Subacute cutaneous lupus erythematosus: report of a patient who subsequently developed a meningioma and whose skin lesions were treated with isotretinoin. Richardson TI, Cohen PR. *Cutis* 2000; 66: 183–8.

This is a good review of the literature regarding malignancy-associated SCLE (Table 1), as well as the use of acitretin and isotretinoin for CLE. Isotretinoin's efficacy has been seen in multiple case reports of three SCLE patients treated with 0.7–1 mg/kg with great response (D'Erme et al. 2012, Farner et al. 1990, Newtown et al. 1998). The response is often not durable, and low-dose maintenance therapy is needed. *Although use in SCLE is limited, it is still a valid option with the advantage of a shorter half-life than acitretin for women of childbearing age.*

Alitretinoin for cutaneous lupus erythematosus. Kuhn A, Patsinakidis N, Luger T. *J Am Acad Dermatol* 2012; 67: e123–6.

The patient with SCLE showed total clearance after 2 months of therapy with 30 mg/day.

Efficacy and tolerance profile of thalidomide in cutaneous lupus erythematosus: a systematic review and meta-analysis. Chasset F, Tounsi T, Cesbron E, et al. *J Am Acad Dermatol* 2018; 78: 342–50.

This is a comprehensive structured review of the use of thalidomide for the treatment of severe CLE documenting an overall response rate of 90%. This is coupled with significant adverse events such as peripheral neuropathy and thromboembolic events.

Thalidomide in the treatment of refractory cutaneous lupus erythematosus: prognostic factors of clinical outcome. Cortes-Hernandez J, Torres-Salido M, Castro-Marrero J, et al. *Br J Dermatol* 2012; 166: 616–23.

In this prospective observational study, 60 patients with refractory CLE (18 SCLE) on prednisone and antimalarials were treated with thalidomide 100 mg/day and followed for a mean of 8 years (range 2–18). Once complete clinical improvement was achieved, dose reduction to 50 mg daily, then 50 mg alternating days, occurred. In total, 98% achieved response, with 85% achieving complete response, typically within a mean of 8 weeks (range 3–16). Mean duration of therapy was 6 months (3–36 months). By the end of the 8 years, 70% who had attained complete remission had at least one relapse, whereas the rest (30%) remained in remission despite medication withdrawal after at least 8 years of follow-up. Neurologic symptoms occurred in 18% of patients (reported as high as 45% in retrospective studies) with nerve conduction studies being positive in half of the cases. Neurologic symptoms and signs on electromyography (EMG) resolved after 12 months (range 6–18) status postwithdrawal.

This is the first prospective thalidomide study utilizing CLASI to measure clinical response. Patients with SCLE had a lower relapse rate and required a lower cumulative dose and duration of therapy of thalidomide compared with other CLE subtypes.

Thalidomide (50–100 mg/day) has been shown to be highly efficacious in the treatment of CLE, including SCLE, and much less effective for SLE (can induce SLE flare). Numerous retrospective studies, and the previously mentioned prospective study, show on average 80% of patients achieving complete response. CLE responds quickly, beginning at 2–4 weeks, and doses can often be tapered lower after improvement. Thalidomide should only be used to treat severe, refractory CLE at the lowest dose possible. Studies have shown that starting with a low dose is as effective as higher doses but, unfortunately, has not been shown to reduce the incidence of neurotoxicity. Although highly efficacious, it is reserved as second-line therapy because of its cost, the degree of monitoring required, its teratogenicity, and adverse effects, including peripheral neuropathy. Thalidomide works well as a rescue medication or for maintenance at low or intermittent dosing (e.g., 25 mg every 2–3 days) to try and minimize toxicity.

Lenalidomide treatment of cutaneous lupus erythematosus: the Mayo Clinic experience. Kindle SA, Wetter DA, Davis MD, et al. *Int J Dermatol* 2016; 55(8): e431–9.

This is a retrospective analysis of nine patients with treatment-refractory CLE (six DLE, one SCLE) treated with lenalidomide 5–10 mg/day. Patients were refractory to at least one antimalarial and one immunosuppressive agent. Patients with lupus panniculitis (two) did not respond. Seven of nine DLE and SCLE patients achieved either complete or partial response, with the initial response occurring within 2–3 months.

Lenalidomide is a thalidomide derivative (both act by binding cereblon) with a better side effect profile than thalidomide. Lenalidomide is helpful in treating refractory CLE, similar to thalidomide, but with less associated sedation, constipation, peripheral neuropathy, and thrombophilic effects than with thalidomide. Similar to thalidomide, it does not work well in the treatment of SLE.

Dapsone as second-line treatment for cutaneous lupus erythematosus? A retrospective analysis of 34 patients and a review of the literature. Klebes M, Wutte N, Aberer E. *Dermatology* 2016; 232: 91–6.

This is a retrospective analysis of 34 CLE patients (8 with SCLE) treated with dapsone, most in combination with antimalarials,

over a 7-year period. The median dose of dapsone was 100 mg/day (50–125 mg/day) for a mean duration of 16 months (ranging 1–82 months). Forty-one percent of patients improved after 2 months, with 18% showing complete remission within 7 months. The best effect was seen in SCLE patients, with disease remission or improvement in six of eight patients. *Of note, no validated activity measurement tools were used. The authors also summarized the literature (case reports and retrospective analyses that include 137 CLE patients, of which seven are SCLE) in Table 1. Of seven SCLE cases in the literature, all had improvement or clearance with 25–150 mg/day dosing.*

Dapsone, given in doses of 25–200 mg daily, is especially effective in the treatment of bullous lupus, but case reports and case series have also shown usefulness in the treatment of CLE, especially SCLE lesions and the vasculitic lesions that may accompany SCLE.

Third-Line Therapies

• Intravenous immunoglobulin	D
• Cyclophosphamide	D
• Belimumab (anti-BLys monoclonal antibody)	E

Efficacy of intravenous immunoglobulin monotherapy in patients with cutaneous lupus erythematosus: results of proof-of-concept study. Ky C, Swasdibutra B, Khademi S, et al. *Dermatol Reports* 2015; 7: 5804.

In this open-label prospective study, 16 treatment-refractory CLE patients (subtypes not listed) were treated as monotherapy with intravenous immunoglobulin (IVIG) 2 g/kg/month for 3 months and followed for 6 months off the drug. The study showed rapid and persistent decreases in disease activity within a few weeks (as measured by CLASI). Three treatment cycles (3 months) were sufficient to achieve clinical response, but three patients had mild relapses.

In general, one could consider IVIG a bridge therapy while waiting for another systemic medication to take effect or to abort an acute flare. There have been a handful of prospective studies with positive results; however, De Pita et al. (1997) showed no improvement of refractory CLE with IVIG 1.5 g/kg/day (a lower dose) monthly for 1 year.

Pulse cyclophosphamide treatment for severe refractory cutaneous lupus erythematosus. Raptopoulou A, Linardakis C, Sidiropoulos P, et al. *Lupus* 2010; 19: 744–7.

Six patients with severe refractory SCLE were treated with monthly cyclophosphamide pulses, followed by azathioprine 100–200 mg/day as maintenance therapy. HCQ was continued as well. Significant improvement in CLASI was seen in all patients, with complete remission in four and partial remission in two patients. The authors report no relapses and no major adverse events in more than 3 years' follow-up.

Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains

in patients with systemic lupus erythematosus: combined results from two phase III trials. Manzi S, Sanchez-Guerrero J, Merrill JT, et al. *Ann Rheum Dis* 2012; 71: 1833–8.

In phase III trials, belimumab (approved for SLE) plus standard therapy showed improvement in mucocutaneous parameters, specifically rash, mucosal ulcers, and alopecia. It remains unclear how well belimumab works for CLE, as these studies employed SLE-specific rather than CLE-specific tools to assess activity and monitor outcomes.

Belimumab for the treatment of recalcitrant cutaneous lupus. Vashisht P, Borghoff K, O'Dell JR, et al. *Lupus* 2017; 26(8): 857–64.

In this open-label study of five patients (three with SCLE), there was a significant improvement in CLASI activity scores at an average time of 4 months, allowing tapering of prednisone.

Belimumab for refractory manifestations of cutaneous lupus: a multicenter, retrospective observational study of 16 patients. Salle R, Chasset F, Kottler D, et al. *J Am Acad Dermatol* 2020; 83(6): 1816–9.

In this retrospective case series of 16 patients with CLE refractory to antimalarial therapy, 75% had DLE and all were treated with belimumab. Half of the patients attained a CLASI-50 response suggesting that this drug may have activity in skin disease.

Successful treatment of arthritis and rash with tofacitinib in systemic lupus erythematosus: the experience from a single centre. You H, Zhang G, Wang Q, et al. *Annals of the Rheumatic Diseases* 2019; 78: 1441–3.

A role for Janus kinase inhibitors (JAKi) in the treatment of CLE is still unclear. This study reports on 10 patients with active SLE who were treated with add-on tofacitinib 5 mg BID for 1 year. There was improvement in skin disease in six patients, with uncertain efficacy in two and lack of response in one. Unfortunately, there was no description of CLE subtype of CLASI scoring. A further single report describes a patient with active SCLE despite prednisone and having failed multiple therapies responding to baricitinib 4 mg daily and allowing prednisone discontinuation (Fornaro 2019). However, a phase II trial of baricitinib 4 mg daily for SLE did not show a significant improvement in a subset of patients with skin disease using the CLASI score, possibly due to low baseline activity (Wallace 2018).

Trial of anifrolumab in active systemic lupus erythematosus (TULIP2). Morand EF, Furie R, Tanaka Y, et al. *NEJM* 2020; 382: 211–21.

This recent phase III trial demonstrated that intravenous anifrolumab (300 mg), an antibody to the type I interferon receptor subunit 1, given every 4 weeks results in a higher percentage of patients with a composite end point response in SLE at 1 year. Among patients with at least moderately active skin disease (CLASI ≥ 10) a reduction of 50% or more in CLASI at week 12 occurred in 24 of 49 patients receiving anifrolumab. A statistically significant improvement was maintained at 1 year. The type of CLE was not specified.

Subcorneal pustular dermatosis

Sarah Elyoussfi, Firas C. Kreeshan, Ian H. Coulson



Courtesy of Frederick A. Pereira, MD

Subcorneal pustular dermatosis is a rare, chronic, neutrophilic dermatosis of unknown etiology, in which flaccid pustules and vesicopustules arise in crops on truncal and flexural skin. The condition can occur at any age, more commonly in females. It usually follows a relapsing and remitting course, but generally the patient remains systemically well.

The condition may be difficult to differentiate from other vesiculopustular dermatoses. Some cases may be a variant of pustular psoriasis, whereas others appear to overlap with the subcorneal pustular variant of immunoglobulin A (IgA) pemphigus. In 'classical' subcorneal pustular dermatosis, immunofluorescence studies are negative; however, there are patients with identical clinical and histologic features that have intercellular IgA deposition in the upper epidermis targeting desmosomal components, most commonly desmocollins.

Subcorneal pustular dermatosis is associated with monoclonal immunoglobulin A (IgA) paraproteinemia and myeloma, which may occur many years after presentation. Other reported associations are pyoderma gangrenosum, inflammatory bowel disease, rheumatoid arthritis, infections (in particular *Mycoplasma pneumoniae*), and drugs.

MANAGEMENT STRATEGY

Dapsone is the treatment of choice (25–200 mg daily) and normally results in resolution of the rash within 4 weeks; the drug usually needs to be continued long term because relapse is common on withdrawal of therapy. After control is gained, the dose should be tapered to the lowest dose required to maintain

remission. Other sulfones (*sulfapyridine*, *salazosulfapyridine*) have also been found to be beneficial in isolated reports.

In a proportion of cases the response to dapsone is poor; *retinoids* (acitretin) can be used at an initial dose of 0.5–1.0 mg/kg daily and then reducing to the lowest dose that will maintain control. Alternatively, for those unable to tolerate dapsone in the dose required, retinoids have been added to dapsone; this has enabled lower doses of each to be used. There are a few case reports detailing good response to *phototherapy* – *psoralen and UVA* (PUVA), *narrowband UVB*, or *broadband UVB* – in combination with dapsone or retinoids.

Both *topical* and *systemic corticosteroids* have been reported in isolated cases to provide some degree of control. Unacceptably high doses of systemic corticosteroids may be required, but combination with other treatments may allow control with lower doses.

A number of *dapsone-resistant* cases have been treated with novel therapies such as *anti-tumor necrosis factor-alpha (TNF-α) inhibitors*, but experience with these newer agents is limited.

Subcorneal pustular dermatosis tends to run a chronic course. Maintenance of a continuing beneficial response may be difficult, as may be inferred from the extensive range of treatment options described.

Specific Investigations

- Full blood count
- Immunoglobulin levels
- Serum protein electrophoresis
- Bence Jones protein
- Autoantibodies
- Skin biopsy with immunofluorescence

Subcorneal pustular dermatosis: a review of 30 years of progress. Watts PJ, Khachemoun A. *Am J Clin Dermatol* 2016; 653–71.

The authors review the available literature from the past 30 years. They argue that no clinical or histological feature truly distinguishes subcorneal pustular dermatosis (SPD) from the annular variant of pustular psoriasis. They suggest that a reappraisal of SPD is required and it should be reclassified as a generalized form of pustular psoriasis.

Subcorneal pustular dermatosis: a clinical study of ten patients. Lutz ME, Daoud MS, McEvoy MT, et al. *Cutis* 1998; 61: 203–8.

Four of the seven patients in whom immunoglobulins were checked had paraproteinemia: three of IgA and one of IgG type; none of these patients had IgA deposits on direct immunofluorescence.

Subcorneal pustular dermatosis and episcleritis associated with poorly controlled ulcerative colitis. Wargo JJ, Adams M, Trevino J. *BMJ Case Rep* 2017 Jan 30; 2017: bcr2016218123.

A case of subcorneal pustular dermatosis associated with poorly controlled ulcerative colitis. The patient was started on dapsone; resolution of symptoms was reported with control of his ulcerative colitis.

Sneddon–Wilkinson disease in association with rheumatoid arthritis. Butt A, Burge SM. *Br J Dermatol* 1995; 132: 313–5.

Useful overview of all reported cases associated with either seronegative or seropositive arthritis.

Subcorneal pustular dermatosis triggered by *Mycoplasma pneumoniae*: a rare clinical association. Bohelay G, Duong TA, Ortonne N, et al. *J Eur Acad Dermatol Venereol* 2015; 29: 1022–5.

A case of subcorneal pustular dermatosis in association with *Mycoplasma pneumoniae* pneumonitis. Literature review identified seven cases associated with *M. pneumoniae*.

Subcorneal pustular dermatosis associated with *Coccidioides immitis*. Iyengar S, Chambers CJ, Chang S, et al. *Dermatol Online J* 2015; 21: 13030/qt35r6z6bx.

Subcorneal pustular dermatosis associated with *Coccidioides immitis*. Symptoms resolved promptly following initiation of systemic antifungal therapy.

Sneddon-Wilkinson disease induced by sorafenib in a patient with advanced hepatocellular carcinoma. Tajiri K, Nakajima T, Kawai K, et al. *Intern Med* 2015; 54: 597–600.

A case of subcorneal pustular dermatosis that developed after sorafenib administration. It improved after cessation of sorafenib and worsened by its readministration.

First-Line Therapy

- Dapsone

C

Subcorneal pustular dermatosis. Sneddon IB, Wilkinson DS. *Br J Dermatol* 1956; 68: 385–93.

Three of six patients responded to dapsone 50–100 mg daily.

Sneddon-Wilkinson disease in association with rheumatoid arthritis. Butt A, Burge SM. *Br J Dermatol* 1995; 132: 313–5.

A further five patients who responded to dapsone.

Subcorneal pustular dermatosis and IgA gammopathy. Burrows D, Bingham EA. *Br J Dermatol* 1984; 111: 91–3.

The addition of etretinate enabled control in a patient intolerant of higher-dose dapsone. *Acitretin starting at 25 mg daily could be substituted.*

Sneddon-Wilkinson disease. Four case reports. Launay F, Albes B, Bayle P, et al. *Rev Med Interne* 2004; 25: 154–9.

Three of four patients responded to dapsone.

Subcorneal pustular dermatosis in the pediatric age. Jardim MML, Ticianá Diniz ACB, Cunha TAC, et al. *An Bras Dermatol* 2018; 93: 116–8.

A 15-year-old female was successfully treated with dapsone (100 mg/day) with a significant improvement after 1 month.

Second-Line Therapies

- Sulfones
- Corticosteroids
- Acitretin
- PUVA
- Narrowband UVB
- Broadband UVB

D

D

E

D

E

E

Subcorneal pustular dermatosis. Sneddon IB, Wilkinson DS. *Br J Dermatol* 1956; 68: 385–93.

Two patients were controlled on sulfapyridine 1 g twice daily.

Sneddon-Wilkinson disease and monoclonal gammopathy of undetermined significance in the elderly: case report. Ceccarelli G, Molinelli E, Campanati A, et al. *Case Rep Dermatol* 2019; 11: 209–14.

A 92-year-old patient with concurrent IgG monoclonal gammopathy of undetermined significance (MGUS) was treated successfully with intravenous (IV) 3 mg betamethasone once daily and topical mometasone furoate. Betamethasone was tapered, and topical mometasone furoate was replaced by methylprednisolone aceponate after 2 weeks.

Role of tumor necrosis factor- α in Sneddon-Wilkinson subcorneal pustular dermatosis. Grob JJ, Mege JL, Capo C, et al. *J Am Acad Dermatol* 1991; 25: 944–7.

Methylprednisolone induced remission in this patient who failed to respond to dapsone, etretinate, or plasma exchange. A maintenance dose of 12 mg daily was required.

An unusual severe case of subcorneal pustular dermatosis treated with cyclosporine and prednisolone. Zachariae CO, Rossen K, Weismann K. *Acta Derm Venereol* 2000; 80: 386–7.

After failure with dapsone and prednisolone (because of abnormal liver enzymes), ciclosporin (400 mg daily) was substituted for dapsone; onset of resolution was swift, and ciclosporin was stopped after 3 weeks; prednisolone was slowly withdrawn over 2 months with no recurrence.

A case of subcorneal pustular dermatosis in association with monoclonal IgA gammopathy successfully treated with acitretin. Canpolat F, Akipinar H, Çevirgen C, et al. *J Dermatol Treat* 2010; 21: 114–6.

A patient who failed to respond to dapsone and topical corticosteroids subsequently responded to acitretin 25 mg daily within 2 weeks. This was reduced to 10 mg daily after 3 months and stopped after 4 months with no subsequent relapse.

Successful treatment of subcorneal pustular dermatosis (Sneddon-Wilkinson disease) by acitretin: report of a case. Marlière V, Beylot-Barry M, Beylot C, et al. *Dermatology* 1999; 199: 153–5.

This paper reviews the use of retinoids for subcorneal pustular dermatosis.

Subcorneal pustular dermatosis treated with PUVA therapy. Bauwens M, De Coninck A, Roseeuw D. *Dermatology* 1999; 198: 203–5.

A patient resistant to dapsone alone responded well to combination with PUVA. This paper contains a useful overview of PUVA therapy.

Subcorneal pustular dermatosis (Sneddon-Wilkinson disease) treated with narrowband (TL-01) UVB phototherapy. Cameron H, Dawe RS. *Br J Dermatol* 1997; 137: 150–1.

This patient was initially controlled with minocycline 200 mg daily and topical corticosteroids, but suffered a flare that was poorly responsive. Narrowband UVB (NB-UVB) phototherapy enabled corticosteroids to be withdrawn and control to be maintained with minocycline alone.

Subcorneal pustular dermatosis responsive to narrowband (TL-01) UVB phototherapy. Orton DI, George SA. *Br J Dermatol* 1997; 137: 149–50.

After long-term PUVA treatment this patient achieved a satisfactory response with NB-UVB phototherapy.

Third-Line Therapies

• Etanercept	E
• Infliximab	E
• Tacalcitol (1- α ,24-dihydroxyvitamin D ₃)	E
• Maxacalcitol (1- α ,25-dihydroxy-22-oxacalcitriol)	E
• Mizoribine	E
• Ketoconazole	E
• Tetracycline, minocycline	E
• Benzylpenicillin	E
• Vitamin E	E
• Mebhydrolin	E
• IV immunoglobulins	E
• Ciclosporin	E
• Pentoxifylline	E
• Nicotinamide	E

Pentoxifylline as a treatment for subcorneal pustular dermatosis. Falcone LM, Pilcher ME, Kovach RE, et al. *Dermatol Ther* 2019;32: 2

A woman was successfully treated with 400 mg oral pentoxifylline three times daily. It is felt to have some TNF- α inhibitor activity.

Complete remission of skin lesions in a patient with subcorneal pustular dermatosis (Sneddon-Wilkinson disease) treated with antimyeloma therapy: association with disappearance of M-protein. von dem Borne PA, Jonkman ME, van Doorn R. *Br J Dermatol* 2017; 176: 1341–4.

A male patient with SPD and concurrent IgA MGUS had been treated with dapsone for 20 years with frequent relapses. The patient was treated with high-dose melphalan with autologous stem cell transplantation. This resulted in a complete remission of the SPD.

A child with subcorneal pustular dermatosis responded to IVIG treatment (Sneddon-Wilkinson disease). Selcen K, Özlem B, Nesrin G, et al. *Reumatologia* 2017; 55: 323–7.

Intravenous immunoglobulin (IVIG) 600 mg/kg in a patient with IgG/IgM deficiency resulted in complete resolution of lesions.

Sneddon-Wilkinson disease treated with etanercept: report of two cases. Berk DR, Hurt MA, Mann C, et al. *Clin Exp Dermatol* 2009; 34: 347–51.

Two patients with refractory disease responded to etanercept 50 mg twice weekly (in combination with low-dose acitretin in one case).

Early but not lasting improvement of recalcitrant subcorneal pustular dermatosis (Sneddon-Wilkinson disease) after infliximab therapy: relationships with variations in cytokine levels in suction blister fluids. Bonifati C, Trento E, Cordiali Fei P, et al. *Clin Exp Dermatol* 2005; 30: 662–5.

Infliximab (antitumor necrosis factor alpha antibody): a novel, highly effective treatment of recalcitrant subcorneal pustular dermatosis (Sneddon-Wilkinson disease). Voigtlander C, Luffl M, Schuler G, et al. *Arch Dermatol* 2001; 137: 1571–4.

The case of SLE associated Sneddon-Wilkinson pustular disease successfully and safely treated with infliximab. Naretto C, Baldovino S, Rossi E, et al. *Lupus* 2009; 18: 856–7.

Three reports of initial, but in one case not sustained, benefit of infliximab given at standard doses.

Recalcitrant subcorneal pustular dermatosis and bullous pemphigoid treated with mizoribine, an immunosuppressive purine biosynthesis inhibitor. Kono T, Terashima T, Oura H, et al. *Br J Dermatol* 2000; 143: 1328–30.

Two patients responded to mizoribine (Bredinin) 150 mg daily: one to mizoribine alone, and the other with combined prednisolone 50 mg and mizoribine 150 mg daily.

Therapie der pustulosis subcornealis Sneddon Wilkinson mit tacalcitol. Muhlhoff C, Megahed M. *Hautarzt* 2009; 60: 360–70.

Two cases of topical vitamin D₃ leading to sustained resolution of lesions.

Successful treatment of subcorneal pustular dermatosis with maxacalcitol. Hoshina D, Tsujiwaki M, Furuya K. *Clin Exp Dermatol* 2016; 41: 102–3.

A case controlled with topical maxacalcitol (1- α ,25-dihydroxy-22-oxacalcitriol), a vitamin D₃ analog.

Ketoconazole as a therapeutic modality in subcorneal pustular dermatosis. Verma KK, Pasricha JS. *Acta Derm Venereol* 1977; 77: 407–8.

After failing to respond to dapsone, a patient achieved remission using ketoconazole 200 mg daily. Although this was initially started in conjunction with dapsone, withdrawal of ketoconazole led to a disease flare; the patient was subsequently satisfactorily controlled on ketoconazole alone.

Subcorneal pustular dermatosis (Sneddon-Wilkinson). Mandel EH, Gonzales V. *Arch Dermatol* 1969; 99: 246–7.

Tetracycline 250 mg four times daily controlled new pustule formation.

Subcorneal pustular dermatosis controlled by vitamin E. Ayres S, Mihan R. *Arch Dermatol* 1974; 109: 74.

Vitamin E (400 IU D- α -tocopheryl acetate), when added to prednisolone 40 mg daily, enabled the dosage of prednisolone to be reduced to 5 mg daily.

Subcorneale pustulose Sneddon-Wilkinson: therapie mit mebhydrolin. Dorittke P, Wassilew SW. *Z Hautkr* 1988; 63: 1025–7 [Article in German].

Treatment with mebhydrolin 50 mg three times daily was successful.

Subcorneal pustulosis with combined lack of IgG/IgM and monoclonal gammopathy type IgA/kappa. Rasch A, Schimmer M, Sander CA. *J Dtsch Dermatol Ges* 2009; 7: 693–6.

IVIG 0.2 g/kg in a patient with IgG/IgM deficiency resulted in complete resolution of lesions, with three weekly cycles maintaining remission.

Successful treatment of recalcitrant subcorneal pustular dermatosis with oral nicotinamide. Yamaguchi Y, Oyama N, Koizumi H, et al. *J Dermatol* 2019; 46(11): e438–40

A male patient was successfully treated with oral nicotinamide 1500 mg/day with 2 months of treatment. Once nicotinamide intake was stopped, the lesion recurred, but improved with 1000 mg/day oral nicotinamide. The dose of nicotinamide was tapered by 500 mg/day and finally withdrawn. His skin lesions did not recur thereafter.

Subcutaneous fat necrosis of the newborn

Muriel Sadlier, Elena Pope



Subcutaneous fat necrosis of the newborn (SCFNN) is an uncommon, self-limiting panniculitis that affects term or post-term infants in the first weeks of life. It is characterized by firm subcutaneous nodules and plaques over areas of fat distribution, predominantly the cheeks, trunk, buttocks, and proximal extremities. These may be flesh-colored, erythematous, or blue. Lesions vary in size from just a few millimeters to large coalescent plaques and can become calcified or fluctuant with liquefied fat. SCFNN generally follows a benign course and resolves spontaneously without residua over weeks to months, though atrophy of the skin or small pitted scars may develop.

The exact etiology of SCFNN is unknown. It is strongly associated with perinatal stress and as such is more common in infants delivered via caesarean section or who experienced birth trauma. Therapeutic hypothermia, which involves whole-body cooling of neonates to reduce the neurologic sequelae associated with birth asphyxia or improve outcomes during cardiac surgery, is a common iatrogenic cause.

The most serious complication of SCFNN is hypercalcemia, which occurs in up to half of patients. Detectable hypercalcemia usually occurs within 30–60 days following onset, as panniculitic lesions are resolving, but can occasionally precede the development of SCFNN.

Hypercalcemic infants may present with lethargy, irritability, hypotonia, poor feeding, vomiting, dehydration, constipation, polyuria, or failure to thrive. Seizures, renal failure, or cardiac arrest are the most serious sequelae. Persistent hypercalcemia can result in nephrolithiasis, or metastatic calcification in the brain, heart, skin, or gastric mucosa. Less common complications of SCFNN include thrombocytopenia, hypoglycemia, hypervitaminosis D, and hyperlipidemia.

MANAGEMENT STRATEGY

A clinical diagnosis can usually be made without the need for biopsy. Fine-needle aspiration of the subcutaneous lesions can

be done if there is diagnostic uncertainty. Typical histology shows a dense mononuclear cell infiltrate within the subcutaneous fat with needle-shaped clefts within adipocytes, and fat necrosis. Imaging is not required for diagnosis, though IT may help exclude other differential diagnoses. Total serum and ionized calcium should be measured at diagnosis, and again at 30, 45, and 60 days, or in any infant showing signs of hypercalcemia within 6 months of diagnosis. Parents should be counseled about symptoms of hypercalcemia and advised to attend a physician should their child develop these symptoms.

Children with mild hypercalcemia should have calcium levels checked weekly for 4 weeks, or until resolution of hypercalcemia. A renal ultrasound should be done in any infant who develops hypertension and considered in those with moderately or persistently elevated serum calcium.

Specific Investigations

- Serum and urine calcium
- Serial calcium measurements
- Renal ultrasound for nephrocalcinosis or nephrolithiasis (check blood pressure)
- Biopsy or fine-needle aspiration for diagnosis

Subcutaneous fat necrosis after moderate therapeutic hypothermia in neonates. Strohm B, Hobson A, Brocklehurst PA, et al. *Pediatrics* 2011; 128: e450–2.

The UK Total Body Hypothermia registry records patients who have therapeutic cooling for hypoxic ischemic encephalopathy. Over a 4-year period 12 patients developed SCFNN from 1239 cases registered ($\approx 1\%$).

The incidence of SCFNN in neonates who have therapeutic hypothermia ranges from 1% to 3%. Skin examination should be done regularly following treatment and parents should be advised of signs of SCFNN and hypercalcemia on discharge.

Subcutaneous fat necrosis of the newborn and associated hypercalcemia: a systematic review of the literature. Stefanko NS, Drolet BA. *Pediatr Dermatol* 2019; 36: 24–30.

This systematic review examined all published cases of SCFNN (126 infants) and the clinical course of those with hypercalcemia (51%). Hypercalcemia was detected within 60 days of onset of skin lesions in the vast majority of patients (95%), within 30 days of onset in 77% and at the time of onset of the skin lesions in 23%. Based on these findings the authors recommend screening for hypercalcemia at time of diagnosis and again at 30, 45, and 60 days. Resolution of hypercalcemia occurred within 28 days of detection in most patients (76%). Calcium levels should be checked twice weekly in patients with moderate hypercalcemia. Patients who are unwell and those with total serum calcium levels of ≥ 14 mg/dL or ionized calcium of ≥ 8 mg/dL should be monitored as inpatients as they are at risk of hypercalcemic crisis.

There are conflicting recommendations in the literature regarding screening for hypercalcemia in asymptomatic patients with SCFNN. Previous recommendations suggested weekly bloods for 6 weeks and continuing to monitor for up to 6 months following diagnosis but were not evidence-based.

Fine-needle aspiration as a method of diagnosis of subcutaneous fat necrosis of the newborn. Schubert PT, Razak R, Vermaak A, et al. *Pediatr Dermatol* 2016; 33: e220–1.

Fine-needle aspiration cytology is a simple bedside test that can be useful in cases with diagnostic uncertainty. The typical pathologic picture

includes clumped lobules of fat with opaque cytoplasm and/or necrotic aspirates of dispersed fat cells with opaque cytoplasm, foamy macrophages, multinucleated giant cells, lymphocytes and neutrophils, and the characteristic radially oriented and loose refractile needle-shaped crystals in the cytoplasm of the fat cells lying in the necrotic background.

Treatment of SCFNN is determined by the presence of hypercalcemia or hypercalciuria and should be undertaken in collaboration with a pediatric endocrinologist or nephrologist. The goals of therapy are to (1) correct dehydration; (2) enhance the renal excretion of calcium; and (3) inhibit intestinal absorption or bone resorption of calcium. First-line management of mildly elevated calcium involves dietary restriction of calcium (*low-calcium feeds*) and *avoiding vitamin D supplementation*. Breast milk is naturally low in calcium and vitamin D. If calcium continues to rise, *intravenous (IV) saline* and *furosemide* are used to promote excretion of calcium.

For moderate-to-severe hypercalcemia, prompt initiation of treatment is crucial. Adjuvant therapies include *calcitonin*, which reduces the serum calcium in the short term; *citrate*, which reduces stone formation during diuresis; and *oral corticosteroids*, which reduce the absorption of calcium in the gut, and decrease bone resorption and 1 α -hydroxylase activity in granulomatous lesions. There are increasing reports of the safe and effective use of *bisphosphonates* (*pamidronate* and *zoledronic acid*), which rapidly reduce osteoclast activity.

First-Line Therapies

- No treatment for the majority of patients **C**
- Low-calcium and low-vitamin D formulas **C**

Second-Line Therapies – if Hypercalcemic

- IV saline at 1.5 times the normal maintenance dose **D**
- Furosemide 1–1.5 mg/kg every 6–12 hours for 5 days **D**

Third-Line Therapies – for Hypercalcemia

- Oral or IV steroids (prednisone and methylprednisolone, 1–2 mg/kg/day for 5 days) **C**
- Subcutaneous calcitonin (4–8 IU/kg every 6–12 hours for 2–3 days) **D**
Note: use is limited by tachyphylaxis
- Bisphosphonates (pamidronate 0.25–0.5 mg/kg/dose for 2–4 days) **D**
- Zoledronic acid 0.025 mg/kg single dose

Pamidronate as first-line treatment of hypercalcemia in neonatal subcutaneous fat necrosis: a case series. Chesover AD, Harrington J, Mahmud FH. *Paediatrics & Child Health* 2019; 1–5.

In this retrospective series of 5 patients, pamidronate was used as first-line therapy for hypercalcemia at a dose of 0.25–0.5 mg/kg/day for 1–2 days without the use of furosemide or glucocorticosteroids. This resulted in faster normalization of serum calcium and reduced frequency of rebound hypercalcemia when compared with previous published cases that used furosemide followed by pamidronate therapy.

Use of zoledronic acid in a neonate with subcutaneous fat necrosis complicated with severe, refractory hypercalcemia. Militello MA, Re MP, Vitaliti G, et al. *Am J Perinatol.* 2019; 36: S134–8.

Zoledronic acid is a third-generation bisphosphonate with a 100- to 200-fold higher potency than pamidronate. A single low dose of zoledronic acid 0.025 mg/kg IV has been reported to result in rapid and persistent normalization of serum calcium in a handful of cases of SCFNN with refractory hypercalcemia. The advantage of zoledronic acid is that a single dose given over 30–40 min is sufficient to induce remission whereas multiple pamidronate infusions are required. Low initiation doses are recommended to prevent rebound hypocalcemia.

SURGICAL MANAGEMENT

Large, fluctuant, liquified nodules, or those complicated by hematoma, may be aspirated with a large bore needle for decompression, to prevent rupture, infection, and skin necrosis.

Surgical management of subcutaneous fat necrosis of the newborn required due to lack of improvement: a very rare case. Beuzeboc Gérard M, Aillet S, Bertheuil N, et al. *Br J Dermatol* 2014; 171: 183–5.

The authors describe a neonate who developed an extensive area of fat necrosis on her back following hypothermia for anoxic encephalopathy that failed to resolve. The fat liquified, resulting in a large swelling on the back. This was treated with multiple incision and drainage procedures, and curettage of the calcified cavities. She became hypercalcemic following the second procedure at 13 months of age, requiring treatment with intravenous fluids and furosemide.

While surgical intervention is rarely needed, this case highlights that manipulation of lesions may induce hypercalcemia. This should be monitored postoperatively.

Sweet syndrome

Asha Gowda, Karolyn A. Wanat, William D. James



Sweet syndrome is a neutrophilic dermatosis that clinically presents with the sudden onset of tender, well-demarcated, edematous, erythematous plaques or nodules on the face, neck, upper trunk, and/or extremities. A pseudovesicular or pustular morphology is possible. Patients can also develop fever, leukocytosis, arthralgias, myalgia, general malaise, and, infrequently, internal organ involvement. Histopathology shows a dense neutrophilic infiltrate in the upper dermis without evidence of primary leukocytoclastic vasculitis. Neutrophilic dermatosis of the dorsal hands is an anatomically limited subset of Sweet syndrome.

MANAGEMENT STRATEGY

Sweet syndrome is often idiopathic, but may be malignancy-associated (most commonly acute myelogenous leukemia, but also lymphomas, dysproteinemias, and carcinomas), drug-induced, or related to conditions such as inflammatory bowel disease, infection (commonly *Streptococcus* or *Yersinia*), radiation, and pregnancy. Workup includes skin biopsy, complete physical examination, and laboratory studies. Treatment of the underlying condition or discontinuation of the causative medication may lead to resolution of symptoms. The standard treatment is corticosteroids. Second- and third-line therapies may be effective for patients with contraindications to corticosteroids or recalcitrant disease. Necrotizing Sweet syndrome should be distinguished from the clinically-resembling necrotizing fasciitis, which has a drastically distinct approach to treatment.

Specific Investigations

- Complete blood count with differential
- Erythrocyte sedimentation rate or C-reactive protein
- Cultures as indicated by history and physical examination

Specific Investigations—cont'd

- Malignancy screening: age-appropriate screening, evaluation if hematologic abnormalities exist, and consideration of serum protein/serum immunofixation electrophoresis; bone marrow biopsy may be considered
- Pregnancy test (in women of childbearing potential)
- Medication history
- Skin biopsy

First-Line Therapies

• Oral corticosteroids	C
• Topical and intralesional corticosteroids	C

Sweet's syndrome: a review of current treatment options. Cohen PR, Kurzrock R. Am J Clin Dermatol 2002; 3: 117–31.

Corticosteroids (oral prednisone 0.5–1.5 mg/kg daily tapered over 4–6 weeks) results in rapid relief of systemic symptoms (1–2 days) and skin lesions (2–10 days). Relapse may occur.

High-potency topical and intralesional corticosteroids may be useful as monotherapy or adjuvant treatment for limited or mild disease.

Second-Line Therapies

• Potassium iodide	C
• Colchicine	C
• Indomethacin	C
• Pulse intravenous corticosteroids	D
• Dapsone	D
• Clofazimine	D
• Doxycycline	E
• Metronidazole	E

Potassium iodide in refractory, recurrent pediatric Sweet syndrome: guidance in dosing and monitoring. Tangtaco JA, Ho N, Drucker A, et al. Pediatr Dermatol 2018; 35: 271–3.

Supersaturated solution of potassium iodide (SSKI) dosing starts at three drops three times daily, is increased by one drop per dose up to 10 drops (500 mg) three times daily until clear, then tapered. SSKI, which is contraindicated in pregnancy, hyperkalemia, and renal disease, requires monitoring of laboratory values including electrolytes and renal and thyroid function tests.

Potassium iodide tablets (300 mg) are usually administered three times daily. Dilution of the liquid formulation or the capsule formulation may help reduce the bitter taste.

Long-term suppression of chronic Sweet's syndrome with colchicine. Ritter S, George R, Serwatka LM, et al. J Am Acad Dermatol 2002; 47: 323–4.

Successful treatment using 0.6 mg colchicine twice daily.

Colchicine 0.5 mg orally three times daily over 10–21 days was effective in 18 patients. Patients may experience gastrointestinal symptoms such as nausea and diarrhea that can improve with tapering.

Neutrophilic dermatosis of the dorsal hands treated with indomethacin. Kaur MR, Bazza MA, Ryatt KS. Br J Dermatol 2006; 154: 1089–90.

A patient treated with indomethacin 150 mg/day for 1 week followed by 100 mg/day for 2 weeks.

This dosing was effective in another study involving 18 patients. Seventeen patients responded within 48 hours without relapse.

Association of acute neutrophilic dermatosis and myelodysplastic syndrome with (6;9) chromosome translocation. Megarbane B, Bodemer C, Valensi F, et al. *Br J Dermatol* 2000; 143: 1322–4.

Pulse corticosteroid therapy successfully used for Sweet syndrome.

Intravenous methylprednisolone up to 1000 mg/day can be used for 3–5 days, followed by a taper of oral corticosteroids with or without another immunosuppressant.

Treatment of giant cellulitis-like Sweet syndrome with dapsone. Koketsu H, Ricotti C, Kerdel FA. *JAMA Dermatol* 2014; 150: 457–9.

Neutrophilic dermatosis of the dorsal hands: response to dapsone monotherapy. Ramos FS, Ferrera FR, Rabay FMO, et al. *An Bras Dermatol* 2018; 93: 730–2.

Two reports describing excellent response to dapsone 100 mg/day.

Alternatively, sulfapyridine 1–4 g/day can be used.

Sweet's syndrome in association with generalized granuloma annulare in a patient with previous breast carcinoma. Anthony F, Holden CA. *Clin Exp Dermatol* 2001; 26: 668–70.

Clofazimine 200 mg/day for 4 weeks followed by 100 mg/day for 4 weeks was effective in six patients.

A case of Sweet syndrome successfully treated by anti-inflammatory property of doxycycline. Liaw TY. *J Formos Med Assoc* 2017; 116: 723–4.

Rapid resolution observed with doxycycline 200 mg daily.

Sweet's syndrome in association with Crohn's disease. Rapaport A, Shaked M, Landau M, et al. *Dis Colon Rectum* 2001; 44: 1526–9.

Successful treatment using metronidazole 500 mg three times daily and prednisone.

Sweet's syndrome: a comprehensive review of an acute febrile neutrophilic dermatosis. Cohen PR. *Orphanet J Rare Dis* 2007; 26: 34

Cyclosporin between 2 mg and 10 mg/kg/day has been effective. Limit to short-term use given its potential renal toxicity when used chronically.

Systemic interferon-alpha treatment for idiopathic Sweet's syndrome. Bianchi L, Masi M, Hagman JH, et al. *Clin Exp Dermatol* 1999; 24: 443–5.

One patient responded to interferon-α 3 million units intramuscularly three times weekly plus hydroxyurea 500 mg twice daily for 30 days, tapered to 500 mg daily for another 30 days. Remission was maintained with monotherapy for 2 years.

Cyclophosphamide therapy in Sweet's syndrome complicating refractory Crohn's disease: efficacy and mechanism of action. Meinhardt C, Buning J, Fellermann K, et al. *J Crohns Colitis* 2011; 5: 633–7.

Cyclophosphamide pulse therapy (15 mg/kg) added to a regimen of prednisolone and azathioprine, yielded rapid response in Crohn-associated Sweet syndrome. Thereafter, treatment was given three times at 4-week intervals.

Histiocytoid Sweet syndrome successfully treated with etanercept. Watson IT, Haugh I, Gardner AR, et al. *Proc (Bayl Univ Med Cent)* 2018; 31: 347–9.

Refractory histiocytoid Sweet syndrome treated with etanercept 1 mg/kg subcutaneously twice weekly.

Thalidomide in the treatment of Sweet's syndrome and eosinophilic folliculitis associated with immune reconstitution inflammatory syndrome. Dong RJ, Huang SZ, Upadhyay P, et al. *Front Med (Lausanne)* 2020; 6: 343.

Thalidomide and lenalidomide for the treatment of refractory dermatologic conditions. Nahmias Z, Nambudiri VE, Vleugels RA. *J Am Acad Dermatol* 2016; 75: 210–2.

Two patients responded to either 50 mg or 100 mg thalidomide twice daily. Another patient with immune reconstitution inflammatory syndrome-associated Sweet syndrome improved with combination therapy with thalidomide 100 mg/day and antiretroviral therapy. Thalidomide is contraindicated in pregnancy.

The use of pulse methylprednisolone and chlorambucil in the treatment of Sweet's syndrome. Case JD, Smith SZ, Callen JP. *Cutis* 1989; 44: 125–9.

Chronic, relapsing Sweet syndrome treated with pulsed intravenous methylprednisolone. Remission was maintained with oral chlorambucil 4 mg/day.

Refractory Sweet syndrome treated with anakinra. Shahid Z, Kalayanamitra R, Patel R, et al. *Cureus* 2019; 11: e4536.

Sweet syndrome refractory to corticosteroids and other immunomodulatory therapies responded to anakinra 100 mg/day.

Favorable outcome of severe, extensive granulocyte colony-stimulating factor-induced, corticosteroid-resistant Sweet's syndrome treated with high-dose intravenous immunoglobulin. Calixto R, Menezes Y, Ostronoff M, et al. *J Clin Oncol* 2014; 32: e1–2.

Granulocyte colony-stimulating factor (G-CSF)-induced Sweet syndrome in a patient with multiple myeloma that persisted despite discontinuation of G-CSF and institution of steroids. A

Third-Line Therapies

• Ciclosporin	E
• Interferon	E
• Cyclophosphamide	E
• Chlorambucil	E
• Etretinate	E
• Etanercept	E
• Thalidomide	E
• Anakinra	E
• Intravenous immunoglobulin (IVIG)	E
• Sulfapyridine	E
• Azathioprine	E
• Azacitidine	E
• Lenalidomide	E
• Rituximab	E
• Adalimumab	E
• Ruxolitinib	E
• Infliximab	E
• Granulocyte and monocyte adsorption apheresis (GCAP)	E

2-day course of IVIG (1 g/kg/day) led to response within hours and complete resolution in 7 days.

Histiocytoid Sweet syndrome treated with azathioprine. Miller J, Lee N, Sami N. *Dermatol Online J* 2015; 21: 13.

Azathioprine 50 mg/day yielded excellent control of cutaneous and systemic symptoms. Studies describe azathioprine's potential to induce Sweet syndrome; thus, azathioprine may be beneficial exclusively in this variant.

Sweet's syndrome associated with clonal hematopoiesis of indeterminate potential responsive to 5-azacytidine. Yaghmour G, Wiedower E, Yaghmour B, et al. *Ther Adv Hematol* 2017; 8: 91–5.

A patient with Sweet syndrome and clonal hematopoiesis of indeterminate potential treated with 5-azacytidine (75 mg/m²) for six cycles (7 days of a 28-day cycle). Multiple reports also describe this drug's tendency to induce Sweet syndrome.

Lenalidomide as a steroid sparing agent in a myelodysplastic syndrome patient with refractory Sweet syndrome. Chaulagain CP, Miller KB. *Int J Blood Res Disord* 2014; 1: 1–3.

A patient with concurrent myelodysplastic syndrome had resolution of cutaneous lesions with 5 mg lenalidomide three times weekly. Few reports indicate lenalidomide's association with Sweet syndrome.

Rituximab for refractory subcutaneous Sweet's syndrome in chronic lymphocytic leukemia. Hashemi SM, Fazeli SA, Vahedi A, et al. *Mol Clin Oncol* 2016; 4: 436–40.

A patient with chronic lymphocytic leukemia treated for Sweet syndrome with IV rituximab (375 mg/m² body surface) on days 1 and 9.

Dosing with 1000 mg/day on days 1 and 15 also has been reported to be effective.

Refractory subcutaneous Sweet syndrome treated with adalimumab. Agarwal A, Barrow W, Selim MA, et al. *JAMA Dermatol* 2016; 152: 842–4.

Sweet syndrome treated with adalimumab (40 mg every other week).

Sweet syndrome successfully treated with ruxolitinib in JAK-2 positive myeloproliferative disorder. Melboucy-Belkhir S, Brigant F, Khentache R, et al. *Int Arch Intern Med* 2018; 2: 008.

Recurrent Sweet syndrome in a patient with controlled myeloproliferative disease improved with ruxolitinib (10 mg orally twice daily) without relapse for 18 months.

Azathioprine-induced Sweet syndrome treated with infliximab. Patel AV, Jotwani PM, Sultan KS. *Am J Ther* 2019; 26: e616–7.

A patient with ulcerative colitis developed azathioprine-induced Sweet syndrome, which improved with infliximab infusions (5 mg/kg).

Sweet's syndrome successfully treated with granulocyte and monocyte adsorption apheresis. Fujii A, Mizutani Y, Hattori Y, et al. *Case Rep Dermatol* 2017; 9: 13–8.

Recurrent Sweet syndrome treated with GCAP weekly for 3 weeks.

Syphilis

Derek Freedman, Eavan G. Muldoon



Syphilis is an ancient disease that many mistakenly believe to be on the decline. The numbers and rates of infectious syphilis fell to their lowest levels in Europe in the early 1990s. In the US in 1999 the Centers for Disease Control launched an ambitious program, *National Campaign to Eliminate Syphilis from the United States*. However, by 2018, the rates had increased more than three-fold, with men accounting for 86% of all patients with syphilis. The advent of PreExposure Prophylaxis (PrEP) for HIV has led to a relaxation of safer sex practices and, consequently, syphilis incidence has increased. This is not limited to men who have sex with men (MSM); diagnoses in other patient cohorts are increasing. An increase in cases among injection drug users, and their sexual contacts, has led to a consequent rise in congenital transmission. The effect of the COVID-19 pandemic on the prevalence of sexually transmitted infections remains to be seen.

A century ago, Sir William Osler said, 'Know syphilis in all its manifestations and relations, and all things clinical will be added unto you.' Syphilis's manifestations are protean, hence the reason it is often known as 'the great pretender.' Caused by the spirochete *Treponema pallidum*, syphilis is an indicator disease for human immunodeficiency virus (HIV). A syphilis diagnosis provides opportunities for screening and early diagnosis of HIV, which will have significant impact on patients' prognoses and further infection transmission. *T. pallidum* facilitates the transmission of HIV, increasing HIV viral load, inducing disruption of the mucous membrane barrier, and increasing HIV shedding. Prompt recognition and treatment of syphilis has significant public and personal health benefits.

MSM, commercial sex workers, or people from areas with a high prevalence of syphilis have a higher risk of syphilis acquisition. A thorough medical and social history is essential and may uncover past potential risks; most are unaware of their risk status, and routine testing is always required. Clinicians must be on high alert to the diagnosis of syphilis in all populations.

Transmission of syphilis is by direct contact with an infectious individual. Sexual contact is the most common mode of transmission. However, transmission by close contact with an active

lesion, such as oral sex, biting, and even kissing, has become more common. Transplacental transmission, blood transfusion, or accidental inoculation can all also occur, but rarely.

MANAGEMENT STRATEGY

The appropriate management is determined by the stage of syphilis infection. Infection is divided into:

- Incubation period
- Primary syphilis characterized by a primary sore or chancre(s)
- Secondary syphilis
- A period of subclinical infection or latent syphilis
- Tertiary syphilis, which does not occur in every patient

The patient is most infectious in the early stages of disease, particularly when the primary chancre, mucous patch, or condyloma lata are present. An immunologically intact person cannot spread syphilis after 4 years of infection.

Incubation Period

T. pallidum penetrates the intact mucous membrane or gains access through abraded skin. Within hours to days it enters the lymphatic system and/or bloodstream and disseminates throughout the body. This occurs soon after contact. Patients have been infected by blood transfusions from donors with negative serology who are in the incubation period. The incubation period is directly proportional to the size of the inoculum. The median incubation period is 3 weeks but can vary from 3 to 90 days.

Primary Syphilis

Classically, a primary chancre is described as a single, painless papule that occurs at the site of inoculation. This is not limited to the genital region. Any area where contact with an infectious lesion has occurred can be involved. The mouth and anal area are common extragenital sites.

The chancre appears after the incubation period, erodes, ulcerates, and becomes indurated. Typically, the chancre has a smooth base, with raised, firm borders and a cartilaginous consistency. The appearance is clean with no exudate, unless it is superinfected. It is usually round but may be elongated if it follows tissue lines. Ulcers are classically painless, with little discomfort or bleeding when the ulcer is scraped, such as while obtaining samples for dark-field microscopy, in contrast to herpes simplex virus (HSV) ulcers; but this is not universal. They are never blistering. Multiple chancres can occur, particularly in the setting of HIV infection. Atypical lesions occur in 60% of patients. All too frequently, the primary lesions are not recognized, due to their painless nature and location in areas where visualization is difficult. The appearance of the lesion depends on the size of the inoculum, the immune status of the patient, and concurrent antibiotic usage. Regional lymphadenopathy with moderately enlarged, firm, non-suppurative, painless lymph nodes frequently accompanies the primary lesion.

The differential diagnosis of a primary chancre is *herpes simplex*, chancroid, and traumatic superinfected lesions. Other diagnoses that should be considered are early warts caused by human papilloma virus, granuloma inguinale, tuberculosis, or atypical mycobacterial infections. Perianal lesions may be dismissed as hemorrhoids. The area should always be visualized and examined.

The chancre heals with the immune response but disseminates systemically to cause the secondary stage.

Secondary Syphilis

Secondary syphilis is when the spirochete multiplies and spreads throughout the body. It lasts until a sufficient host response develops to control the organism. Classically, it begins 2–8 weeks after the appearance of the chancre; however, this is highly variable, and the signs of primary and secondary infection may overlap. Many patients with secondary syphilis do not recall a primary chancre. The manifestations of secondary syphilis are protean and varied.

Dermatological manifestations are the most commonly recognized signs of secondary syphilis. The rash is usually mild and non-pruritic, and may be macular, maculopapular, papular, pustular, or a combination of all of these. Vesicular lesions occur only in congenital syphilis. Skin lesions usually begin on the trunk and proximal extremities. Classically, they are pink-red macular lesions 3–10 mm in diameter. Any surface area can become involved, but palmar and plantar rashes are highly suggestive of syphilis. The rash can last from a few days to up to 8 weeks. The lesions may evolve into papules and in some patients into pustules, known as pustular syphilids. All forms of the rash may coexist. Fever and lymphadenopathy may accompany the rash, and the clinical syndrome can be mistaken for acute HIV infection, infectious mononucleosis, or a non-specific viral syndrome.

Alopecia occurs with hair follicle involvement. In warm, moist areas, such as the genital and perianal areas, inner aspects of the thighs, the skin under breasts, nasolabial folds, axillae, antecubital fossae, and webs of fingers and toes, the papules can coalesce and erode, resulting in painless, broad, gray-white, highly infectious plaques called condylomata lata. They can be easily mistaken for warts or hemorrhoids. Lesions may also develop on mucous membranes, or so-called mucous patches. Enlargement of the epitrochlear lymph nodes is a unique finding that should always suggest a diagnosis of syphilis.

Other less common manifestations of secondary syphilis include hepatitis, splenomegaly, periostitis, arthritis, aortitis, and glomerulonephritis. Meningitis, cranial nerve palsies, auricular and ophthalmic abnormalities (such as uveitis, retinitis, otitis, and papillar edema), and meningovascular syphilis (stroke, myelitis) may also occur.

Neurological Syphilis

Neurosyphilis, i.e., syphilitic infection of the central nervous system, can present at any time after infection. It can be classified into early and late disease. Early neurosyphilis will involve the cerebrospinal fluid (CSF), meninges, and vasculature, while later tertiary syphilis affects the brain parenchyma and spinal cord.

Latent Syphilis

Latent syphilis is the asymptomatic period following infection with positive serology. It is usually divided into early latent disease (within 2 years of infection) and late latent disease (after 2 years of infection). Up to a quarter of early latent cases may relapse to recurrent infectious secondary syphilis. Careful history is required to attempt to stage asymptomatic disease. Sexual history, obstetric history, and travel history will all offer valuable clues, but an accurate conclusion is frequently elusive.

Tertiary Syphilis

Progression to tertiary syphilis is only seen in approximately 25% of untreated patients. It takes the form of neurological disease,

cardiovascular disease, and gummatous disease. It is rarely seen today due to antibiotic therapy, often inadvertent; however, it may be more prevalent in certain migrant populations.

DIAGNOSTICS AND TREATMENT

The diagnosis of syphilis depends on the stage of the disease. *T. pallidum* is too slender to be visualized by direct microscopy and the bacterium cannot be cultured. Dark-ground (dark-field) microscopy, a specialized technique that utilizes an oblique light to visualize the organism, is classically used in cases when patients have demonstrable clinical lesions; it has a sensitivity of only 50% in experienced hands. Moist lesions containing large numbers of treponemes such as primary chancres, condyloma lata, or mucous patches are particularly amenable to dark-field microscopy. It is not used for oral lesions, as commensal oral spirochetes are indistinguishable from *T. pallidum*. Although no *T. pallidum* molecular detection tests are commercially available, some laboratories provide locally developed and validated polymerase chain reaction (PCR) tests for the detection of *T. pallidum* DNA. However, these tests are not 100% sensitive, and retesting with serology is mandatory to confirm or exclude a diagnosis.

The vast majority of cases of syphilis are diagnosed by serology, an indirect diagnostic method.

Serological tests fall into two categories, non-treponemal tests and treponemal tests. Non-treponemal tests, such as rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL) tests, have traditionally been used for screening, and may still be used in resource limited settings. Automated enzyme immunoassay (EIA) is now recommended for screening prior to non-treponemal and treponemal tests. Positive tests are then confirmed with a treponemal test such as *T. pallidum* passive particle agglutination (TPPA) or *T. pallidum* hemagglutination (TPHA) test. False positive reactions may be seen with the non-treponemal tests in autoimmune conditions and various other infections, including HIV. Quantitative non-treponemal tests are useful for providing a baseline from which change can be measured. Re-infection can be demonstrated by a fourfold rise in titre. The reactivity of the test can differ depending on variation in antigen preparation and for this reason it is recommended that sequential tests be performed using the same laboratory method and preferably performed by the same laboratory. If the clinical suspicion for syphilis is high, and the non-treponemal tests are negative, a 'prozone' phenomenon caused by very high antibody titres should be considered. Dilution of the serum unmasks the test to positive. Anti-*T. pallidum* IgM tests may indicate early infection, but they lack sensitivity.

Rapid point of care tests have recently evolved to have better performance and have utility in outreach programs, but are not recommended where appropriate laboratory diagnosis is available.

Guidelines on treatment may differ; however, the basic principles are the same. *Long-acting penicillin* is the treatment of choice for all patients. Patients with neurological or ocular involvement will need daily treatment for a minimum of 10–14 days with parenteral penicillin. For those allergic to penicillin, *doxycycline* is an alternative to penicillin; however, penicillin desensitization is preferred. Patients must be followed with regular serology post-treatment to ensure adequate response to therapy.

The Jarisch–Herxheimer reaction may occur within hours of treatment, manifested by fever, chills, headache, myalgias, exacerbation of skin lesions, and other systemic symptoms. Treatment

with non-steroidal antiinflammatory agents or, rarely, in severe cases, systemic steroids, may be necessary.

Syphilis is an easily treatable disease with diverse manifestations. It is an indicator disease for HIV; consequently, all patients diagnosed with syphilis must be screened for HIV and all other sexually transmitted infections, from all sites of sexual activity. Tracing and management of sex partners forms part of the management of patients with syphilis. Sexual transmission is thought to be limited to the time when mucocutaneous lesions are present and is unusual after the first year of infection. Persons who have had sexual contact within 90 days with a person who has primary, secondary, or early latent syphilis should be treated presumptively.

If syphilis is not considered during the evaluation of patients presenting with symptoms of unclear etiology, the diagnosis may easily be missed. Careful history-taking regarding risk factors for the acquisition of the infection, possible chancrous lesions, systemic illness, and rash may offer vital clues in making the diagnosis of this curable disease, but routine serological testing of all patients is a mandatory safeguard to avoid missing the diagnosis.

Specific Investigations

- Dark-field microscopy
- Enzyme immunoassay
- VDRL or RPR and FTA-ABS or TPPA
- HIV test
- Sexually transmitted infection screen
- Contact tracing
- CSF analysis if neurological, ophthalmological, or auditory symptoms

The modern epidemic of syphilis. Ghanem KG, Ram S, Rice PA. *N Engl J Med* 2020; 382(9): 845–54.

This comprehensive current review addresses the epidemiology, natural history, and clinical presentation of syphilis today. Particular attention is drawn to recent visual or hearing loss/tinnitus of ocular or auditory syphilis. The loss of capacity to carry out dark-ground microscopy is noted, with replacement by nucleic acid amplification tests, which still await Food and Drug Administration (FDA) approval. Serological testing is noted as the mainstay of diagnosis. The conundrums of CSF examination are discussed. Serological response target of a decline factor of 4 or more for non-treponemal tests by 6–12 months is noted and the question of non-response addressed.

Emerging and reemerging sexually transmitted infections. Williamson DA, Chen MC. *N Engl J Med* 2020; 382: 2023–32.

Syphilis persists as a major public health problem, with serious morbidity, and 6 million new cases were estimated worldwide by the World Health Organization (WHO) in 2016. The incidence has particularly increased in MSM, particularly those using PrEP for HIV. Use of multiplex PCR testing for the simultaneous detection of *T. pallidum* and herpes simplex virus enhances diagnostic accuracy, particularly for anal and oral lesions, and has highlighted the potential for transmission from asymptomatic sites.

Congenital and heterosexual syphilis: still part of the problem. Torrone EA, Miller WC. *Sex Transm Dis* 2018; 45(9): S20–2.

HIV nucleotide sequencing has shown an increased number of men who have sex with both men and women serving as bridges, facilitating the spread of syphilis. Congenital syphilis is entirely

preventable and a high priority for public health. This emphasizes the need for widespread screening.

Neurosyphilis. Ropper AH. *N Engl J Med* 2019; 381: 1358–63.

Neurosyphilis is thankfully rare today, despite the increased incidence of syphilis. Nervous system invasion occurs within days of the primary infection, and early neurosyphilis varies from asymptomatic meningitis to symptomatic, with headache, meningismus, cranial nerve palsies, and ophthalmic/auditory manifestations. Late symptomatic neurosyphilis, occurring decades after the primary infection, is considered to be as a result of chronic meningeal reaction and destruction of adjacent neural tissue. It manifests typically as general paresis of the insane and/or tabes dorsalis. The Argyll Robertson pupil is a pathognomonic sign (pupils constrict on accommodation, but not on illumination).

First-Line Therapies

• Benzathine penicillin	A
• Procaine plus probenecid	A

2020 European guideline on the management of syphilis. Janier M, Unemo M, Dupin N, et al. *JEADV* 2020 22 October. doi.org/10.1111/jdv.16946 [Epub ahead of print].

These are the most up-to-date and comprehensive guidelines. They emphasize the importance of routine testing.

Penicillin remains the treatment of choice; for early syphilis, benzathine penicillin G (BPG) 2.4 MU remains the optimal first-line therapy. Daily procaine penicillin 600,000 units IM daily × 10–14 days is an alternative. Doxycycline 200 mg daily × 14 days is second-line therapy in case of allergy or bleeding disorders, where penicillin desensitization is not achievable.

For late latent syphilis or syphilis of unknown duration, a course of three doses of 2.4 MU BPG is recommended at weekly intervals. Procaine penicillin 600,000 mcg IM daily × 17–21 days is an alternative. Doxycycline is administered as a course of 21–28 days.

Ocular, auricular, and neurosyphilis require regimens that reach treponemicidal levels in the CSF, and IV therapy of benzyl penicillin 18–24 million IU daily for 10–14 days is optimal.

Follow-up and test of cure at 1, 3, 6, and 12 months is always advised, but often not achieved. A serological response of a four-fold fall in non-treponemal antibody levels is sought within 6 months.

It should be noted that azithromycin is not recommended for treatment, due to the rapid emergence of resistance in the spirochete, as well as other sexually transmitted pathogens.

Second-Line Therapies

• Doxycycline	B
• Tetracycline	B
• Amoxicillin plus probenecid	B
• Ceftriaxone	B

The great imitator revealed: syphilis. Klausner JD. *Top Antivir Med* 2019; 27(2): 71–4.

Lack of staff and resources in many counties and jurisdictions to follow up cases of syphilis and their contacts, as well as prevention and testing campaigns, are cited among

significant factors in the rising rates of syphilis infection seen today. Chemoprophylaxis with doxycycline 100 mg daily resulted in a 73% reduction of syphilis acquisition in a population of Los Angeles MSM over a 1-year period, while a French study showed a 73% reduction with doxycycline 200 mg taken once after sex. Ongoing trials on efficacy and safety are awaited.

Frequency of syphilis diagnoses by dermatologists. Cossman JP, Fournier JB. JAMA Dermatol 2017; 153(7): 718–9.

Only 2.5% of reported cases of syphilis seen in Rhode Island from 2010 to 2014 were seen by dermatologists. The majority were seen in primary care (35%), by infectious disease specialists (25%), in emergency care (18%), or in STI clinics (11%). The disengagement of dermatology from venereology was lamented.

Stages of Syphilis Infection



Syringomata

Robert F. Duffy



Syringomata are benign appendageal tumors of the intraepidermal eccrine sweat duct that have a characteristic histologic appearance. Typically skin- or tan-colored papules, with a rounded or flat surface, 1–5 mm in diameter, appear around puberty. Single tumors can occur, but more commonly they are multiple and symmetric, more common in females, and from adolescence onward. Syringomata most often involve the lower eyelids, although they may occur at other sites, including the cheeks, axillae, abdomen, and vulva. Linear, familial eruptive and generalized forms have all been described. Histologically, syringomata are situated in the upper to mid-dermis, the depth of which affects treatment modalities.

MANAGEMENT STRATEGY

This chapter will focus on facial syringomata. Available treatments, most of which are ablative, remove or flatten the papule produced by each syringoma. Some patients with only a few individual lesions may consider *excision*. Ablative modalities include *scissor excision* with secondary-intention healing, surgical excision of the entire cosmetic unit of the lower eyelids in patients who would also benefit from lower eyelid blepharoplasty, as well as *electrocautery*, *electrodesiccation*, *intralesional electrodesiccation*, *dermabrasion*, *cryotherapy*, *radiofrequency ablation*, and *laser treatment* (CO₂ monotherapy or in conjunction with other treatment modalities, neodymium:yttrium-aluminum-garnet [Nd:YAG], or erbium:YAG [Er:YAG]). When determining which laser therapy to choose, there are no studies comparing different lasers. There is one study analyzing CO₂ laser monotherapy in comparison to CO₂ laser combined with botulinum A toxin. This study concluded that the combination was more efficacious than the laser alone.

Topical or locally injected anesthesia is needed before treatment. Local anesthetic injections producing a field block are most commonly employed, as good anesthesia is helpful when using ablative treatments near the eye. Patients should be warned about

the possibility of postoperative bruising. Eye protection is of paramount importance, and specific precautions relevant to the use of lasers must be taken if laser treatment is used.

Ablative treatments will produce some degree of scarring and the aim is to make this imperceptible for excellent cosmetic results. Possible sequelae, including scarring and hypo- or hyperpigmentation (especially with increasing skin pigmentation), should always be discussed before treatment.

In addition to ablation, there are case studies analyzing pharmacotherapy for novel treatment types. These include *topical trichloroacetic acid*, *atropine*, and *tretinoin*. As more treatment options and efficacy studies become available, these non-surgical routes may become more feasible options.

Due to the lack of follow-up data and high level of evidence clinical trials, choosing a modality for treatment can be challenging. Because each modality has pitfalls in addition to benefits, determining the treatment option with the most user-experience may be wisest. Ultimately, treatment should be determined through a discussion between the patient and physician.

Specific Investigations

The clinical features of periorbital syringomata are usually diagnostic, and a skin biopsy may be undertaken for confirmation or when there is uncertainty.

First-Line Therapies

• Surgical excision	E
• Snip excision and secondary-intention healing	E
• Electrocautery	E
• Intralesional electrodesiccation	D
• CO ₂ laser	D

An easy method for removal of syringoma. Maloney ME. J Dermatol Surg Oncol 1982; 8: 973–5.

A single case is reported with a good outcome after removal of four to six lesions per session in 12 sessions over 5 months.

A good photographic demonstration of the removal of periorbital syringomata with fine ophthalmic spring-action scissors.

True electrocautery in the treatment of syringomas and other benign cutaneous lesions. Langtry JAA, Carruthers JA. J Cutan Med Surg 1997; 2: 60–3.

The technique of electrocautery is described, and good results reported in a number of benign skin lesions, including syringomata.

Intralesional electrodesiccation of syringomas. Karam P, Benedetto AV. Dermatol Surg 1997; 23: 921–4.

Twelve patients were treated with electrodesiccation via a fine electrode into the center of the syringoma with the aim of localizing the effect and minimizing scarring. All reported excellent results and no recurrence after a follow-up of 18–48 months. Two patients with Fitzpatrick skin type IV had focal hyperpigmentation, which cleared in 2–3 months.

Intralesional electrocoagulation with insulated microneedle for the treatment of periorbital syringomas: a retrospective analysis. Ahn GR, Jeong GJ, Kim JM, et al. Aesthet Surg J 2019 Oct 21. pii: sjz288. <https://doi.org/10.1093/asj/sjz288> [Epub ahead of print].

Fifty-five patients with periorbital syringoma underwent intralesional electrosurgery with approximately half experiencing marked reduction after one treatment. As treatments continued, number of lesions and remaining lesion severity decreased.

Carbon dioxide laser combined with botulinum toxin A for patients with periorbital syringomas. Seo H, Choi J, Min J, et al. *J Cosmet Laser Ther* 2016; 18(3): 149–53.

Syringomata in 44 patients were treated with CO₂ laser alone while 48 patients were treated with topical application of botulinum toxin A (BTXA) immediately following CO₂ laser treatment. The patient group treated with CO₂ laser alone saw an excellent or good response in 70.5% of patients. The patient group treated with CO₂ laser and topical application of BTXA saw an excellent or good response in 87.5% of patients. This shows that both techniques are effective with the application of topical BTXA potentially increasing efficacy.

Treatment of syringoma using an ablative 10,600-nm carbon dioxide fractional laser. Cho SB, Kim HJ, Lee SJ, et al. *Dermatol Surg* 2011; 37: 433–8.

Thirty-five patients with periorbital syringomata were treated with two sessions of fractional CO₂ laser at 10-month intervals. At 2 months' follow-up, clinical improvement was total in 9%, marked in 43%, moderate in 34%, and minimal in 14%.

Periorbital syringoma treated with radiofrequency and carbon dioxide (CO₂) laser in five patients. Hasson A, Farias MM, Nicklas C, et al. *J Drugs Dermatol* 2012; 11: 879–80.

Good cosmetic results reported in five patients with periorbital syringomata treated with the combination of radiofrequency and CO₂ laser.

Second-Line Therapies

• Electrodesiccation and curettage	E
• Combination of CO ₂ laser and trichloroacetic acid	D
• Nd:YAG laser	D

Syringoma: removal by electrodesiccation and curettage. Stevenson TR, Swanson SA. *Am Plast Surg* 1985; 15: 151–4.

The technique is described and good results are reported, but there is no description of numbers of patients treated, clinical details, or follow-up data using this technique.

A new treatment for syringoma. Combination of carbon dioxide laser and trichloroacetic acid. Kang H, Kim NS, Kim YB, et al. *Dermatol Surg* 1998; 24: 1370–4.

This study evaluates the histopathology and efficacy of combined CO₂ laser and 50% trichloroacetic acid treatment in 20 Korean patients with periorbital syringomata. Results were reported as excellent (11 patients), good (6), and fair (3), without

complications such as scarring, infection, or textural change, using the technique detailed.

Periorbital syringomas treated with an externally used 1,444 nm neodymium-doped yttrium aluminum garnet laser. Kim JY, Lee JW, Chung KY. *Dermatol Surg* 2017; 43: 381–8.

Nineteen patients had their periorbital syringomata treated twice with 1444 nm Nd:YAG laser in 2-month intervals. Greater than 50% improvement was seen in 68.4% of patients and in 100% of patients 6 months after the second treatment.

Erbium YAG laser treatment of periorbital syringomas by using the multiple ovoid-shape ablation method. Kitano Y. *J Cosmet Laser Ther* 2016; 18: 280–5.

Forty-nine patients with syringomata were treated every 2 months with an Er:YAG laser, ablating multiple 2- to 4-mm egg-shaped fields. More than 75% of syringomata disappeared in 43 of 49 patients after an average of 3.77 treatments.

Third-Line Therapies

• Dermabrasion	E
• Trichloroacetic acid	E
• Topical atropine	E
• Topical tretinoin	E

Dermabrasion by diamond fraises revolving at 85000 revolutions per minute. Fulton JE. *J Dermatol Surg Oncol* 1978; 4: 777–9.

High-speed dermabrasion is described, and good results are reported in 65 patients with acne scarring, actinic damage, adenoma sebaceum, and syringomata.

The treatment of eruptive syringomas in an African American patient with a combination of trichloroacetic acid and CO₂ laser destruction. Frazier CC, Camacho AP, Cockerell CJ. *Dermatol Surg* 2001; 27: 489–92.

A single case report of eruptive facial syringomata in an African American woman treated by 35% trichloroacetic acid peel, followed 2 weeks later by CO₂ laser, with acceptable cosmetic results and without significant side effects.

Eruptive pruritic syringomas: treatment with topical atropine. Sanchez TS, Dauden E, Casas AP, et al. *J Am Acad Dermatol* 2001; 44: 148–9.

A single case report of pruritic syringomata of the chest and neck improving with topical 1% atropine applied once daily.

Eruptive syringoma: treatment with topical tretinoin. Gomez MI, Perez B, Azana JM, et al. *Dermatology* 1994; 189: 105–6.

A 23-year-old woman with asymptomatic eruptive syringoma treated with 0.1% tretinoin cream daily for 4 months, resulting in flattening of the lesions in the areas treated.

Tinea capitis

Mariana L. Noy, L. Claire Fuller



Courtesy of Dr. E. E. Merika

Tinea capitis is a fungal infection of the scalp caused by dermatophyte species, most commonly *Microsporum* and *Trichophyton*, which are identified on microscopy and culture. Infections localized to the inside of the hair shaft, known as *endothrix* infections, are most commonly caused by *Trichophyton* species and principally occur in children, although they can occasionally be seen in adults. However, the condition is rare in adults and investigating for underlying causes of immunocompromise should be considered in these cases. Ectothrix infections, which affect both the inside and the outside of the hair shaft, are most commonly caused by *Microsporum* species and almost always affect children.

Tinea capitis typically presents as patchy alopecia with varying degrees of erythema and scale with associated lymphadenopathy. Ectothrix infections may appear as non-inflammatory patches of alopecia with fine scale. By contrast, a 'black dot' appearance, caused by breakage of hair shafts, indicates an infection with an endothrix species such as *Trichophyton*. The term *kerion celsi* refers to tinea capitis presenting as a boggy, tender swelling caused by the host's inflammatory response. This can be misdiagnosed as a bacterial abscess. Secondary bacterial infection contamination can occur, which is rarely of pathological significance but can confuse the diagnosis if fungus is not suspected.

Scrapings and samples of loose fractured hairs should be processed for microscopy and culture. Swabs (taken using bacterial

transport media) may provide an accurate, non-invasive alternative. Wood lamp examination may also aid diagnosis (ectothrix *Microsporum* exhibit green fluorescence), and trichoscopy is a useful, non-invasive diagnostic adjunct and may help distinguish the condition from alopecia areata.

MANAGEMENT STRATEGY

Treatment of tinea capitis is with oral antifungal agents as topical therapy alone is insufficient. Topical antifungal creams and shampoos may help when used in conjunction with systemic treatment in reducing infectivity by reducing fungal elements and the shedding of spores but **should not** be used alone or as prophylaxis as this does not reduce reinfection rates.

The aim is to eradicate the organism to prevent scarring and further transmission to others. Where possible, one should await confirmation of a fungal infection. However, this will delay treatment and can result in further spread; therefore, in patients presenting with kerion or obvious clinical signs (scaling, alopecia, or lymphadenopathy) it is reasonable to start treatment. The response of different dermatophyte species to different systemic agents is variable and treatment should be tailored accordingly. General consensus is that griseofulvin is more effective for the treatment of *Microsporum* infections and terbinafine against *Trichophyton*. While griseofulvin is an established therapeutic, evidence suggests that newer systemic antifungals (terbinafine and itraconazole) are equally safe and may be more cost effective. Their shorter treatment duration may also increase compliance. This is reflected in changes to medication licensing and prescribing practices in Europe and the United States.

Griseofulvin is a fungistatic drug, typically given at a dose of 15–20 mg/kg/day (in single or divided dose) for those <50 kg and 1 g/day for those >50 kg (in single or divided dose) for 6–8 weeks (British Association of Dermatology). Side effects include gastrointestinal disturbance, rash, and headache. Griseofulvin is contraindicated in pregnancy. In adults with tinea capitis due to *Trichophyton* species, terbinafine is given for 2–4 weeks (62.5 mg/day for those <20 kg; 125 mg/day for those 20–40 kg and 250 mg/day for those >40 kg) (British Association of Dermatology). Terbinafine is a fungicidal drug and is generally well tolerated; side effects are less commonly seen than with griseofulvin (gastrointestinal upset and rash).

Itraconazole has both fungistatic and fungicidal activity and can be given second-line if required. Itraconazole has activity against both *Microsporum* and *Trichophyton* species (50–100 mg/day for 4 weeks, or 5 mg/kg/day for 2–4 weeks).

The use of intermittent or pulsed treatment regimens using itraconazole or fluconazole has been explored, utilizing the long half-life of these agents in keratin. While this does not appear to confer any additional benefit in terms of cure, it may reduce the cost of treatment and compliance.

As a gold standard, mycologic cure should be confirmed with appropriate sampling following completion of treatment. Family members should be screened where possible to detect subtle subclinical infection/carriage to prevent relapse and reinfection of the index case.

Specific Investigations

- Examination of hair and scalp scale by direct microscopy and culture
- Wood lamp examination
- Dermoscopy/trichoscopy
- Screen contacts, particularly siblings, where possible

Efficacies and merits of the cotton swab technique for diagnosing tinea capitis in the pediatric population. Le M, Gabrielli S, Ghazawi FM, et al. *J Am Acad Dermatol* 2020; 83(3): 920–922.

A prospective study of 25 children with tinea capitis showed 100% concordance between swab and scraping results, and both endothrix and ectothrix species were isolated.

Trichoscopy of tinea capitis: a systematic review. Waskiel-Burnat A, Rakowska A, Sikora M, et al. *Dermatol Ther (Heidelb)* 2020; 10(1): 43–52.

A systematic review identified 37 eligible articles. The most commonly occurring dermatoscopic findings were of comma, corkscrew, barcode, bent, and block hairs, as well as perifollicular and diffuse scaling. The authors also conclude that trichoscopy may help distinguish between *Microsporum* and *Trichophyton* causes of tinea capitis.

Trichoscopy in paediatric patients with tinea capitis: a useful method to differentiate from alopecia areata. Ekiz O, Sen BB, Rifaioğlu EN, et al. *J Eur Acad Dermatol Venereol* 2014; 28(9): 1255–8.

A study of 25 children (15 with tinea capitis and 10 with alopecia areata) identified distinctive features on dermoscopy of the hair and scalp in children with fungal infections, including broken, dystrophic, corkscrew, barcode, and comma hairs, as well as black dots.

Screening for asymptomatic carriage of *Trichophyton tonsurans* in household contacts of patients with tinea capitis: results of 209 patients from south London. White JM, Higgins EM, Fuller LC. *J Eur Acad Dermatol Venereol* 2007; 21: 1061–4.

Over 50% of household contacts in this study had positive fungal cultures (7.1% were overt infection and 44.5% silent fungal carriage). Children under 16 were most likely to be affected ($p < 0.01$).

First-Line Therapies

• Griseofulvin (generally more effective against <i>Microsporum</i> species)	A
• Terbinafine (generally more effective against <i>Trichophyton</i> species)	A

British Association of Dermatologists' guidelines for the management of tinea capitis 2014. Fuller LC, Barton RC, Mohd Mustapa MF, et al. *Br J Dermatol* 2014; 171(3): 454–63.

Griseofulvin remains the only licensed treatment for tinea capitis in children in the UK. Griseofulvin generally remains first-line treatment for *Microsporum* infections and terbinafine for *Trichophyton* species. Terbinafine requires a shorter course of treatment and compliance may therefore be higher. Itraconazole is a safe and effective second-line option. Other options, including fluconazole and voriconazole, can be used in refractory, exceptional cases.

'Children receiving appropriate therapy should be allowed to attend school or nursery'.

Guidelines for the management of tinea capitis in children. Kakourou T, Uksal U. *Pediatr Dermatol* 2010; 27: 226–8.

Tinea capitis always requires systemic management, although topical treatments can be used as adjuncts. Griseofulvin is the treatment of choice for tinea capitis caused by *Microsporum* species (although this may no longer be available in some European countries). The newer systemic antifungals, terbinafine, itraconazole and fluconazole, have similar efficacy to griseofulvin when used to treat *Trichophyton* species and require shorter courses. They may, however, be more expensive. The guidelines recommend that clinical and mycologic examinations of children should occur at regular 2–4 weekly intervals and that treatment can be stopped once cultures are negative or hair regrowth is observed.

Tinea capitis in children: a systematic review of management. Gupta AK, Mays RR, Versteeg SG, et al. *J Eur Acad Dermatol Venereol* 2018; 32(12): 2264–74.

A systematic review identified 21 randomized control trials and 17 clinical trials. Griseofulvin and terbinafine had the highest mycological (79% and 72%, respectively) and complete cure rates (81% and 92%, respectively) and continuous itraconazole and terbinafine had the highest mycological cure rates. *Microsporum* infections were more effectively treated by griseofulvin and *Trichophyton* by terbinafine and itraconazole. Adverse events were rare. The authors note that using a hairbrush, toothbrush, or cotton swab for mycological sampling is a non-invasive, effective method in children.

Tinea in tots: cases and literature review of oral antifungal treatment of tinea capitis in children under 2 years of age. Zampella JG, Kwatra SG, Blanck J, et al. *J Pediatr* 2017; 183: 12–8. e3.

A literature review of 18 studies involving children younger than 2 years of age included 168 cases of tinea capitis. *Microsporum canis* was the most common causative dermatophyte. There were no adverse events. They conclude that terbinafine should be used in cases caused by *Trichophyton* species and griseofulvin for *Microsporum* infections and that, overall, terbinafine is the most cost-effective solution.

Terbinafine hydrochloride oral granules versus oral griseofulvin suspension in children with tinea capitis: results of two randomised, investigator-blinded, multicentre, international, controlled trials. Elewski BE, Cáceres HW, Deleon L, et al. *J Am Acad Dermatol* 2008; 59(1): 41–54.

A multicenter, investigator-blinded, randomized, controlled study comparing 6-week treatment with griseofulvin 10–20 mg/kg/day ($n = 509$) with terbinafine 5–8 mg/kg/day ($n = 1040$) in children with microscopy-proven tinea capitis. Complete cure rates (45.1% vs. 33.01%) and mycologic cure (61.55% vs. 55.5%) were significantly higher for terbinafine than for griseofulvin ($p < 0.05$), even at higher doses (> 20 mg/kg/day). Subgroup analysis revealed that terbinafine was significantly better than griseofulvin for all cure rates (clinical, mycologic, and complete) in *Trichophyton tonsurans* infection ($p < 0.001$), but not for *M. canis*. In contrast, for *M. canis*, mycologic and clinical cure rates were significantly better with griseofulvin ($p < 0.05$). Fifty percent of patients in each group reported mild adverse effects with treatment, with no reported incidences of hepatotoxicity such as transaminitis.

Griseofulvin vs terbinafine for paediatric tinea capitis: when and for how long. Bar J, Samuelov L, Sprecher E, et al. *Mycoses* 2019; 62(10): 949–53.

A retrospective cohort study of 304 cases comparing treatment with griseofulvin suspension for 12 weeks with griseofulvin

suspension for 8 weeks and terbinafine for 4 weeks; 12 weeks of griseofulvin gave a better cure rate than 4 weeks of terbinafine. There was no difference between the different durations of griseofulvin. Treatment was more effective when the causative agent was *Microsporum audouinii* or *Trichophyton soudanense* in comparison to *Trichophyton violaceum* (the most common causative organisms).

Therapeutic options for the treatment of tinea capitis caused by *Trichophyton* species: griseofulvin versus the new oral antifungal agents, terbinafine, itraconazole and fluconazole. Gupta AK, Adam P, Dlova N, et al. *Pediatr Dermatol* 2001; 18(5): 433–8.

A multicenter, prospective, randomized, single-blinded study compared treatment with griseofulvin (20 mg/kg/day for six weeks), terbinafine (> 40 kg, 250 mg; 20–40 kg, 125 mg; <20 kg, 62.5 mg for 2–3 weeks), itraconazole (5 mg/kg/day for 2–3 weeks), and fluconazole (6 mg/kg/day for 2–3 weeks) in the management of tinea capitis caused by *Trichophyton* species (*T. tonsurans* and *T. violaceum*). A total of 200 patients were included and divided equally among the four groups. Efficacy was similar in all treatment groups: griseofulvin, 92.0%; terbinafine, 94.0%; itraconazole, 86.0%; and fluconazole, 84.0% ($p=0.33$). Adverse effects were rare (gastrointestinal effects in six patients in the griseofulvin group).

Second-Line Therapy

- Itraconazole

A

Tinea capitis in early infancy treated with itraconazole: a pilot study. Binder B, Richtig E, Weger W, et al. *J Eur Acad Dermatol Venereol* 2009; 23: 1161–3.

In a pilot study of seven infants younger than 1 year of age with *M. canis* tinea capitis, itraconazole was found to be effective and well tolerated. Itraconazole has been shown to be safe in the treatment of young infants, including neonates, although study numbers were inevitably small.

Third-Line Therapies

- Fluconazole
- Voriconazole
- 2% ketoconazole
- Selenium sulfide shampoo

C

C

B

B

Once weekly fluconazole is effective in children in the treatment of tinea capitis: a prospective multicentre study. Gupta AK, Dlova N, Taborda P, et al. *Br J Dermatol* 2000; 142: 965–8.

An open, multicenter assessment of 61 children treated with oral fluconazole 8 mg/kg once weekly for 8 weeks (extended for a further 4 weeks if clinically indicated). Causal organisms were *T. violaceum* ($n=33$), *T. tonsurans* ($n=11$), and *M. canis* ($n=17$). All 44 children with *Trichophyton* infections had mycologic and clinical cure at 16 weeks after the start of treatment; the majority (35/44) only required 8 weeks of therapy; however, 9 out of 33 of the *T. violaceum* group required treatment for 12 weeks, and 12 out of 17 of the *M. canis* group were clinically clear after 8 weeks. Treatment was extended for a total of 12 weeks in one patient and 16 weeks in three patients, but, overall, 16 of 17 children in this group had complete cure 2 months after the end of therapy. One child had asymptomatic and reversible elevation of liver function tests.

Treatment of tinea capitis – griseofulvin versus fluconazole – a comparative study. Shemer A, Plotnik IB, Davidovici B, et al. *J Dtsch Dermatol Ges* 2013; 11(8): 737–41.

In this study, 113 patients with tinea capitis were treated with griseofulvin 15 mg/kg/day or 25 mg/kg/day or fluconazole 4 mg/kg/day or 6 mg/kg/day, all for up to 12 weeks. There was no statistical difference between the two groups, and the authors concluded that treatment choices should be based on tolerability, availability, and cost of medications.

A retrospective study of the management of pediatric kerion in *Trichophyton tonsurans* infection. Proudfoot LE, Higgins EM, Morris-Jones R. *Pediatr Dermatol* 2011; 28(6): 655–7.

A retrospective study of all children less than 10 years of age presenting with kerion infection to a single unit over a 6-year period revealed no advantage in concomitant use of oral or intralesional steroids compared with oral antifungal use alone.

A randomized, comparative trial of treatment of kerion celsi with griseofulvin plus oral prednisolone vs. griseofulvin alone. Hussain I, Muzaffar F, Rashid T, et al. *Med Mycol* 1999; 37: 97–9.

In this randomized study, the efficacy of combination therapy with oral griseofulvin and oral prednisolone ($n=17$) was compared to oral griseofulvin alone ($n=13$) in the treatment of kerion celsi. Both groups were treated with oral griseofulvin for 8 weeks whereas oral prednisolone was given in tapering doses for 3–4 weeks to the first group only. The final evaluation at week 12 showed a cure rate of 100% in both groups without any significant difference in terms of clinical or mycological cure ($P>0.05$). No adverse events were noted in either group. In our opinion the combination of oral prednisolone with griseofulvin does not result in additional objective or subjective improvement compared to griseofulvin alone in cases with kerion celsi.

A randomized, double-blind study comparing the efficacy of selenium sulfide shampoo 1% and ciclopirox shampoo 1% as adjunctive treatments for tinea capitis in children. Chen C, Koch LH, Dice JE, et al. *Pediatr Dermatol* 2010; 27: 459–62.

A total of 40 children (ages 1–11) were randomized to either selenium sulfide 1% or ciclopirox 1% shampoo in addition to an 8-week course of griseofulvin. Children were reviewed for clinical evaluation and scalp cultures at weeks 2, 4, and 8, and 4 weeks after finishing treatment. By the 8-week review, 90.9% ($n=33$) showed mycological cure. Both selenium sulfide 1% and ciclopirox 1% shampoo demonstrated equal efficacy adjunctive treatments.

Successful treatment of tinea capitis with 2% ketoconazole shampoo. Greer DL. *Int J Dermatol* 2000; 39: 302–4.

A total of 16 children aged 3–6 years with *T. tonsurans* tinea capitis were treated with 2% ketoconazole shampoo daily for 8 weeks. All showed clinical improvement, some as early as 2 weeks. Six of 15 (40%) had negative cultures at 8 weeks, and 5 (33%) remained clear 1 year later.

Prophylactic ketoconazole shampoo for tinea capitis in a high-risk pediatric population. Bookstaver PB, Watson HJ, Winters SD, et al. *J Pediatr Pharmacol Ther* 2011; 16(3): 199–203.

A retrospective analysis of 97 vulnerable children considered at high risk of tinea capitis showed no benefit from twice-weekly use of 2% ketoconazole shampoo in the prevention of infection.

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Tinea corporis and tinea cruris

Shyam B. Verma, Resham Vasani



Tinea corporis is a dermatophyte infection of the skin of the trunk and extremities, excluding the hair, nails, palms, soles, and the groin. Tinea cruris refers to the infection of the groin. While tinea corporis and cruris occurs worldwide, they are most common in tropical and subtropical regions. The free availability and misuse of potent topical steroid-containing creams also containing an antifungal and antibacterial agent have become the bane of dermatologists in developing countries.

Trichophyton rubrum is the most common agent worldwide, followed by *T. mentagrophytes*.

There is an ongoing epidemic like situation of widespread, often inflammatory recalcitrant dermatophytosis in South Asia, Middle Eastern countries and several countries in Europe due to a specific genotype of *T. mentagrophytes* complex called *T. mentagrophytes* ITS genotype VIII/Indian genotype (Nenoff et al.) It is known to be associated with terbinafine resistance and is responsive to itraconazole in higher doses for a higher duration.

The current Indian epidemic of superficial dermatophytosis due to *Trichophyton mentagrophytes* - a molecular study. Nenoff P, Verma SB, Vasani R, et al. *Mycoses*. 2019; 62: 336–356.

MANAGEMENT STRATEGY

Topical therapies are the first line of defense when treating localized tinea corporis and tinea cruris. Oral antifungal treatments are recommended in extensive, recurrent, or chronic infections not

responsive to topical antifungal treatment, especially against the backdrop of topical steroid abuse. Topical therapies alone may be a judicious choice in special situations in which oral antifungals are contraindicated, as in patients with comorbidities and concomitant medications that contraindicate antifungals, in infants, and in the first trimester of pregnancy. Some preventative measures, including educational programs, maintaining proper hygiene, avoiding communal areas, and using antimicrobial fabrics, may help limit relapse and prevent transmission.

Specific Investigations in Superficial Dermatophytosis

- Direct microscopy on KOH (potassium hydroxide) specimens
- Fungal culture
- Molecular diagnosis
- Dermoscopy
- Antifungal susceptibility testing and genomic analysis

Epidemiological aspects of dermatophytosis in Khuzestan, southwestern Iran, an update. Rezaei-Matehkolaei A, Rafiei A, Makimura K, et al. *Mycopathologia* 2016; 181(7–8): 547–53.

This was a 1-year survey where 4120 skin, hair, and nail samples obtained from outpatients with symptoms suggestive of tinea were analyzed using direct microscopy, culture, and molecular sequencing. *T. interdigitale* (58.7%) was the predominant isolate followed by *Epidermophyton floccosum* (35.4%), *Microsporum canis* (3%), *T. rubrum* (1.5%), *Trichophyton* species of *Arthroderma benhamiae* (0.5%), *T. tonsurans* (0.3%), and *T. violaceum* (0.3%).

Reappraisal of conventional diagnosis for dermatophytes. Pihet M, Le Govic Y. *Mycopathologia* 2017; 182(1–2): 169–80.

Tinea corporis and intertriginous lesions should be scraped from the edge using a dermal blunt curette (Brocq curette) rather than a scalpel blade. Swabbing following scraping is recommended in inflammatory or oozing lesions.

Direct microscopic examination in 10% potassium hydroxide mount is an efficient screening technique that allows quick diagnosis to clinicians who can provide antifungal therapy pending culture results. Quality of specimen and skill of the observer determine the success of mycological examination. False negative results are seen in 15%–30% in routine practice.

Fungal culture is used for definitive identification but often lacks sensitivity, is time consuming, and identification of filamentous fungi at the species level using morphological characteristics needs experienced staff.

Molecular techniques are being increasingly employed in the clinical microbiological laboratories for identification and direct detection of organisms in clinical specimens because of high sensitivity and specificity and small turnaround time. Nucleic acid-based techniques are more specific than the phenotypic characteristics since genotypic characteristics are less affected by the external environment.

Dermoscopy can be helpful in identifying vellus hair involvement, and antifungal susceptibility testing and genomic analysis can document drug resistance. A plethora of reports and studies document terbinafine resistance in *T. mentagrophytes* and *T. interdigitale*.

Using dermoscopy to detect tinea of vellus hair. Gómez-Moyano E, Crespo Erchiga V, Martínez Pilar L, et al. *Br J Dermatol* 2015; 174(3): 636–8.

Dermoscopy is not a substitute for mycological studies but can be supplementary. Vellus hair involvement can be identified only by dermoscopy or by mycological examination of vellus hair and not by culture. Hence, the dermoscope becomes useful where mycological facilities are not available. Vellus hair involvement is considered a criterion for systemic therapy in skin dermatophytosis.

Antifungal drug susceptibility profile of clinically important dermatophytes and determination of point mutations in terbinafine-resistant isolates. Salehi Z, Shams-Ghahfarokhi M, Razzaghi-Abyaneh M. Eur J Clin Microbiol Infect Dis 2018; 37(10): 1841–6.

In this study from Iran, 97 isolates of dermatophytes were identified at species level and subjected to antifungal susceptibility testing to nine antifungal drugs. Terbinafine resistance was reported for two species, *T. rubrum* and *T. tonsurans*, at a total rate of 2%, which was due to Leu393Phe substitution in both species.

Terbinafine resistance of trichophyton clinical isolates caused by specific point mutations in the squalene epoxidase gene. Yamada T, Maeda M, Alshahni M, et al. Antimicrob Agents Chemother 2017; 61(7).

In this Swiss study of 2056 trichophyton isolates collected over 3 years, approximately 1% showed reduced terbinafine susceptibility, and all of these were found to harbor *SQLE* gene allele with different single point mutations leading to a single amino acid substitution at one of the four proteins: Leu393, Phe397, Phe 415, or His440 of *SQLE* protein.

Alarming India-wide phenomenon of antifungal resistance in dermatophytes: a multicentre study. Ebert A, Monod M, Salamin K, et al. Mycoses 2020.

In this study, 402 samples originating from eight locations in India were identified by microbiological and molecular methods and tested for antifungal susceptibility to terbinafine, itraconazole, and voriconazole. *T. mentagrophytes* internal transcribed spacer type VIII was found in 78% of the samples while 5% had species in *T. mentagrophytes/interdigitale* complex and 5% had *T. rubrum*; 71% of the isolates were found to be resistant to terbinafine. This study also suggests squalene epoxidase substitutions between Leu393 and Ser443 could serve as markers of resistance in the future.

First-Line Therapies

Topical

• 1% luliconazole cream	A
• 2% sertaconazole nitrate cream	A
• 1% eberconazole cream	A
• Oxiconazole	A
• 1% naftifine hydrochloride	A
• Clotrimazole	A
• Miconazole	A
• 1% terbinafine as cream, solution, gel, or film-forming solution	A
• 1% ciclopirox (hydroxypyridone) cream	A
• 0.25% amorolfine cream	A
• 2% fenticonazole cream	A
• 2% ketoconazole cream	D

Evidence-based topical treatments for tinea cruris and tinea corporis: a summary of a Cochrane systematic review. Van

Zuuren EJ, Fedorowicz Z, El-Gohary M. Br J Dermatol 2015; 172: 616–41.

This review was aimed to assess the evidence for effectiveness and safety of topical treatments for tinea cruris and corporis. It did not find significant difference in effectiveness between azoles and benzylamines in pooled studies, as well as once-daily vs. twice-daily application of eberconazole, terbinafine, oxiconazole, and naftifine.

Second-Line Therapies

Systemic

• Itraconazole	A
• Fluconazole	A
• Terbinafine	A
• Griseofulvin	A

Itraconazole in the treatment of tinea corporis and tinea cruris. Katsambas A, Antonoiu C, Frangouli G, et al. Clin Exp Dermatol 1993; 18(4): 322–5.

In total, 45 patients with tinea corporis or tinea cruris were treated with oral itraconazole 100 mg daily for 15 days. Response rates at the last visit 6 weeks after therapy remained at the same satisfactory levels as the first follow-up visit 2 weeks posttreatment, even though treatment was stopped after 2 weeks. Itraconazole appeared to be well tolerated by the patients.

A comparison of the efficacy of oral fluconazole, 150 mg/week versus 50 mg/day, in the treatment of tinea corporis, tinea cruris, tinea pedis and cutaneous candidosis. Nozickova M, Koudelkova V, Kulikova Z, et al. Int J Dermatol 1998; 37: 703–5.

To determine the efficacy of fluconazole, patients with dermatophytoses and cutaneous candidosis were treated for 4–6 weeks ($n=245$). Positive clinical responses (cure and marked improvement) were found in 79%–88% of non-pedis–infected patients and in 79%–93% of pedis–infected patients.

A comparative double-blind study of terbinafine (Lamisil) and griseofulvin in tinea corporis and tinea cruris. del Palacio Hernandez A, Lopez Gomez S, Gonzalez Lastra F, et al. Clin Exp Dermatol 1990; 15: 210–6.

This study compared terbinafine with griseofulvin, 92 patients received oral terbinafine 125 mg twice daily, and the other cohort received oral griseofulvin 500 mg twice daily. Treatment continued for 6 weeks, and results were comparable, with 77% of the terbinafine patients treated effectively compared with 82% of the griseofulvin cohort.

As mentioned in the sections above, an epidemic-like situation of recalcitrant, chronic, recurrent, relapsing dermatophytosis has been reported from India, and the situation is similar in many other developing countries. The standard textbook recommendations for treating this condition have lost relevance.

Expert Consensus on the Management of Dermatophytosis in India (ECTODERM India). Rajagopalan M, Inamadar A, Mittal A, et al. BMC Dermatol 2018; 18: Article 6. <https://doi.org/10.1186/s12895-018-0073-1>.

An experience-driven consensus on the management of dermatophytosis specific to the Indian public health problem was formulated by experts in clinical dermatology and mycology. Topical monotherapy was recommended for naive cases of localized tinea corporis and tinea cruris. A combination of topical and oral

Table 241.1 Standard and modified treatment regimens for tinea corporis/cruris

Antifungal	Standard recommendation	Modification
Terbinafine	250mg OD for 2–3 weeks	250mg for longer durations
Itraconazole	Short, fixed duration 100mg OD × 15 days 200mg OD × 7 days	Higher doses, longer durations
Fluconazole	150mg/week × 6 weeks	50–100mg OD
Ketoconazole	Use restricted to many countries owing to hepatotoxic adverse effects	200–400mg per day for recalcitrant infections with careful monitoring of liver function tests
Combination of topicals	Topical azoles and allylamines prescribed for limited disease	Salicylic acid improves desquamation. Increasing use of amorolfine and ciclopirox olamine as topical antifungals

Itraconazole is the drug of choice in recalcitrant widespread dermatophytosis in infections caused by *T. mentagrophytes* genotype VIII/T. *indotinae* and is given in doses of 100 mg twice daily for 4–6 weeks with topical azoles. This variant shows a striking resistance to terbinafine due to SQLE mutations and is shows variable resistance to fluconazole and ketoconazole too.

antifungals should be used for extensive or recalcitrant lesions of corporis and cruris. Among the topical antifungals, azoles with antiinflammatory, antibacterial properties are preferred. Itraconazole and terbinafine are the preferred systemic drugs. The minimum duration of treatment should be 2–4 weeks for naive cases and more than 4 weeks in recalcitrant cases. Use of topical steroids even in the initial phase of the disease is discouraged considering the alarming misuse and self-medication.

Antifungal resistance in dermatophytes: recent trends and therapeutic implications. Khurana A, Sardana K, Chowdhary A. *Fungal Genet Biol* 2019; 132: 103255.

A comprehensive review of the available literature and in vitro and in vivo resistance to clinically used antifungals among dermatophytes is provided. Recent trends in therapeutics are outlined as illustrated in Table 241.1.

Tinea pedis

Shikhar Ganjoo, Shyam B. Verma



Tinea pedis is the most common form of cutaneous morphological pattern of superficial dermatophytosis in Western countries. Tinea pedis denotes infection of the feet, including toes, with a dermatophyte. It is colloquially known as athlete's foot or foot ringworm. Tinea pedis affects quality of life – cosmetically due to disfiguring skin lesions causing social embarrassment, and symptomatically due to significant itching, leading to social and emotional distress. The role of fomites cannot be ignored in its propagation. Many studies have indicated the viability of fungal spores in house dust, which may be a factor in causing chronic and recurrent disease. An additional and important factor in disease causation is its geographical distribution – the disease being more prevalent in tropical regions due to the extremes of temperature and humidity. The worldwide disease prevalence is estimated to be in the range of 10%. Thus, safe and effective treatments are required to address this important public health concern. The disease often begins as a lateral toe cleft involvement that progresses to involve the rest of the foot, occlusive footwear being a major factor in spread. The disease is classified based on the character as well as distribution of lesions – vesicular (involving the soles of the feet), moccasin (involving the lateral aspect of the feet), and interdigital (involvement between the toes).

MANAGEMENT STRATEGY

For minor interdigital toenails' involvement, topical preparations that include imidazoles and allylamines, twice daily for a duration of 2–4 weeks, are sufficient. For a more extensive infection, a severe inflammatory reaction, or infections complicated by a secondary bacterial infection, systemic treatments may be necessary. Condy compresses containing potassium permanganate, or aluminum chloride 20% solution, can help decrease the bacterial load and quell inflammation. Adjunctive agents such as topical urea may be valuable in tinea pedis that is dry or hyperkeratotic. Oral antifungal agents like itraconazole 200–400 mg/day for 2 weeks and terbinafine 250 mg/day for 2–4 weeks are currently commonly prescribed. The clinical efficacy and mycological cure rates for both itraconazole and terbinafine far exceeds both fluconazole and griseofulvin. Oral ketoconazole has fallen out of favor due to its propensity to cause hepatotoxicity. A longer duration of therapy may be required in patients with recurrent/chronic tinea pedis.

Control of community spread is an important epidemiological strategy, although it comes riddled with difficult practical implementations. Eradication of the dermatophyte from an individual affected toe cleft is a demanding and laborious process; according to some schools of thought, this may not be completely achievable. Frequent cleaning of community showers and religious places where barefoot walking is mandatory needs to be strictly implemented to diminish the community burden of tinea pedis infections. The use of open footwear and loose-fitting socks goes a long way in helping achieve clinical remissions in affected patients. Additionally, the use of topical therapies like ciclopirox olamine, ketoconazole, naftifine hydrochloride, sulconazole nitrate, and miconazole nitrate possessing additional antibacterial activity can aid patients with mixed infections. Erratic treatment in terms of dose and duration hinders both clinical as well as mycological cure.

Tinea pedis: the etiology and global epidemiology of a common fungal infection. Ilkit M, Durdu M. Crit Rev Microbiol 2015; 43: 374–88.

Trichophyton rubrum is the predominant causative agent. Interdigital tinea pedis is the most common form. Tinea pedis may induce a T-helper 2 response, which may accentuate atopy and thus contribute to refractory atopic dermatitis. The prevalence increases with age and it is rare in children. One study also demonstrated a higher prevalence of tinea pedis in comparison to tinea capitis in schoolchildren. Developed countries have a higher prevalence of infection. It is also the most common concomitant mycosis associated with toenail onychomycosis. No conclusive prevalence differences are observed in diabetics. An id reaction (autoeczematization) is a specific complication with the active vesicobullous variant but not with other subtypes.

Prevalence and epidemiology of tinea pedis and toenail onychomycosis and antifungal susceptibility of the causative agents in patients with type 2 diabetes in Turkey. Oz Y, Qoraan I, Oz A, et al. Int J Dermatol 2017; 56: 68–74.

A case control study with 600 diabetic patients and 152 control non-diabetic patients was performed. The development of tinea pedis was significantly related to increasing age and male gender. *Trichophyton rubrum* (53%) outnumbered other isolates in diabetics by a significant proportion. Non-dermatophytic fungal isolates (28%) were not uncommon.

Increased risk of tinea pedis and onychomycosis among swimming pool employees in Netanya Area, Israel. Shemer A, Gupta AK, Amichai B, et al. Mycopathologia 2016; 181: 851–6.

A prospective study was conducted on 169 employees in 21 swimming pool centers in Netanya in which 30% employees had only tinea pedis and 46% had a concomitant onychomycosis. Swimming pools remain an important source of fungal disease causation and spread among close contacts. *T. mentagrophytes* was the most common isolate seen in about 1 in 3 employees with tinea pedis.

Internal environment of footwear is a risk factor for tinea pedis. Sasagawa Y. J Dermatol 2019; 46: 940–6.

This was a cross-sectional, observational study involving 420 patients. The internal environment of the footwear associated with a high dew point (which is an index of content of degree of moisture in the environment) had a significantly higher incidence of tinea pedis and this was influenced by climate. It was also observed that a higher external temperature and humidity were associated with a higher incidence of tinea unguium.

compared with tinea pedis. Use of leather shoes and high heels had a stronger association with the disease compared with other footwear. Penetration and proliferation of both *T. rubrum* and *T. mentagrophytes* in the stratum corneum is seen at a critical level of 90% footwear humidity. Thus, the length of time a footwear is worn also becomes important in disease causation.

The current Indian epidemic of superficial dermatophytosis due to *Trichophyton mentagrophytes* – a molecular study. Nenoff P, Verma SB, Vasani R, et al. *Mycoses* 2019; 62: 336–56.

A prospective study of 201 Indian patients with dermatophytic infections involving various areas of the body. Fungal culture material was identified by genomic Sanger sequencing of the internal transcribed spacer (ITS) region and the translation elongation factor (TEF)-1 α gene. Of the dermatophyte positive patients, 93% showed *T. mentagrophytes* and 7% showed *T. rubrum*. This was the first time that a switch from *T. rubrum* to *T. mentagrophytes* was demonstrated in India by molecular methods. The causative *T. mentagrophytes* ITS genotype VIII is now increasingly being identified in countries in Central Asia and Europe.

Specific Investigations

1. **Direct microscopic examination** of wet mount using 10% potassium hydroxide after scraping the edges of lesion with a No.15 blade. The number of false positives with direct microscopy is high due to its inability to differentiate between dermatophytic and non-dermatophytic organisms. Skill of the technician is important to prevent false negative reports.
2. **Culture using Sabouraud dextrose agar** with chloramphenicol alone and separately on Sabouraud dextrose agar with both chloramphenicol and cycloheximide, incubated at 37°C and 25°C, respectively, for up to 4–6 weeks. Culture is considered the gold standard but delayed results and poor sensitivity are a concern.
3. **Antifungal susceptibility testing** – MIC 50 and MIC 90 are calculated. Testing is performed using microbroth dilution technique of Clinical and Laboratory Standards Institute guidelines (CLSI M38-A2). It is important for achieving good therapeutic outcomes and decreasing antifungal resistance in the community.
4. **Histopathological examination** and periodic acid–Schiff staining of specimens to highlight the fungal hyphae. It takes about 2–3 days for preparation and is not specific for dermatophytes.
5. **Real-time polymerase chain reaction (RT-PCR)** targeting the chitin synthase 1 gene (CHS1) of dermatophytes.

Molecular diagnostics are gaining popularity. They are rapid, more sensitive, more specific, and more cost-effective in diagnosing the fungal infection than the already available traditional methods.

6. **The Dermatophyte Test Strip** detects dermatophytic antigen by immunochromatography using monoclonal antibodies that react with dermatophytes. It has a sensitivity of 84% and a specificity of 77%. It has a positive predictive value of 67% and negative predictive value of 90%. The positive and negative concordance rate is said to be about 80%.

Clinical application of a molecular assay for the detection of dermatophytosis and a novel non-invasive sampling technique. Gordon AK, McIver C, Kim M, et al. *Pathology* 2016; 48: 720–6.

Diagnosis of tinea pedis by the Dermatophyte Test Strip. Tsunemi Y, Takehara K, Miura Y, et al. *Br J Dermatol* 2015; 173(5): 1323–4.

First-Line Therapies

Topical therapy is recommended for most patients with tinea pedis. Gels and sprays are often used in interdigital involvement with maceration. Creams and ointments are used for the dry hyperkeratotic variant.

Topical

• Sertaconazole nitrate	A
• Econazole nitrate	A
• Naftifine hydrochloride	A
• Luliconazole	A
• Terbinafine (film-forming solution)	A
• Ciclopirox olamine	A
• Butenafine	A
• Bifonazole	A

A randomized, double-blind, vehicle-controlled trial of luliconazole cream 1% in the treatment of interdigital tinea pedis. Draelos ZD, Vlahovic TC, Gold MH, et al. *J Clin Aesthet Dermatol* 2014; 7: 20–7.

A vehicle-controlled study of 1% luliconazole cream once daily for 14 days was performed in 322 interdigital tinea pedis patients 12 years or older. At 6 weeks, complete clinical and mycological clearance was achieved by a higher percentage of patients on luliconazole in comparison to those applying the vehicle. The MIC 50/90 for luliconazole cream was 6–12 times lower for all species and isolates. No patient reported any adverse effects to treatment.

Comparative evaluation of the activity and clinical effectiveness of terbinafine and bifonazole preparations in the treatment of pedal mycosis. Korting HC, Kresimon J, Rychlik R. *Akt Dermatol* 2004; 30: 210–7.

The efficacy of terbinafine is similar to that of bifonazole with a shorter duration of treatment. It is available as a cream, gel, spray, and film-forming solution. This review evaluated eight placebo-controlled trials and found terbinafine to produce 80%–100% higher mycological cure rates than a placebo.

Fungicidal activity plus reservoir effect allow short treatment courses with terbinafine in tinea pedis. Schäfer-Korting M, Schoellmann C, Korting HC. *Skin Pharmacol Physiol* 2008; 21: 203–10.

It has been reliably demonstrated that even a 1-week, single daily application of terbinafine is superior to 4 weeks' application of azoles. The innovative film-forming solution delivers terbinafine to the affected tissue for as long as 13 days following a single application. Thus, the reservoir effect of the fungicidal terbinafine in the stratum corneum makes it superior according to the study.

The role of naftifine HCl 2% gel and cream in treating moccasin tinea pedis. Vlahovic TC. J Drugs Dermatol 2016; 15(2 Suppl): s56–9.

Naftifine 2%, an allylamine, is effective for the treatment of moccasin variant of tinea pedis. A clinical trial done to study its effectiveness demonstrated a superior clinical efficacy with naftifine gel compared with the vehicle at the end of 2 weeks of treatment. This beneficial effect of the gel over vehicle was maintained even at 4 weeks posttreatment. Combining this molecule with urea 39% is said to be beneficial for patients with hyperkeratotic moccasin tinea pedis. Naftifine additionally has antiinflammatory and antibacterial properties, thus helping in addressing superinfections.

Recent research has focused on compliance enhancing drug formulations for the treatment of tinea pedis. The innovative water-lipid delivery system in a foam formulation is found to be easier to apply and hence more acceptable; econazole in a foam formulation is an example.

Treatment of signs and symptoms (pruritus) of interdigital tinea pedis with econazole nitrate foam, 1. Hoffman LK, Raymond I, Kircik L. J Drugs Dermatol 2018; 17: 229–32.

This investigator-blinded, split-body, observational pilot study compared econazole nitrate topical foam (1%) with twice daily application of ketoconazole cream (2%) for 2 weeks in 20 patients. The reduction in pruritus, assessed by a visual analog scale, was much higher with econazole foam compared with ketoconazole cream. The foam formulation was rated as good or excellent by all the patients assessed.

Evaluation of the efficacy of ciclopirox 0.77% gel in the treatment of tinea pedis interdigitalis (dermatophytosis complex) in a randomized, double-blind, placebo-controlled trial. Gupta AK, Skinner AR, Cooper EA. Int J Dermatol 2005; 44: 590–3.

Ciclopirox is an antifungal agent with activity against both Gram-positive and Gram-negative bacteria, making it a useful therapeutic option in mixed infections. This was a prospective, randomized, double-blind, placebo-controlled clinical study of 100 patients. At week 8, the difference in mycologic cure between twice-daily use and vehicle was 37%; the difference between once-daily use and vehicle was 39%. Mycologic cure was significantly higher with twice-daily ciclopirox at week 8 compared with vehicle (50.0% vs. 12.5%, respectively). It also led to a significant reduction of bacterial counts in the affected area, thus making it an agent of choice for concomitant bacterial infections, also known as ‘dermatophytosis complex’. There was no difference between once-daily and twice-daily ciclopirox application.

Second-Line Therapies

Topical

- Ketoconazole
- Dapconazole tosylate

D
D

Dapconazole versus ketoconazole in the treatment of interdigital tinea pedis. Gobbato AAM, Gobbato CARS, Moreno RA, et al. Int J Clin Pharmacol Ther 2018; 56: 31–3.

This is a double-blind, observational study of 48 patients with interdigital tinea pedis of both feet. Patients were treated with either dapconazole tosylate 2% cream or ketoconazole 2% cream twice a day for 14 consecutive days. Clinical and mycological per-protocol cure was achieved in 66.0% and 68.1% of feet treated with ketoconazole and dapconazole, respectively.

Third-Line Therapies

Topical

- Tolnaftate
- Photodynamic therapy

D
D

Enhancement of the topical tolnaftate delivery for the treatment of tinea pedis via provesicular gel systems. Abou Samra MM, Salama AH. J Liposome Res 2017; 27: 324–34.

Tolnaftate is a thiocarbamate antifungal used in tinea pedis but has the limitation of achieving insufficient penetration in the currently available formulations. Provesicular systems for drug delivery become diluted with moisture when they make contact with the skin. Confocal laser scanning microscopy shows enhanced penetration of a drug using provesicular systems in patients with tinea pedis compared with those using a cream.

5-Aminolevulinic acid-photodynamic treatment for dermatophytic tinea pedis of interdigital type: a small clinical study. Sotiriou E, Koussidou T, Patsatsi A, et al. J Eur Acad Dermatol Venereol 2009; 23: 203–4.

Twenty patients with tinea pedis were treated with 20% topical 5-aminolevulinic acid (ALA) under occlusion in this study. Tinea pedis lesions were treated with red light from a non-coherent source 3 hours after application. Only three patients had a complete clinical and mycological cure. The possible lack of significant efficacy was postulated to be uneven application of ALA in interdigital spaces due to their irregular shape.

Third-Line Therapies

Systemic

- Itraconazole
- Terbinafine
- Fluconazole
- Griseofulvin

A
A
A
A

Expert Consensus on The Management of Dermatophytosis in India (ECTODERM India). Rajagopalan M, Inamadar A, Mittal A, et al. BMC Dermatol 2018; 18: 6.

Systemic therapy is only reserved for patients who have failed topical therapy or have a chronic and recurrent disease. Their current recommendations include terbinafine 250 mg once a day for 2 weeks or itraconazole 200 mg once a day for 4 weeks. They recommend terbinafine 250 mg once a day for 2 weeks in treatment-naïve patients and 200–400 mg itraconazole in recalcitrant disease.

The beneficial role of health education programs as preventive measures for development of tinea pedis is also highlighted.

A prospective study of the epidemiological and clinical patterns of recurrent dermatophytosis at a tertiary care hospital in India. Pathania S, Rudramurthy SM, Narang T, et al. Indian J Dermatol Venereol Leprol 2018; 84: 678–84.

This cross-sectional study was done involving 150 patients with recurrent dermatophytosis. Sharing of footwear, clothes, and towels was commonly observed among household contacts. More than half of the patients used topical steroids alone or in combination with antibacterial and antifungal agents.

T. mentagrophytes was the most commonly isolated organism. Itraconazole was the most effective drug against *T. mentagrophytes*, *T. rubrum*, and *T. interdigitale*. A high MIC for terbinafine was noted in few isolates and has been postulated to be due to mutation of the squalene epoxidase gene in *T. rubrum*. Fluconazole was moderately effective and griseofulvin was the least effective antifungal agent.

A simple interdigital separator to aid the management of tinea pedis. Kaliyadan F, Ashique KT. Indian Dermatol Online J 2019; 10: 347–8.

A polystyrene thermocol spacer cut to the size of a patient's interdigital space and is hollowed to fit silica gel granules. It

acts both by the desiccant effect of silica granules having a drying effect and physical distancing between the toes. This simple device is thought to be most effective in individuals using occlusive footwear.

New antifungal agents and new formulations against dermatophytes. Gupta AK, Foley KA, Versteeg SG. Mycopathologia 2017; 182: 127–41.

Drugs currently in development (e.g., phase II and phase III clinical trials) for the treatment of tinea pedis include VT1161, Drug 33525, LAS41003, and nitric oxide.

Tinea unguium

Antonella Tosti, Matilde Iorizzo



Onychomycosis accounts for about half of all nail abnormalities and a third of all fungal infections of the skin. It affects about 10% of the general population, with figures that vary in different areas of the world. The majority of cases of onychomycosis are due to dermatophytes, the most common being *Trichophyton rubrum* and *Trichophyton interdigitale*, but this also varies depending on the part of the world. The prevalence of onychomycosis increases with age, and the toenails are most frequently affected. Tinea pedis is associated in most patients. Predisposing factors for onychomycosis include old age, diabetes, HIV infection, peripheral vascular impairment, peripheral neuropathies, podiatric abnormalities, sports activities, and traumatic nail disorders.

MANAGEMENT STRATEGY

Different clinical patterns of nail infection result from the way in which fungi colonize the nail.

The type of nail invasion depends on both the causative fungus (dermatophyte, mold or yeast) and host susceptibility. In distal subungual onychomycosis (DSO), the most common type, fungi reach the nail from the hyponychium and colonize the nail bed, producing onycholysis and subungual hyperkeratosis. In proximal subungual onychomycosis (PSO), fungi penetrate the nail matrix via the proximal nailfold and colonize the deep portion of proximal nail plate, resulting in a subungual white patch located in the lunula area. In white superficial onychomycosis (WSO), fungi are localized on the nail plate surface and produce whitish opaque, friable areas on the nail plate. The nail plate can also be deeply invaded (deep WSO) in cases of infection due to molds, in children, and in immunocompromised patients. Host factors, including the thinner nail plate typically seen in children, may contribute to the severity of WSO.

Onychomycosis is an infection and should always be treated. The goals for antifungal therapy are mycological cure and a

normal-looking nail. The latter can be impossible to achieve when onychomycosis is associated with traumatic nail dystrophies. Signs of a good response are no proximal progression and growth of a proximal area of normal-appearing nail.

Treatment of onychomycosis depends on the clinical type of the onychomycosis, the number of affected nails, the severity of involvement, presence of comorbidities, and concomitant drugs.

A systemic treatment is always required in PSO, in DSO involving >50% of the nail plate or the lunula region, and in deep WSO. Superficial WSO and DSO limited to the distal nail can be treated with a topical agent such as efinaconazole, tavaborole, amorolfine, or ciclopirox. Combined systemic and topical treatments are useful to increase the cure rate.

In recent years, the number of patients with AIDS-related or iatrogenic immunosuppression has substantially increased, leading to the appearance of new patterns of nail invasion by fungi. Migratory flows have also changed the pattern of pathogens with new emerging agents. These factors substantially changed treatment options.

Terbinafine is an allylamine with fungicidal properties. Interactions of terbinafine with other drugs are extremely rare. Adverse effects may involve gastrointestinal function and the skin. Patients with known lupus erythematosus or photosensitivity are predisposed to drug-induced or drug-exacerbated disease. Liver toxicity and taste disturbances can occasionally occur. Recent evaluations confirm that among pregnant women exposed to terbinafine, no increased risk of major malformations or spontaneous abortion is identified (pregnancy category B). It is, however, excreted into breast milk. Terbinafine is usually administered at a dose of 250 mg daily; treatment duration is 6 weeks for fingernails and 12 weeks for toenails. Clinical trials have repeatedly demonstrated a higher efficacy of terbinafine compared with other antifungal treatments. A meta-analysis of 18 studies on terbinafine for onychomycosis showed a mycological cure rate of 76%. Since terbinafine persists in the nail for at least 30 weeks after the completion of treatment, it is also effective if administered as a pulse regimen (not US Food and Drug Administration [FDA] approved) at a dose of 250 mg/day for 1 month, every other month (2 pulses), or 500 mg/day for 1 week a month for 2–4 months.

Itraconazole is a synthetic triazole with fungistatic activity and a broad spectrum of action. It is approved at a daily 200 mg dose. It can also be administered as pulse therapy at a dose of 400 mg daily for 1 week per month (3–4 pulses). Treatment duration is 6 weeks for fingernails and 12 weeks for toenails. The drug should be administered with a high-fat meal and/or an acidic beverage to improve its absorption. It is now not widely prescribed due to safety profile and drug interactions. Adverse effects may involve the gastrointestinal system, the liver, and the skin. Its use has also been associated with congestive heart failure. A meta-analysis of six studies on pulse itraconazole for onychomycosis showed a mycological cure rate of 63%.

Supplemental (booster) therapy has been suggested to improve cure rates in patients with poor prognostic factors. An additional 4 weeks of terbinafine or itraconazole is advisable in these patients, but it is not FDA approved.

Poor prognostic factors include nail involvement >50%, involvement of the lateral portion of the nail plate, subungual hyperkeratosis thicker than 2 mm, white/yellow or orange/brown streaks in the nail (including dermatophytoma), matrix involvement, and immunosuppression. Recurrence (relapse or reinfection) of onychomycosis is, however, not uncommon, with reported rates ranging from 10% to 53%.

Fluconazole is a bis-triazole broad-spectrum fungistatic drug with high oral bioavailability, widely utilized, but not approved

for onychomycosis. It is administered as pulse treatment, with regimens ranging from 150 to 450 mg once a week for 6 (fingernails) to 9 (toenails) months. A meta-analysis of three studies on fluconazole for onychomycosis showed a mycological cure rate of 48%.

Posaconazole is a new azole that has been evaluated in onychomycosis at 200 mg daily and its use is likely to be limited to second-line treatment in terbinafine-refractory infections, those with non-dermatophyte mold infections, or those sensitive to or intolerant of terbinafine. It showed a mycological cure rate of 48%.

A new systemic antifungal, *VT-1161*, a potent and selective inhibitor of fungal CYP51, showed promising results in phase IIb clinical trials on toenail onychomycosis (61%–72% mycological cure).

Efinaconazole 10% solution is a topical triazole antifungal solution with a broad spectrum of activity. It should be applied daily and results from clinical studies indicate that 25% of patients achieve complete or almost complete cure, defined as $\leq 5\%$ affected target nail area and mycological cure after 48 weeks of treatment.

Tavaborole 5% solution is a novel, broad-spectrum, oxaborole antifungal agent with strong antifungal activity against *T. rubrum* and *T. mentagrophytes*. It should be applied daily and results from clinical studies show that 16.6% of patients achieve almost complete cure, defined as $\leq 5\%$ affected target nail area and mycological cure after 48 weeks of therapy.

Other topical antifungals include *amorolfine* 5% nail lacquer (not FDA approved) and *ciclopiroxolamine* 8% nail lacquer. Amorolfine is applied once a week, whereas ciclopiroxolamine should be applied daily.

The clinical efficacy of monotherapy with nail lacquers is low, but topical antifungals might increase cure rate when combined with oral treatment. Surgical or chemical debridement of the thickened nail plate also increases cure rate. Several new topical formulations are, however, currently on trials.

At present there is no FDA-approved treatment for onychomycosis in children and available drugs should be used off label. In a review of 26 studies, oral treatment of onychomycosis resulted in an overall 70.8% complete cure rate with a favorable safety profile. The same is for topical therapy.

Photodynamic therapy has recently been reported to be effective in *T. rubrum* onychomycosis, but affected toenails need to be filed or treated with urea before application of ALA.

Laser devices have also been utilized to treat onychomycosis, including neodymium:yttrium-aluminum-garnet (Nd:YAG) laser and diode laser. Penetration of the nail plate and targeting of fungi occurs at wavelengths of 750–1300 nm. Evidence-based data on efficacy of these different lasers are, however, still poor.

Specific Investigations

- Direct microscopy of 40% potassium hydroxide (KOH) preparations of subungual scales
- Cultures of nail scrapings in Sabouraud-agar-chloramphenicol and Sabouraud-agar-chloramphenicol + actidione media
- Histopathology of periodic acid–Schiff (PAS)-stained nail clippings
- Polymerase chain reaction (PCR)
- Dermatophyte test strip
- Dermoscopy
- Record onychomycosis severity

The diagnosis of onychomycosis always requires laboratory confirmation, as differential diagnosis from psoriasis or traumatic onychodystrophy is often impossible on a clinical basis.

Dermoscopy is extremely helpful because it identifies three recurring patterns, two of which were present only in DSO (jagged proximal edge with spikes of the onycholytic area and longitudinal striae) and one only in traumatic onycholysis (linear edge – without spikes – of the onycholytic area). Fungal elements in the affected nails can be detected using KOH preparations of the nail samples or histopathology of PAS-stained nail clippings. An immunochromatography test, the dermatophyte test strip, can also be used to detect dermatophytes by visualizing mycotic antigens. PCR has high sensitivity and provides fast results, but it might be too sensitive, producing false positive results. All these methods, however, do not detect fungal viability.

Culture is the gold standard to identify the responsible species of fungi, mandatory not only from an epidemiological point of view, but also to introduce the correct treatment. However, cultures have high rates of false negative results.

Cost-effectiveness of diagnostic tests for toenail onychomycosis: a repeated-measure, single-blinded, cross-sectional evaluation of 7 diagnostic tests. Lilly KK, Koshnick RL, Grill JP, et al. *J Am Acad Dermatol* 2006; 55: 620–6.

This study compared the cost-effectiveness of diagnostic tests for onychomycosis. KOH and PAS were equally sensitive. Identification of the responsible fungus can only be done using cultures. A negative mycological result does not rule out onychomycosis, as direct microscopy is negative in up to 10% of cases and culture in up to 30%. Correct sampling of nail debris is mandatory for obtaining reliable mycological results. In the most common variety of onychomycosis (DSO), culture sensitivity improves the more proximal the location of the sample.

Optimising the diagnostic strategy for onychomycosis from sample collection to FUNGAL identification evaluation of a diagnostic kit for real-time PCR. Petinataud D, Berger S, Ferdynus C, et al. *Mycoses* 2016; 59: 304–11.

This study evaluates a commercial real time PCR kit on 180 nail samples showing that the kit has high specificity and sensitivity in detecting dermatophytes, regardless of sample quality.

Clinical study of Dermatophyte Test Strip, an immunochromatographic method, to detect tinea unguium dermatophytes. Tsunemi Y, Hiruma M. *J Dermatol* 2016; 43: 1417–23.

This test allows easy and fast detection of dermatophytes by visualizing mycotic antigens by immunochromatography. It only identifies dermatophyte infections that in this study were positive in 90.5% of specimens.

Nail digital dermoscopy (onychoscopia) in the diagnosis of onychomycosis. Piraccini BM, Balestri R, Starace M, et al. *J Eur Acad Dermatol Venereol* 2013; 27: 509–13.

Since onychomycosis might be difficult to differentiate from traumatic onycholysis and psoriasis on a clinical basis, dermoscopy of the nail unit can be a valid aid to perform the correct diagnosis. Specific patterns of the three diseases have been identified and, in selected cases, they help to avoid unnecessary mycology.

A new classification system for grading the severity of onychomycosis: Onychomycosis Severity Index. Carney C, Tosti A, Daniel R, et al. *Arch Dermatol* 2011; 147: 1277–82.

The onychomycosis severity index has recently been proposed to grade the severity of DSO and monitor response to therapy. This score is obtained by multiplying the score for the area of involvement (range 0–5) by the score for the proximity of disease to the matrix (range 1–5). Ten points are added for the presence of a longitudinal streaking or a patch (dermatophytoma) or for greater than 2 mm of subungual hyperkeratosis. Mild onychomycosis is scored 1–5; moderate, 6–15; severe, 16–35.

First-Line Therapy

- Oral terbinafine 250 mg/day

A

Onychomycosis: diagnosis and definition of cure. Scher RK, Tavakkol A, Sigurgeirsson B, et al. *J Am Acad Dermatol* 2007; 56: 939–44.

Guidelines for the correct management of onychomycosis, including criteria for diagnosis of dermatophyte onychomycosis, list of poor prognostic factors, criteria for assessing cure, and risks of relapses.

Oral therapy for onychomycosis: an evidence-based review. de Sá DC, Lamas AP, Tosti A. *Am J Clin Dermatol* 2014; 15: 17–36.

Terbinafine 250 mg daily is the most effective oral treatment of onychomycosis.

Treatment of dermatophyte nail infections: an open randomized study comparing intermittent terbinafine therapy with continuous terbinafine treatment and intermittent itraconazole therapy. Tosti A, Piraccini BM, Stinchi C, et al. *J Am Acad Dermatol* 1996; 34: 595–600.

An open, randomized study of 63 patients has been performed with three treatment regimens.

At the end of the follow-up period (6 months after discontinuation of treatment), 16 of the 17 patients (94.1%) with toenail onychomycosis were mycologically cured in the terbinafine 250 mg group, 16 of 20 (80%) in the terbinafine 500 mg group, and 15 of 20 (75%) in the itraconazole group.

The successful treatment of *Trichophyton rubrum* nail bed (distal subungual) onychomycosis with intermittent pulse-dosed terbinafine. Zaias N, Rebell G. *Arch Dermatol* 2004; 140: 691–5.

The objective of this study has been to determine the effectiveness of intermittent administration of oral terbinafine (250 mg/day for 7 consecutive days every 2–4 months) to cure DSO and to determine the maximum effective treatment interval. Terbinafine has the best efficacy when pulse-dosed for 7 days every 3 months.

The efficacy and safety of pulse vs. continuous therapy for dermatophyte toenail onychomycosis. Gupta AK, Stec N, Bamimore MA, et al. *J Eur Acad Dermatol Venereol* 2020; 34: 580–8.

This systematic review and network meta-analysis compared the efficacy (mycological cure) and adverse event rates of terbinafine, itraconazole, and fluconazole. Thirty studies have been evaluated. Use of continuous terbinafine for 24 weeks – but not 12 weeks – was significantly more likely to result in mycological cure than continuous itraconazole for 12 weeks or weekly fluconazole for 9–12 months. However, continuous and pulse regimens for terbinafine and itraconazole have similar efficacies and rates of adverse events.

Second-Line Therapies

- Oral itraconazole 200 mg/day or 400 mg/day for 1 week a month A
- Oral fluconazole 300–450 mg/week A
- Oral posaconazole 200/day A

Antifungal pulse therapy for onychomycosis. A pharmacokinetic and pharmacodynamic investigation of monthly cycles of 1-week pulse therapy with itraconazole. De Doncker P, Decroix J, Piérard GE, et al. *Arch Dermatol* 1996; 132: 34–41.

After stopping the last pulse, itraconazole remains in the nail plate at levels above 300 ng/g for several months. Clinical cure rates between 76% and 84% and negative mycological examination findings between 72% and 80%, respectively, were observed. These data suggest that pulse therapy is an effective and safe treatment option.

Double blind, randomised study of continuous terbinafine compared with intermittent itraconazole in treatment of toenail onychomycosis. The LION Study Group. Evans EG, Sigurgeirsson B. *BMJ* 1999; 318: 1031–5.

Continuous terbinafine is significantly more effective than intermittent itraconazole in the treatment of patients with toenail onychomycosis.

Evidence-based optimal fluconazole dosing regimen for onychomycosis treatment. Gupta AK, Drummond-Main C, Paquet M. *J Dermatolog Treat* 2013; 24: 75–80.

Duration of treatment is more important than weekly fluconazole doses for cure of toenail, and possibly fingernail, onychomycosis.

A randomized, placebo- and active-controlled, parallel-group, multicentre, investigator blinded study of four treatment regimens of posaconazole in adults with toenail onychomycosis. Elewski B, Pollak R, Ashton S, et al. *Br J Dermatol* 2012; 166: 389–98.

The objective of this study has been to evaluate the efficacy of four posaconazole regimens compared with placebo, to assess the safety and tolerability of the drug and to estimate the relative efficacy against terbinafine. The efficacy and favorable safety profile of posaconazole 200 mg/day suggests a potential new treatment for onychomycosis. The availability of low-cost generic terbinafine may limit posaconazole use to second-line treatment of infections refractory to, or patients intolerant of, terbinafine, or mold infections.

Third-Line Therapies

- Photodynamic therapy (PDT) B
- Lasers A

Usefulness of photodynamic therapy in the management of onychomycosis. Robres P, Aspiroz C, Rezusta A, et al. *Actas Dermosifiliogr* 2015; 106: 795–805.

According with their own experience and review of previous studies the authors propose a protocol of three PDT sessions, separated by an interval of 1 or 2 weeks, using methyl-aminolevulinate 16% and red light. Treatment should be preceded by nail plate avulsion using 40% urea.

A critical review of improvement rates for laser therapy used to treat toenail onychomycosis. Gupta AK, Versteeg SG. *J Eur Acad Dermatol Venereol* 2017; 31: 1111–8.

Lasers provide preliminary evidence of clinical improvement and clear nail growth in toenail onychomycosis, consistent with the FDA clearance for aesthetic end points. They, however, do not provide efficacy rates for medical end points that equate or exceed those found with traditional therapies.

Topical Therapies

• Amorolfine 5% nail lacquer	A
• Ciclopiroxolamine 8% nail lacquer	A
• Efinaconazole 10% solution	A
• Tavaborole 5% solution	A

Efinaconazole 10% solution in the treatment of toenail onychomycosis: two phase III multicenter, randomized, double-blind studies. Elewski BE, Rich P, Pollak R, et al. *J Am Acad Dermatol* 2013; 68: 600–8.

Efficacy of efinaconazole 10% solution was evaluated in two 52-week prospective, multicenter, randomized, double-blind studies in patients 18–70 years of age with mild-to-moderate distal lateral subungual onychomycosis (DLSO), without dermatophytoma or lunula involvement. These studies enrolled 1655 subjects, who were treated for 48 weeks, with a 4-week follow-up. Pooled data from the two studies show that at the end of the study, 54.4% of subjects treated with efinaconazole 10% solution obtained mycological cure compared with 16.9% with vehicle, and 16.5% achieved clinical cure compared with 4.4% with vehicle. A complete or almost complete cure, defined as $\leq 5\%$ affected target nail area and mycological cure, was achieved in 25% of patients on efinaconazole and 7.2% of patients on vehicle. Treatment success, defined as affected target toenail area of $\leq 10\%$, was obtained in 42.6% of patients treated with efinaconazole 10% solution compared with 16.1% with vehicle.

Successful treatment of dermatophytomas in 19 patients using efinaconazole 10% solution. Wang C, Cantrell W, Canavan T, et al. *Skin Appendage Disord* 2019; 5: 304–8.

In this study efinaconazole solution has been evaluated in patients with onychomycosis complicated by dermatophytomas. Cure was achieved in 65% of target great toenails. All dermatophytomas resolved and did not recur during the study. The median time to dermatophytoma resolution was 16 weeks.

Efficacy and safety of tavaborole topical solution, 5%, a novel boron-based antifungal agent, for the treatment of toenail onychomycosis: results from 2 randomized phase-III studies. Elewski BE, Aly R, Baldwin SL, et al. *J Am Acad Dermatol* 2015; 73: 62–9.

Efficacy of tavaborole 5% solution was evaluated in two 52-week prospective, multicenter, randomized, double-blind studies in patients 18–70 years of age with mild-to-moderate DLSO (20–60% nail involvement), without dermatophytoma or lunula (matrix) involvement. These studies enrolled 1198 subjects, who were treated for 48 weeks, with a 4-week follow-up.

Pooled data from both studies show that 33.5% of subjects treated with tavaborole 5% solution obtained mycological cure compared with 9.7% with vehicle, and 7.8% achieved clinical cure compared with 1% with vehicle. A complete or almost complete cure, defined as $\leq 5\%$ affected target nail area and mycological cure, was achieved in 16.6% of patients on tavaborole and in 2.7% of patients on vehicle.

A multicentre, randomized, controlled study of the efficacy, safety and cost-effectiveness of a combination therapy with amorolfine nail lacquer and oral terbinafine compared with oral terbinafine alone for the treatment of onychomycosis with matrix involvement. Baran R, Sigurgeirsson B, de Berker D, et al. *Br J Dermatol* 2007; 157: 149–57.

In this study, 249 patients were randomized to receive either a combination of amorolfine hydrochloride 5% nail lacquer once weekly for 12 months plus terbinafine 250 mg once daily for 3 months, or terbinafine alone once daily for 3 months. A significantly higher success rate was observed for patients in the combination group relative to those in the terbinafine monotherapy group at 18 months (59.2% vs. 45.0%).

Patient-reported outcomes from two randomised studies comparing once-weekly application of amorolfine 5% nail lacquer to other methods of topical treatment in distal and lateral subungual onychomycosis. Schaller M, Sigurgeirsson B, Sarkany M. *Mycoses* 2017; 60: 800–7.

The objective of this study was to investigate patient-reported outcomes (treatment utilization, adherence, and satisfaction) in onychomycosis treated with once-weekly amorolfine 5% nail lacquer versus once-daily ciclopirox 8% nail lacquer (Study A) or once-daily urea 40% ointment/bifonazole 1% cream combination regimen (Study B). More subjects adhered to amorolfine (85%) than to ciclopirox (60%) and urea/bifonazole combination (59.1%). Overall, patients were satisfied with amorolfine and ciclopirox, but not with urea/bifonazole.

Ciclopirox nail lacquer topical solution 8% in the treatment of toenail onychomycosis. Gupta AK, Fleckman P, Baran R. *J Am Acad Dermatol* 2000; 43: S70–80.

Studies conducted worldwide demonstrate the efficacy of ciclopirox nail lacquer for the treatment of finger and toe onychomycosis.

Tinea versicolor (pityriasis versicolor)

Aditya K. Gupta, Elizabeth A. Cooper, Kelly A. Foley



Pityriasis (tinea) versicolor (PV), a superficial fungal infection of the skin, is caused by the lipophilic yeast species *Malassezia*, which are present in body areas rich in sebum, such as the face, back, upper trunk, etc. *Malassezia* fungi are a normal part of human commensal skin flora, and PV results when they are converted from the yeast phase to a mycelial phase, and then are able to infect the stratum corneum, producing the characteristic hypo- or hyperpigmented lesions.

Infection is associated with sebaceous gland activity; hence, infection is most often seen in adults and postpubescent adolescents, rarely in prepubescent children. An equal prevalence between the sexes has been noted. The risk factors are both endogenous and environmental, such as high temperature and humidity, malnutrition, the use of oral contraceptives, hyperhidrosis, genetic susceptibility, increased plasma cortisol levels, and immunodeficiency.

Initially, only two species of *Malassezia* (formerly known as *Pityrosporum*) were described. Genetic research in the 1990s confirmed at least seven species of *Malassezia*, and more have since been discovered. Thus far, 14 species of the genus *Malassezia* have been identified, of which nine have been isolated from human skin.

MANAGEMENT STRATEGY

Topical treatment is the first-line therapy in most cases. Topical azoles formulated as gels, creams, solutions, or shampoos (ketoconazole, fluconazole, bifonazole, clotrimazole, miconazole, etc.) have demonstrated efficacy for PV. The allylamine *terbinafine* has several topical formulations (solution, cream, gel, or spray)

that have been used effectively, as have formulations of the benzylamine *butenafine*. Topical *ciclopirox* provides both antifungal and anti-inflammatory activity against *Malassezia*.

Systemic antifungal therapies may be warranted in severe cases, or cases with widespread body involvement, patients with recurrent disease, or those who are immunocompromised. Patients may also prefer a short-duration oral therapy to frequent application of a topical agent.

Second-line therapy for cases refractive to topical therapy may be treated with oral antifungals. *Itraconazole*, *fluconazole*, and *ketoconazole* show high efficacy in the literature; however, it is now recommended by the US Food and Drug Administration and Health Canada that oral ketoconazole not be used for superficial fungal infections when less hepatotoxic alternatives are available. In contrast to topical terbinafine, oral terbinafine is not effective, and nor is griseofulvin.

Treatment does not vary with hyperpigmented versus hypopigmented disease. Although fungal organisms may be eradicated after 2–4 weeks of therapy, it may take significantly longer before the skin's normal pigmentation is restored, particularly with hypopigmented lesions.

Relapse of PV is common owing to endogenous host factors: recurrence rates have been reported as high as 60%–90% 2 years after treatment. Both ketoconazole (a single 400 mg dose or 200 mg daily for 3 days once monthly) and itraconazole (a single 400 mg dose once monthly for 6 months) have been used in prophylactic regimens for PV, though oral ketoconazole is no longer recommended because of its potential for hepatotoxicity.

Specific Investigations

- Wood light
- Direct microscopy on potassium hydroxide (KOH) specimens
- Dermoscopy

Malassezia organisms should be identified by skin scrapings for definitive diagnosis, and are easily identified with potassium hydroxide (KOH) microscopic examination, which reveals fungal hyphae in a typical 'spaghetti and meatball' pattern. Addition of a contrast stain such as 1% Chicago sky blue 6B and 8% KOH can assist microscopic visualization of *Malassezia* fungal species.

PV lesions fluoresce yellow/green or gold under Wood light; however, the examination is positive in only one-third of all PV cases, most likely when the causative organism is *M. furfur*.

Besides KOH microscopy and Wood light examination, dermoscopy is an adjunct diagnostic method for PV. White scaly patches on skin furrows with distinct demarcations are unique clinical features of PV that are visualized by dermoscopy.

First-Line Therapies

Topical antifungal agents

• Ketoconazole	A
• Bifonazole	A
• Terbinafine	A
• Clotrimazole	A
• Econazole	A
• Oxiconazole	A
• Butenafine	A
• Ciclopirox	A
• Fluconazole shampoo	A
• Selenium sulfide 2.5%	B
• Tioconazole	B
• Zinc pyrithione shampoo	B

Pityriasis versicolor: a review of pharmacological treatment options. Gupta AK, Kogan N, Batra R. *Exp Opin Pharmacother* 2005; 6: 165–78.

This is a thorough summary of peer-reviewed studies of topical and oral therapies in the treatment of tinea versicolor until 2005. Azole topical agents have shown good mycological cure, clinical cure, and complete cure in many double-blind randomized clinical trials, as have the non-specific topical agents (zinc pyrithione shampoo, selenium sulfide, etc.) and terbinafine.

Terbinafine 1% cream and ketoconazole 2% cream in the treatment of pityriasis versicolor: a randomized comparative clinical trial. Rad F, Nik-Khoo B, Yaghmaee R, et al. *Pak J Med Sci* 2014; 30: 1273–6.

A randomized, single-blind trial, with terbinafine 1% cream or ketoconazole 2% cream applied twice daily for 2 weeks. Cure rates (negative KOH microscopy with clinical cure) at 2 weeks (terbinafine: 72.1%; ketoconazole: 64.3%) and 8 weeks (terbinafine: 70.8%; ketoconazole: 61.9%) were not significantly different between treatments.

Can pityriasis versicolor be treated with 2% ketoconazole foam? Cantrell WC, Elewski BE. *J Drugs Dermatol* 2014; 13: 855–9.

Eleven patients in this pilot study applied ketoconazole 2% foam twice daily for 2 weeks. Clinical improvement was observed over 4 weeks and seven patients showed negative KOH microscopy.

A randomized controlled trial of combination treatment with ketoconazole 2% cream and adapalene 0.1% gel in pityriasis versicolor. Shi T-W, Zhang J-A, Tang Y-B, et al. *J Dermatol Treat* 2015; 26: 143–6.

A double-blind trial comparing combination once daily ketoconazole cream and adapalene gel with twice daily ketoconazole cream for 2 weeks. Total improvement rate (clinical improvement with negative microscopy) at 4 weeks was 92% in the combination group and 72% in the ketoconazole group ($p=0.009$).

Second-Line Therapies

Oral antifungal agents

- Itraconazole **A**
- Fluconazole **A**

Oral prophylaxis

- Itraconazole **A**

Systematic review of systemic treatments for tinea versicolor and evidence-based dosing regimen recommendations. Gupta AK, Lane D, Paquet M. *J Cutan Med Surg* 2014; 18: 79–90.

This is an extensive evidence-based review of clinical trials published up to mid-2013 that reported mycological cure for PV. The literature supports regimens for itraconazole (200 mg/day for 5 or 7 days) and fluconazole (150 or 300 mg weekly for 2 or 4 weeks).

Efficacy of itraconazole in the prophylactic treatment of pityriasis (tinea) versicolor. Faergemann J, Gupta AK, Al Mofadi A, et al. *Arch Dermatol* 2002; 138: 69–73.

Patients achieving mycological cure after open treatment with itraconazole 200 mg once daily for 7 days entered a double-blind, placebo-controlled trial of itraconazole prophylaxis (itraconazole or placebo: 200 mg twice daily 1 day per month for 6 consecutive

months). At the end of prophylaxis, 88% of itraconazole patients remained mycologically negative, compared with only 57% of placebo-treated patients ($p<0.001$).

Single-dose oral fluconazole versus topical clotrimazole in patients with pityriasis versicolor: a double-blind randomized controlled trial. Dehghan M, Akbari N, Alborzi N, et al. *J Dermatol* 2010; 37: 699–702.

Patients were randomized to receive a single 400mg dose of oral fluconazole with placebo cream or a placebo capsule with 1% clotrimazole cream, each applied twice daily for 2 weeks. At 12 weeks, 92% of the fluconazole group achieved complete cure whereas 81.8% of the clotrimazole group achieved complete cure ($p=0.77$).

Third-Line Therapies

- Pramiconazole (oral triazole) **A**
- Adapalene **A**
- Naftifine (topical allylamine) **B**
- Dapacozazole tosylate (topical imidazole) **B**
- *Cymbopogon citratus* (DC) Stapf essential oil **B**
- Isotretinoin **E**

A double-blind, randomized, placebo-controlled, dose-finding study of oral pramiconazole in the treatment of pityriasis versicolor. Faergemann J, Todd G, Pather S, et al. *J Am Acad Dermatol* 2009; 61: 971–6.

Participants were randomized into six pramiconazole treatment groups: (1) 100 mg taken once; (2) 200 mg taken once; (3) 200 mg taken once daily for 2 days; (4) 200 mg taken once daily for 3 days; (5) 400 mg taken once; (6) placebo taken once daily for 3 days. The primary efficacy outcome was effective treatment (negative KOH microscopy and resolution or minimal residuals of clinical signs for participants with severe baseline scores). At day 28, the highest proportion of participants with an effective cure received 200 mg daily for 2 days, 84.0% (95% CI: 69.6–98.4) and 200 mg daily for 3 days, 84.6% (95% CI: 70.7–98.5).

Pramiconazole is not currently approved or marketed. As more data accumulates, the level of evidence may alter.

Role of adapalene in the treatment of pityriasis versicolor. Shi T, Ren X, Yu H, et al. *Dermatol* 2012; 224: 184–8.

A prospective, randomized, double-blind clinical trial compared adapalene cream and 2% ketoconazole cream applied to the torso twice daily for 2 weeks. No significant difference between treatments was found at 4 weeks. Participants experienced 75% and 70% mycological cure in the adapalene and ketoconazole groups, respectively.

Adapalene is not an antifungal drug; results are based on alterations in the skin's properties.

An open-label study of naftifine hydrochloride 1% gel in the treatment of tinea versicolor. Gold MH, Bridges T, Avakian E, et al. *Skinmed* 2011; 9: 283–6.

Participants received 1% naftifine gel twice daily for 2 weeks. At 6 weeks' posttreatment, 50% of the participants had achieved a mycological cure.

A randomized double-blind, non-inferiority Phase II trial, comparing dapacozazole tosylate 2% cream with ketoconazole 2% cream in the treatment of Pityriasis versicolor. Gobbato AA, Babadopoulos T, Gobbato CA, et al. *Expert Opin Investig Drugs* 2015; 24: 1399–407.

Treatment once daily for 28 days with dapaconazole tosylate 2% cream was non-inferior to ketoconazole 2% cream for clinical and mycological cure.

Treatment of pityriasis versicolor with topical application of essential oil of *Cymbopogon citratus* (DC) Stapf – therapeutic pilot study. Carmo ES, de Oliveira Pereira F, Cavalcante NM, et al. *An Bras Dermatol* 2013; 88: 381–5.

A phase I and phase II study of essential oil formulations compared with ketoconazole cream. Improvement was seen in both groups, with significantly more patients achieving mycological cure in the ketoconazole cream group ($p < 0.05$).

Tinea versicolor clearance with oral isotretinoin therapy. Bartell H, Ransdell BL, Ali A. *J Drugs Dermatol* 2006; 5: 74–5.

This is a single case report of a 14-year-old boy presenting with acne vulgaris recalcitrant to oral antibiotic therapy, who also presented with PV infection on the upper back and shoulders. One month after starting oral isotretinoin 40 mg twice daily, the PV lesions had completely resolved. Resolution was attributed to the sebum-altering properties of isotretinoin.

The use of isotretinoin cannot be advocated because of the potential for serious side effects, particularly in females. In cases of concomitant PV and acne, no additional medication may be required for the PV infection.

Alternative, new treatment options 308-nm excimer laser: a hopeful and optional therapy for pityriasis versicolor. Fathima M. Khattab, Farida H, et al. *J Dermatolog Treat* 2020 Mar 6; 1–5. doi: 10.1080/09546634.2020.1713972 [Epub ahead of print].

A prospective, inpatient, placebo-controlled study of PV patients with lesions on their upper trunk and both hands and

feet, who failed to respond to initial oral or topical antifungals. They were randomized to receive laser therapy with 308-nm Quantum xenon chloride excimer laser on the left or right side and topical placebo therapy on the other side for 8 weeks. Significant reduction in clinical response from laser therapy was observed, from a score of 7.1 at baseline to 1.56 at week 4 compared with placebo.

Fluconazole-loaded solid lipid nanoparticles topical gel for treatment of pityriasis versicolor: formulation and clinical study. El-Housiny S, Shams Eldeen MA, El-Attar YA, et al. *Drug Deliv* 2018; 25(1): 78–90.

Solid lipid nanoparticles (SLNs) are a novel topical formulation of fluconazole (FLZ) for the treatment of PV. This is a randomized, prospective controlled trial of PV patients with three treatment groups where the efficacy and safety of two 1% topical FLZ-SLN gels are compared with commercial topical clotrimazole 1% cream. Clinical and mycological evaluation (KOH microscopy) showed higher skin penetration of the prepared topical FLZ-SLN gels and superseding efficacy compared with the commercial clotrimazole 1% cream in the market.

Efficacy and tolerability of a spray product containing hydroxypropyl chitosan, climbazole and piroctone olamine, applied twice weekly for the treatment of the pityriasis versicolor. Fabbrocini G, Panariello L, DE Padova M, et al. *Ital Dermatol Venereol* 2017; 152(6): 565–8.

Spray product containing hydroxypropyl chitosan, climbazole, and piroctone olamine showed significant improvement from baseline in all 30 patients with PV after 2 months of twice weekly application. The clinical response was assessed through dermoscopy and digital photographs.

Toxic epidermal necrolysis and Stevens-Johnson syndrome

Saskia Ingen-Housz-Oro, Tu-Anh Duong,
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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) belong to the same spectrum ('epidermal necrolysis') of rare, potentially life-threatening conditions caused by drugs in 85% of cases (other causes may be due to autoimmunity or infections such as *Mycoplasma pneumoniae*). SJS and TEN manifest with widespread erythematous or purpuric macules, or atypical target lesions, evolving to vesicle and blisters, associated with severe erosions of mucous membranes. Confluence of cutaneous lesions leads to epidermal loss, which by definition involves less than 10% of total body surface area in SJS, 10%–29% in overlap cases, and 30% or more in TEN. Main complications are infections and respiratory failure (resulting mainly from specific bronchial involvement). Overall mortality rate is around 15% (but up to 40% in the most severe cases) and may be predicted by the SCORTEN (SCORE of Toxic Epidermal Necrosis) scale, based on seven clinical and biological parameters at admission. Whatever is the cause of SJS/TEN, standard of care delivered by centers of reference is key for decreasing mortality and risk of chronic sequelae. *This chapter only deals with management at the acute phase.*

The epithelial changes are caused by extensive apoptosis, a process initiated by drug-induced cytotoxic T lymphocytes (in most cases). A number of proapoptotic molecules, including cytokines such as tumor necrosis factor- α (TNF- α) and interferon- γ (IFN- γ), and apoptotic mediators such as granzyme B, perforin, and granulysin, link immune responses to keratinocyte damage.

MANAGEMENT STRATEGY

The causative drug should be quickly identified and discontinued. In general, drugs introduced 4–28 days before the onset of

symptoms must be considered as suspects. The most common drugs causing SJS/TEN are antibacterial sulfonamides (including cotrimoxazole, sulfasalazine, and dapsone), allopurinol, antiepileptics of the aromatic amines family (carbamazepine, oxcarbazepine, phenobarbital, and phenytoin), lamotrigine, non-steroidal antiinflammatory drugs (NSAIDs) of the oxicam family, and nevirapine.

Extensive epidermal loss in SJS/TEN is accompanied by numerous systemic involvements, many of which may be life-threatening such as respiratory failure. Therefore, the patient should be managed in a center of reference, i.e., a specialist dermatology department, intensive care or burn unit, for critical care management and specialist nursing delivery. Supportive therapy is critical, including fluid replacement, maintaining a warm environment, nutritional support, analgesia, organ support (when necessary), surveillance for infection, and appropriate dressings. *Fluid replacement* requirements depend on the extent of involvement of the skin and may be 5–7 L in the first 24 hours. *The ambient temperature* should be raised to 28–32°C. *Nutritional support* may require nasogastric tube feeding (except in case of severe esophageal involvement) until the oral mucosa has healed. *Analgesia* with opiates is often necessary. *Infection surveillance* includes taking skin swabs or skin cultures from lesional skin throughout the acute phase and sending these for bacteriology. Administration of prophylactic antibiotics is not recommended, as it may favor skin colonization (particularly with *Candida albicans*) and promote resistance. All lines should be checked daily for signs of infection and changed at least every 3 days, and the tips of all discarded lines and catheters sent for culture. If signs of sepsis develop, including rising or falling temperature, rigors, hypotension, fall in urine output, or deterioration of respiratory status, diabetic control, or level of consciousness, initial antibiotic therapy can be guided by the results of skin samples, then adapted to results of blood and/or urine cultures. Blisters should be decompressed by piercing and expression of tissue fluid. Blister roofs and detached epidermis must be left in situ to act as a biologic dressing.

Ophthalmologic review should be obtained as soon as possible from admission to minimize the risk of long-term severe ocular sequelae resulting from conjunctival scarring and corneal ulcerations. Regular instillation of an ocular lubricant without preservatives, and/or topical vitamin A, is recommended. The efficacy of topical steroids is controversial. Topical antibiotics are not recommended. Separation of conjunctival adhesions must be carried out daily by an ophthalmologist or ophthalmically trained nurse.

Oral and nasal debris should be removed regularly. Analgesic and antiseptic mouthwashes must be used frequently.

Tracheal and bronchial involvement is a marker of disease severity and thus must be closely investigated. Respiratory failure can occur, requiring mechanical ventilation.

The cornerstone of the management of SJS/TEN is supportive care in the center used to treat the disease. Macrolides are indicated in cases triggered by *Mycoplasma pneumoniae*. To date, the efficacy of immunomodulatory agents at the acute phase of the disease remains debatable. Systemic steroids and ciclosporin are the most controversial.

Systemic corticosteroids: several reports suggest that they may increase morbidity and mortality, usually by increasing the risk of sepsis. Conversely, a number of case reports and case studies advocate the use of high-dose corticosteroids at the early stage. Recently, a large epidemiological Japanese study did not show any benefit of systemic steroids on the in-hospital mortality (see

below). However, in cases of lupus or dermatomyositis-related TEN, corticosteroids may be used as part of the auto-immune trigger/component accordingly.

Ciclosporin: a French prospective trial and several retrospective case series showed benefits in terms of mortality at the acute phase. However, these results were not confirmed in a large monocenter French study using propensity scores (see later).

Several other potential disease-modifying treatments, especially *intravenous immunoglobulin* (IVIG) and *anti-TNF agents* (especially *etanercept*), have been reported in small numbers of patients, but there is currently no strong evidence base for recommending any specific intervention other than supportive care.

Survivors of SJS/TEN should lifelong avoid exposure to the culprit drug and related compounds.

Specific Investigations

- Histology and direct immunofluorescence of a skin biopsy
- Hematologic, biochemical, and infectious monitoring
- Chest X-ray
- Autoimmunity and infectious (especially *Mycoplasma pneumoniae*) investigations if no trigger drug

Established SJS/TEN can usually be diagnosed clinically. Biopsy for histology and direct immunofluorescence of an affected area of skin can exclude conditions such as staphylococcal scalded skin syndrome, linear immunoglobulin A (IgA) bullous dermatosis, and paraneoplastic pemphigus.

Severe cutaneous adverse reactions to drugs. Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O. *Lancet* 2017; 390: 1996–2011.

This seminar is a complete overview of epidemiology, pathophysiology, triggers, clinical features, and management of severe cutaneous adverse reactions (SCARs), including SJS/TEN.

Epidermal necrolysis and autoimmune diseases: two more observations supporting the concept that ‘toxic’ epidermal necrolysis can be ‘non-toxic’. Dumas M, Hua C, Hotz C, et al. *J Eur Acad Dermatol Venereol* 2018; 32: e360–1.

The authors report two cases, one patient with TEN-like subacute lupus, and one with anti-MDA5 TEN-like dermatomyositis, supporting the fact that TEN may be ‘non-toxic’ (not drug-induced). As other diseases such as graft versus host disease, SJS/TEN belong to the spectrum of ASAP (acute syndrome of pan-epidermolysis).

Stevens–Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR study. Mockenhaupt M, Viboud C, Dunant A, et al. *J Invest Dermatol* 2008; 128: 35–44.

The results of a multinational case-control study of risk for developing SJS and TEN from various drugs, showing a strong association for nevirapine and lamotrigine; a weaker association for sertraline, pantoprazole, and tramadol; and confirming a strong association for previously recognized culprit drugs: sulfonamide antibiotics, allopurinol, carbamazepine, phenobarbital, phenytoin, and oxicam NSAIDs.

SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. Bastuji-Garin S, Fouchard N, Bertocchi M, et al. *J Invest Dermatol* 2000; 115: 149–53.

Assessment of seven clinical parameters within the first 24 hours of admission (age over 40 years; history of malignancy; tachycardia >120 beats/min; skin loss >10%; urea >10 mmol/L; glucose >14 mmol/L; bicarbonate <20 mmol/L) can be used to predict risk of mortality at the acute phase (score 0 or 1: 3% risk of death; 2: 12%; 3: 35%; 4: 58%; 5+: 90%).

Comprehensive survival analysis of a cohort of patients with Stevens–Johnson syndrome and toxic epidermal necrolysis. Sekula P, Dunant A, Mockenhaupt M, et al. for the RegiSCAR Study Group. *J Invest Dermatol* 2013; 133: 1197–204.

All-cause mortality rates at 6 weeks in this cohort of 460 patients (recruited between 2003 and 2007) were 12%, 29%, and 46% for SJS, SJS/TEN overlap, and TEN, respectively.

Incidence, causative factors and mortality rates of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in northern Italy: data from the REACT registry. Diphoorn J, Cazzaniga S, Gamba C, et al. *Pharmacoepidemiol Drug Saf* 2016; 25: 196–203.

This epidemiological study was conducted in Lombardy (Italy) from 2009 to 2014. Seventeen cases of TEN and 59 cases of SJS were collected, meaning an incidence of 1.40 cases (95% CI, 1.12–1.76)/10⁶/year. The mortality rate ranged from 16.9% for SJS to 29.4% for TEN. Five patients (6.6%) had no causative drug. Allopurinol, cotrimoxazole, and lamotrigine were the most frequent trigger drugs, as expected.

Incidence of and mortality from epidermal necrolysis (Stevens–Johnson syndrome/toxic epidermal necrolysis) in France during 2003–16: a four-source capture-recapture estimate. Chaby G, Maldini C, Haddad C, et al. *Br J Dermatol* 2020; 182: 618–24.

In this French epidemiological study (2003–2016) using a four-source capture-recapture method, the annual incidence was found higher than expected: 6.5 (95% CI 4.1–8.9). Incidence increased with age from 4.1 before 20 years old to 13.7 after 65 years old. Mortality from epidermal necrolysis was estimated to be 0.9 (0.1–1.8) cases/10⁶.

First-Line Therapies

• Supportive measures	D
• Withdrawal of culprit drug	D
• Transfer to a specialist unit	D

UK guidelines for the management of Stevens–Johnson syndrome/toxic epidermal necrolysis in adults 2016. Creamer D, Walsh SA, Dziewulski P, et al. *Br J Dermatol* 2016; 174: 1194–227.

British Association of Dermatologists guidelines for the management of Stevens–Johnson syndrome/toxic epidermal necrolysis in children and young people 2018. McPherson T, Exton LS, Biswas S, et al. *Br J Dermatol* 2019; 181: 37–54.

Epidermal necrolysis French national diagnosis and care protocol (PNDS; protocole national de diagnostic et de soins). Ingen-Housz-Oro S, Duong TA, Bensaid B, et al. *Orphanet J Rare Dis* 2018; 13: 56.

These British and French guidelines are a review of all aspects of SJS/TEN management in adults and children at the acute phase, concentrating on the details of the main importance of supportive care in specialized units. Recommendations for practical use are highlighted. They also focus on the prevention and the long-term multidisciplinary management of sequelae.

Toxic epidermal necrolysis and Stevens–Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? Garcia-Doval I, LeCleach L, Bocquet H, et al. *Arch Dermatol* 2000; 136: 323–7.

Early discontinuation of the causative drug improved prognosis in this 10-year (1987–1997) monocenter observational study of 113 patients. The adjusted model showed that the earlier the trigger drug was withdrawn, the better the prognosis (OR 0.69 for each day; 95% CI, 0.53–0.89).

ALDEN, an algorithm for assessment of drug causality in Stevens–Johnson syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Sassolas B, Haddad C, Mockenhaupt M, et al. *Clin Pharmacol Ther* 2010; 88: 60–8.

Drugs cause 70%–80% of cases of SJS, TEN, and SJS/TEN overlap. This paper describes a validated algorithm for assessing the likelihood of causality of drugs in such cases.

Stevens–Johnson syndrome/toxic epidermal necrolysis: a multicenter retrospective study of 377 adult patients from the United States. Micheletti RG, Chiesa-Fuxench Z, Noe MH, et al. *J Invest Dermatol* 2018; 138: 2315–21.

This multicenter, retrospective study included patients with SJS/TEN seen by inpatient consultative dermatologists at 18 centers in the United States between 2000 and 2015 ($n=377$). Of these, 90% were drug-triggered. Most received pharmacologic therapy (71%, steroids 42.5%, IVIG 35%, both 20%) versus supportive care alone (29%). According to baseline SCORTEN, predicted mortality was 21%, but the observed mortality was 14.7%. The association steroids + IVIG was associated with a trend to a lower mortality.

Pediatric Stevens–Johnson syndrome and toxic epidermal necrolysis in the United States. Hsu DY, Brieve J, Silverberg NB, et al. *J Am Acad Dermatol* 2017; 76: 811–7. e4.

This cross-sectional study (2009–2012) of Nationwide Inpatient Sample showed that incidence of SJS, SJS/TEN overlap, and TEN were 5.3, 0.8, and 0.4 cases/10⁶/year in the US, respectively. SJS/TEN was responsible for prolonged hospitalizations (from 9.4 days for SJS to 20.4 days for TEN) and high costs of care (from \$24,947 for SJS to \$102,243 for TEN) compared with other diseases (4.6 days, \$10,496). Mortality ranged from 0% for SJS to 16% for TEN. Predictors of mortality included renal failure, malignancy, septicemia, bacterial infection, and epilepsy.

Individual- and hospital-level factors associated with epidermal necrolysis mortality: a nationwide multilevel study, France, 2012–2016. Traikia C, Hua C, Le Cleach L, et al. *Br J Dermatol* 2020; 182: 900–6.

This French retrospective cohort (2012–2016) investigated the mortality rate according to the experience of the centers (number of patients seen each year). The authors show that survival was higher in centers with a high volume of procedures, confirming the importance of expertise in early diagnosis and management of SJS/TEN. There was no association between interhospital transfer and survival. These results support the early transfer of patients with suspected or diagnosed SJS/TEN to centers with experience (dermatology, burn units, intensive care units).

Second-Line Therapies

• Ciclosporin	B, D
• Systemic corticosteroids	B, D
• Intravenous immunoglobulins (IVIG)	D
• Anti-TNF therapy	A, E
• Thalidomide	A

Systemic immunomodulating therapies for Stevens–Johnson syndrome and toxic epidermal necrolysis. A systematic review and meta-analysis. Zimmermann S, Sekula P, Venhoff M, et al. *JAMA Dermatol* 2017; 153: 514–22.

This literature review (1990–2012, updated in 2015) included 96 studies (3248 patients). Applied therapies were supportive care or systemic immunomodulating therapies (systemic steroids, IVIG, ciclosporin, plasmapheresis, thalidomide, cyclophosphamide, hemoperfusion, tumor necrosis factor inhibitors, and G-CSF). Steroids showed a survival benefit, but significantly in only one study. Ciclosporin was associated with promising significant results with a low number of studies and patients treated. No beneficial findings were observed for other therapies, including IVIG.

Systematic review of treatments for Stevens–Johnson syndrome and toxic epidermal necrolysis using the SCORTEN score as a tool for evaluating mortality. Roujeau JC, Bastuji-Garin S. *Ther Adv Drug Saf* 2011; 2: 87–94.

A pooled analysis of published series addressing treatment efficacy by comparing the mortality observed with the mortality predicted by the SCORTEN score. The analyzed series comprised a total of 439 patients. Supportive care was used only in 199 patients with a pooled mortality ratio (MR) of 0.89 (CI 0.67–1.16; $p=0.43$); corticosteroids were administered to 78 patients with a pooled MR of 0.92 (CI 0.53–1.48; $p=0.84$), and IVIG in 162 with a pooled MR of 0.82 (CI 0.58–1.12, $p=0.23$). In conclusion, even though this analysis had some limitations, it strongly suggested that neither corticosteroids nor IVIG provide any important improvement in mortality over that predicted by SCORTEN in SJS/TEN.

Open trial of cyclosporin treatment for Stevens–Johnson syndrome and toxic epidermal necrolysis. Valeyrie-Allanore L, Wolkenstein P, Brochard L, et al. *Br J Dermatol* 2010; 163: 847–53.

Twenty-nine patients (mean age 34 years) with SJS ($n=10$), SJS/TEN overlap ($n=12$), and TEN ($n=7$) were prospectively included and treated with ciclosporin at a dose of 3 mg/kg for 10 days, then 2 mg/kg for 10 days, and finally 1 mg/kg for 10 days. Treatment was tolerated well in most patients, and although SCORTEN predicted 2.75 deaths, none occurred. In addition, the progression of detachment of epidermis seemed lower than expected. However, this study included a small number of patients, mostly young patients without comorbidities, and was not controlled.

Cyclosporine use in epidermal necrolysis is associated with an important mortality reduction: evidence from three different approaches. González-Herrada C, Rodríguez-Martín S, Cachafeiro L, et al. *J Invest Dermatol* 2017; 137: 2092–100.

The authors performed a retrospective study in which they compared the mortality rate of patients admitted in two burn units in Madrid (2001–2015): one unit using ciclosporin ($n=26$, 3 mg/kg/day until complete reepithelialization and then 10-mg/day reduction every 48 hours) and one not ($n=16$, among whom

11 received IVIG). They pooled the results of the 26 patients who had received ciclosporin with those of 23 other patients treated with ciclosporin in other Madrid hospitals and observed in total five deaths instead of the 11.8 predicted. They also pooled the data of these 49 patients treated with ciclosporin with other published retrospective or prospective studies ($n=85$). They showed an overall benefit on mortality (overall mortality rate ratio 0.41, CI 0.21–0.80). However, results should be considered with caution because the study was non-randomized, and compared patients treated in different hospitals, with various regimens.

Cyclosporine for epidermal necrolysis: absence of beneficial effect in a retrospective cohort of 174 patients-exposed/unexposed and propensity score-matched analyses. Poizeau F, Gaudin O, Le Cleach L, et al. *J Invest Dermatol* 2018; 138: 1293–300.

This retrospective study (2005–2016) was performed in the same center as the prospective trial conducted by Valeyrie-Allanore et al. (see earlier). Among the 174 patients seen in the dermatology department over the study period, 95 received ciclosporin (3 mg/kg/day), and 79 received supportive care only. Two methods were used to compare mortality rate and healing in both groups: exposed/unexposed method and a propensity score-matching method. There was no difference among groups in terms of progression of skin detachment, time to reepithelialization, and deaths. No outcome significantly favored ciclosporin. Thus, this epidemiological study did not show a beneficial effect of ciclosporin in patients with SJS/TEN treated in this reference center, with optimized supportive care.

Trends in mortality rates for Stevens–Johnson syndrome and toxic epidermal necrolysis: experience of a single centre in France between 1997 and 2017. Bettuzzi T, Penso L, de Prost N, et al. *Br J Dermatol* 2020; 182: 247–8.

This retrospective study performed in the same French reference center showed by linear regression and multivariate analysis a significant decrease of mortality rate in SJS/TEN over time, attributed to an improvement of supportive care during the study period. This study confirms that supportive care remains to date the cornerstone of SJS/TEN treatment.

Retrospective review of Stevens–Johnson syndrome/toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with ciclosporin. Kirchhof MG, Miliszewski MA, Sikora S, et al. *J Am Acad Dermatol* 2014; 71: 941–7.

In this single-center, retrospective study of 64 patients with SJS/TEN, predicted mortality based on SCORTEN was compared with actual mortality for patients treated with either ciclosporin (3–5 mg/kg/day for up to 7 days) or IVIG (2–5 g/kg total dose). The results showed an apparently improved mortality with ciclosporin over that predicted by SCORTEN (standardized mortality ratio [SMR] 0.43) compared with an apparently increased mortality with IVIG (SMR 1.43). Although aware of the limitations of the study, the authors concluded that the results suggested a possible benefit from using ciclosporin in the treatment of SJS/TEN.

Corticosteroids in Stevens–Johnson syndrome/toxic epidermal necrolysis: current evidence and implications for future research. Law EH, Leung M. *Ann Pharmacother* 2015; 49: 335–42.

Six studies that used steroids for SJS/TEN were included in this review. All were retrospective cohort studies with no case-control or cross-sectional studies. Only one reported a statistically significant mortality benefit with steroid use (odds ratio = 0.4; 95%

confidence interval [CI] = 0.2–0.9). None of the studies reported adverse event rates. The authors concluded that there is a need for prospective, randomized controlled trials to provide more definitive evidence supporting steroid use in patients with SJS, TEN, and/or overlap.

Association of early systemic corticosteroid therapy with mortality in patients with Stevens–Johnson syndrome or toxic epidermal necrolysis: a retrospective cohort study using a nationwide claims database. Morita K, Matsui H, Michihata N, et al. *Am J Clin Dermatol* 2019; 20: 579–92.

The aim of this retrospective nationwide study with propensity-score method was to investigate the impact of early (day 0 or day 1) systemic steroids on the in-hospital mortality of 1846 patients with SJS/TEN, among whom 793 received a dose of ≤ 2 mg/kg/day, 558 received a dose of > 2 mg/kg/day, and 495 received no steroids. Early systemic steroid use was not significantly associated with lower in-hospital mortality by propensity-score matching between patients with or without steroids, whatever the dose.

The efficacy of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis: a systematic review and meta-analysis. Huang YC, Li YC, Chen TJ. *Br J Dermatol* 2012; 167: 424–32.

A meta-analysis evidence-based examination of IVIG efficacy in TEN compared the clinical differences between (1) high-dose (≥ 2 g/kg) and low-dose (< 2 g/kg) in adult and pediatric patients. Although high-dose IVIG exhibited a trend toward improved mortality and children treated with IVIG had a good prognosis, the authors concluded that the evidence overall did not support a clinical benefit of IVIG and stated that randomized controlled trials are necessary.

The role of intravenous immunoglobulin in toxic epidermal necrolysis: a retrospective analysis of 64 patients managed in a specialized center. Lee HY, Lim YL, Thirumoorthy T, et al. *Br J Dermatol* 2013; 169: 1304–9.

This single-center study of use of IVIG in the management of 64 patients with SJS/TEN overlap and TEN demonstrated no survival benefit even when corrected for IVIG dosages.

Intravenous immunoglobulin in the treatment of Stevens–Johnson syndrome and toxic epidermal necrolysis: a meta-analysis with metaregression of observational studies. Barron SJ, Del Vecchio MT, Aronoff SC. *Int J Dermatol* 2015; 54: 108–15.

Thirteen studies met the inclusion criteria for this meta-analysis, eight of which included a control group. Although there was no significant overall benefit of using IVIG in SJS/TEN (overall standardized MR 0.814, 95% CI 0.617–1.076), the metaregression found a strong inverse correlation between IVIG dosage and mortality, and the authors concluded that IVIG at dosages of ≥ 2 g/kg appears to significantly decrease mortality.

A retrospective cohort study of the management and outcomes of children hospitalized with Stevens–Johnson syndrome or toxic epidermal necrolysis. Antoon JW, Goldman JL, Shah SS, et al. *J Allergy Clin Immunol Pract* 2019; 7: 244–50. e1.

This large, retrospective study of childhood SJS/TEN included 898 patients (SJS 86%, male 59%, mean age 10.8 years). Patients with previous similar episode and length of stay < 3 days were excluded. Patients were treated with systemic steroids for 2–6 days in 18.6% of cases, IVIG for 2–3 days in 25.5%, and both in 17%.

Median length of stay was 8 days. Readmissions within 30 days occurred in 9.9% of cases with recurrence rate of 2.7%, raising the question of differential diagnosis with erythema multiforme major, often misdiagnosed with SJS in children. Overall hospital mortality in children was low (0.56%, SJS 0.13%, TEN 3.23%). There was no association between pharmacologic treatment and duration of hospitalization or need of mechanical ventilation.

Etanercept therapy for toxic epidermal necrolysis. Paradisi A, Abeni D, Bergamo F, et al. *J Am Acad Dermatol* 2014; 71: 278–83.

Ten patients with SJS/TEN were treated with a single dose of etanercept (50 mg). There was no control group. None of the patients died, despite a mean predicted mortality rate of 50%.

Randomized, controlled trial of TNF- α antagonist in CTL-mediated severe cutaneous adverse reactions. Wang CW, Yang LY, Chen CB, et al. *J Clin Invest*. 2018; 128: 985–96.

Clinical, randomized uncontrolled trial performed between 2009 and 2015 ($n=96$, SJS 60%). Patients received either etanercept 25 mg or 50 mg (depending on weight) twice a week or intravenous prednisolone 1–1.5 mg/kg/day until healing. Primary objective was the time to healing. Mortality was a secondary objective. Patients were compared with a historical cohort treated with supportive care only. Etanercept decreased the SCORTEN-based predicted mortality rate (predicted and observed rates, 17.7% and 8.3%, respectively). Compared with corticosteroids,

etanercept significantly reduced the time to healing (14 and 19 days for etanercept and corticosteroids, respectively) but not the mortality ($p=0.27$). Mortality in the historical cohort was 26%. Despite these encouraging results, caution is needed for the interpretation of results in this study with methodological weaknesses.

Biologic TNF- α inhibitors in the treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review. Zhang S, Tang S, Li S, et al. *J Dermatolog Treat* 2020; 31: 66–73.

This review included 21 case reports, four case series, and two randomized controlled trials (RCTs), comprising 91 patients. TNF- α inhibitors were used as monotherapy, second-line therapy, or combination therapy. Among them, 79 patients (86.8%) responded well and were discharged with few side effects and complications. However, larger RCTs are needed for stronger conclusions. There is a lack of knowledge today about the best regimen, contraindications, and the risk of infections.

Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. Wolkenstein P, Latarjet J, Roujeau J-C, et al. *Lancet* 1998; 352: 1586–9.

Patients with TEN were randomized to either a 5-day course of thalidomide 400 mg daily (12 patients) or placebo (10 patients). The study was stopped early because of excess mortality in the treatment arm. Thalidomide is thus contraindicated in SJS/TEN.

Transient acantholytic dermatosis (Grover disease)

William Haw, Ian H. Coulson



Grover disease was described by the American dermatologist Ralph Grover in 1970. It is an uncommon disorder characterized clinically by discrete erythematous, edematous papulovesicles or keratotic papules, which are usually pruritic, and histologically focal acantholytic dyskeratosis. It can be self-limiting or chronic. It is more common in middle-aged and elderly people, with a male predilection, and involves mainly the trunk. The evolution can be acute or chronic, lasting weeks to months, and it may be persistent or recurrent. The etiology is unknown, but excessive ultraviolet (UV) exposure, heat, sweating, and ionizing radiation are linked to the disease. Drugs, chemotherapeutic agents, dialysis, and cancers are also reported triggers.

MANAGEMENT STRATEGY

The diagnosis can be made on clinical grounds, although histology can also be helpful. Focal acantholysis is the characteristic epidermal change. Hyperkeratosis, parakeratosis, and spongiosis are other common histologic changes, and may mimic Darier disease, pemphigus, and Hailey–Hailey disease. Immunofluorescence does not aid in diagnosis.

Treatment is difficult; nearly all evidence for therapies comes from case series, case reports, and clinical experience. Patients should be advised to *avoid known triggers* such as excessive sun exposure, strenuous exercise, heat, and occlusive fabrics. In

mild cases, simple antipruritic measures such as *avoidance of soap, simple emollients, and soothing baths with bath oils or colloidal oatmeal* may be of benefit. Wet compresses with zinc oxide, calamine, or *potent topical corticosteroids* may help relieve the itching. *Antihistamines* may be helpful for symptomatic relief of itching.

Topical calcipotriol (ointment) twice daily 50 mcg/g may be helpful after 3–4 weeks of treatment.

Systemic therapy may be indicated in more extensive and persistent disease. *Oral vitamin A* has been recommended in the past. The aromatic retinoid *acitretin* has been used successfully in doses of 0.5 mg/kg daily. *Isotretinoin* 40 mg daily has been used for periods ranging from 2 to 12 weeks. It may be administered on a reducing regimen if the initial response is rapid, with a maintenance dose of 10 mg daily.

Systemic corticosteroids have been used to suppress inflammation and pruritus, but relapses frequently occur on drug withdrawal.

Psoralen with UVA (PUVA) may be useful, but an initial exacerbation may occur. There are reports of the success of narrowband UVB and of medium-dose UVA1 phototherapy.

Topical 5-fluorouracil, dapsone, antibiotics, and cryotherapy are ineffective. Off-label uses of *biologics* (e.g., rituximab and etanercept) have been reported to be useful.

Specific Investigation

- Skin biopsy

First-Line Therapies

• Emollients	D
• Avoid heat/sweating	D
• Topical corticosteroids	D

Transient acantholytic dermatosis. Heenan PJ, Quirk CJ. *Br J Dermatol* 1980; 102: 515–20.

This study looked at a series of 24 cases of transient acantholytic dermatosis. Most of them required topical fluorinated corticosteroids to control the pruritus, and two required intermittent courses of oral corticosteroids.

Incidence of transient acantholytic dermatosis (Grover's disease) in a hospital setting. French LE, Piletta PA, Etienne A, et al. *Dermatology* 1999; 198: 410–1.

A prospective study of 28 hospital inpatients diagnosed with Grover disease. In over 80% of cases the duration of hospitalization exceeded 2 weeks and was associated with strict bed rest. The authors suggested a sweat-related pathogenesis.

Second-Line Therapies

• Calcipotriol	E
• Tacalcitol	E
• Systemic corticosteroids	D
• Vitamin A	D

Treatment of Grover's disease with calcipotriol (Dovonex). Keohane SG, Cork MJ. *Br J Dermatol* 1995; 132: 832–3.

A 50-year-old man had a 13-month history of Grover disease that responded poorly to oxytetracycline, topical corticosteroids,

dapsone, and etretinate. Lesions cleared after hospitalization and prednisone 100 mg daily, but he relapsed with any reduction in dose. Oral corticosteroids were stopped, and he was commenced on an alternating regimen of calcipotriol ointment at night and 0.025% betamethasone valerate ointment (we presume in the morning). There was complete clearance of lesions after 1 month of treatment, but the disease relapsed when treatment was stopped.

Successful treatment of Grover's disease with calcipotriol. Mota AV, Correia TM, Lopes JM, et al. *Eur J Dermatol* 1998; 8: 33–5.

An 84-year-old man with a 2-year history of Grover disease improved significantly, despite initial moderate irritation, after a 3-week course of calcipotriol 50 mcg/g twice daily. Lesions did not recur during a 6-month follow-up.

Treatment of Grover's disease with tacalcitol. Hayashi H. *Clin Exp Dermatol* 2002; 27: 160–1.

A 31-year-old man with a 2-month history of Grover disease who failed to respond to topical corticosteroid was commenced on tacalcitol ointment twice daily. He improved dramatically within 1 week and was in remission after 1 month.

Treatment of transient acantholytic dermatosis. Rohr JR, Quirk CJ. *Arch Dermatol* 1979; 115: 1033–4.

Eight patients were treated with vitamin A 50,000 units three times a day for up to 2 weeks; all patients responded. Once initial improvement was noted, the dose was reduced to 50,000 units daily as maintenance or for several weeks. No signs of toxicity were noted. One patient required reinstitution of the drug due to recurrence on cessation of treatment.

Third-Line Therapies

• Systemic retinoids (acitretin/etretinate/isotretinoin)	E
• PUVA	E
• UVA1	E
• Photodynamic therapy	E
• Trichloroacetic acid	E
• Etanercept	E
• Rituximab	E

Persistent acantholytic dermatosis. Dodd HJ, Sarkany I. *Clin Exp Dermatol* 1984; 9: 431–4.

A case report of a 41-year-old man with a 5-year history of an itchy truncal and lower limb rash consistent with persistent acantholytic dermatosis. Bath emollients and aqueous cream British pharmacopoeia afforded minor relief. Etretinate (50 mg daily) cleared the skin lesions and reduced the itching.

Etretinate has been replaced by its active metabolite acitretin. Lower doses of the latter may be effective.

Grover's disease treated with isotretinoin. Helfman RJ, Gables C. *J Am Acad Dermatol* 1985; 12: 981–4.

Four patients with biopsy-proven Grover disease responded to 40 mg daily of isotretinoin for 2–4 months. Their dose was reduced by 10 mg daily for a further 8 weeks. One patient required 40 mg daily for 8 weeks. These patients remained in remission for up to 10 months after treatment. The final patient obtained partial relief and then discontinued treatment because of elevated triglycerides.

Persistent generalized Grover disease: complete remission after treatment with oral acitretin. Pasmatzis E, Kousparos G, Mytidou C, et al. *Dermatol Online J* 2019; 15: 25.

A 56-year-old woman with a 5-month history of generalized pruritic skin lesions; skin biopsy was diagnostic of Grover disease. Oral treatment with 0.8 mg/kg/day acitretin was initiated. After 1 week of treatment, there was a dramatic resolution of pruritus and a significant improvement of the eruption; complete remission was observed after 6 weeks of continuous treatment. Acitretin was well tolerated by the patient, who experienced a moderate but reversible hair loss and discrete paronychia. The patient subsequently completed 26 months' follow-up and showed no evidence of relapse.

Response of transient acantholytic dermatosis to photochemotherapy. Paul BS, Arndt KA. *Arch Dermatol* 1984; 120: 121–2.

A 59-year-old man with persistent Grover disease was unresponsive to oral prednisone and vitamin A (300,000 units daily). PUVA was initiated with 50 mg (0.6 mg/kg) methoxsalen and 2 J/cm² of UVA. Treatment was twice weekly, and the UVA dosage was increased by 0.5 J/cm² with each treatment. The patient experienced a flare after four treatments, but improved by week 6, with maximal improvement by week 8. Therapy was then tapered off over the next 4 weeks, with complete clearing. No recurrence had occurred 25 months after therapy.

Reports show that approximately 10 treatments are required for resolution of pruritus, and 20–30 treatments may be needed to clear the eruption.

Medium-dose ultraviolet A1 phototherapy in transient acantholytic dermatosis (Grover's disease). Breuckmann F, Appelhans C, Altmeyer P, et al. *J Am Acad Dermatol* 2005; 52: 169–70.

A 78-year-old man with persistent Grover disease had failed to respond to topical and oral corticosteroids. He was treated with a medium-dose UVA1 cold light monophototherapy containing a special filtering and cooling system (21 °C). Irradiation (50 J/cm², 1.9 J/cm²/minute; 26 minutes), six times weekly for 3 weeks, then three times weekly for 3 weeks. A total of 24 treatments was given with a cumulative dose of 1200 J/cm². Complete remission was achieved after 4 weeks, with no subsequent relapse.

Successful novel treatment of recalcitrant transient acantholytic dermatosis (Grover disease) using red light 5-aminolevulinic acid photodynamic therapy. Liu S, Letada PR. *Dermatol Surg* 2013; 39: 960–1.

A 45-year-old man with biopsy-proven recurrent Grover disease affecting his abdomen and chest. He failed to respond to topical steroids, calcipotriol, and tretinoin. Topical 20% 5-aminolevulinic acid (ALA) was applied to the entire abdomen and lower chest, which was then allowed to incubate for 90 minutes. The area was then irradiated with a 633-nm light-emitting diode continuous-wave red light source at a dose of 126 J/cm² for 19 minutes and 57 seconds. A cold air cooling device was used during the procedure for comfort. The patient reported significant improvement in pruritus within a few days, with fewer lesions, not requiring any further topical therapy, and no flare at 3- and 8-month follow-up visits.

Effective treatment of persistent Grover's disease with trichloroacetic acid peeling. Kouba DJ, Dasgeb B, Deng AC, et al. *Dermatol Surg* 2006; 32: 1083–8.

A 46-year-old woman had a 6-month history of progressive Grover disease with intractable pruritus. She failed to respond to topical calcipotriene (Dovonex). She was treated with an even, light application of 40% (w/v) trichloroacetic acid (TCA) – single-pass strokes with TCA-dampened gauze. Individual lesions of Grover disease were identified and were re-treated with 40% TCA using a cotton-tipped applicator. Three weeks postprocedure she had reepithelialized, was disease free, and was still in remission 8 months later.

The authors stress that practitioners not accustomed to using TCA in office applications should use low-strength formulations such as 20%–30% to avoid scarring.

Use of etanercept in treating pruritus and preventing new lesions in Grover disease. Norman R, Chau V. *J Am Acad Dermatol* 2011; 64: 796–8.

A 55-year-old man had a 2-year history of Grover disease that did not respond to topical or oral steroids and antihistamines.

Isotretinoin given for 2 months resulted in improvement of his pruritus but was discontinued after he had a myocardial infarction. He was prescribed etanercept 50 mg subcutaneously twice weekly for 6 weeks, which reduced the pruritus by 98%. Over the next 4 months he had very mild symptoms and did not develop any new lesions.

Remission of transient acantholytic dermatosis after the treatment with rituximab for follicular lymphoma. Ishibashi M, Nagasaka T, Chen KR. *Clin Exp Dermatol* 2008; 33: 206–7.

An 80-year-old woman developed Grover disease simultaneously with a relapse of follicular lymphoma. Six years before this episode her lymphoma had been treated with rituximab. She was given rituximab again, and her skin lesions cleared within a week. The lymphoma improved initially, but after nine cycles of treatment she suffered another relapse. Her skin lesions did not recur.

Trichotillomania

Stephanie Chan, Quinn Thibodeaux,
Mio Nakamura, John Y.M. Koo



Trichotillomania, or hair-pulling disorder, is the impulsive, repetitive action of pulling out hair, resulting in significant hair loss. Any region of the body with hair can be involved, with the eyebrows, eyelashes, and scalp comprising the most common sites. The reported prevalence of trichotillomania is approximately 0.6% in the general population with a mean age of onset between 11 and 13 years. It is predominantly observed in females.

The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), categorizes trichotillomania as an 'obsessive-compulsive disorder,' which is a change from the DSM-4, which categorized trichotillomania as an 'impulse disorder.' Obsessive-compulsive disorders include intrusive thoughts or urges that are experienced as unwanted (obsession), often necessitating repetitive behaviors or rituals to help alleviate the otherwise intolerable anxiety (compulsion). The DSM-5 diagnostic criteria for trichotillomania are:

- A. Recurrent pulling out of one's hair resulting in noticeable hair loss
- B. An increasing sense of tension immediately before pulling out the hair or when attempting to resist the behavior
- C. Pleasure, gratification, or relief when pulling out the hair
- D. The disturbance is not better accounted for by another mental disorder and is not due to general medical conditions
- E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

Patients with trichotillomania often admit to hair pulling; however, some patients are unwilling or ashamed to acknowledge the self-inflicted nature of their skin findings, whereas others are not conscious of their hair pulling. Some patients practice specific rituals after hair pulling including rolling the hair between the fingers, running the hair over the lips or through the teeth, and biting the hair. In rare cases, the patient may also eat the hair root (trichorhizophagia) as a secretive activity, and in even

rarer cases the whole hair is eaten (trichophagia). It is possible to develop gastrointestinal hairballs (trichobezoars), which have a high morbidity and can be fatal. Children with trichotillomania who present with episodes of obscure abdominal pain, weight loss, nausea, vomiting, anorexia, and foul breath should be investigated for gastric trichobezoars.

Many patients with trichotillomania have underlying psychiatric disease. It is estimated that up to 80% of patients with trichotillomania have comorbid psychiatric disease, most commonly anxiety and depression. Patients with trichotillomania may have other types of obsessive-compulsive disorders, specifically body-focused repetitive behavioral disorders, such as skin picking and nail biting. The patient may be delusional in cases such as trichophobia, in which an individual has an irrational ideation that something must be picked out of the skin in order for their hair to grow normally, resulting in a clinical presentation of psychogenic excoriation.

DIAGNOSIS

Patients with trichotillomania present with alopecia that is generally irregular and non-scarring. Broken, sparse hair on a background of excoriations is often observed. Hairs are broken at different lengths on the scalp. The diagnosis of trichotillomania can be made on a clinical basis with careful examination of the scalp. Dermatologic differential diagnoses that should be ruled out include alopecia areata, androgenic alopecia, alopecia mucinosa, tinea capitis, lichen planopilaris, folliculitis decalvans, and discoid lupus erythematosus. Tinea capitis may be ruled out by the absence of scaling and negative fungal scraping or culture. Laboratory investigations such as complete blood count, thyroid function tests, and iron levels may also be indicated. Dermoscopy can be useful to detect black dots ('exclamation point hair'), or broken or curled hairs. A skin biopsy may be warranted if the dermoscopy findings of trichotillomania overlap with other causes of hair loss. Trichotillomania presents histologically as empty follicles, follicular keratin debris, melanin pigment casts, an increased number of catagen hairs, and traumatized hair bulbs in the absence of perifollicular inflammation (trichomalacia).

MANAGEMENT STRATEGY

Trichotillomania can cause significant social isolation and psychological disability; therefore, treatment of this disorder is important to restore the patient's quality of life. There are currently no US Food and Drug Administration treatments approved for trichotillomania. However, there are psychotherapeutic and pharmacologic treatments that are effective in alleviating symptoms of trichotillomania. *Psychotherapy*, including behavioral therapy, has been shown to be the most effective treatment in both pediatric and adult populations. *Habit-reversal training* is a form of behavioral therapy that focuses on four key aspects: awareness (increase consciousness of hair-pulling behavior), competing response training (perform a specific action when there is an urge to pull hair), social support or contingency management (a person who reinforces the former), and stimulus control (minimize the influence of environmental factors on pulling behavior). Habit-reversal training has been shown to decrease repetitive, self-inflicted behaviors, and can especially benefit children from disease progression into adulthood.

Effective pharmacologic treatments involve treating any underlying psychiatric disease. The first-line pharmaceutical approach depends on the underlying causes of trichotillomania, such as obsessive-compulsive disorder, anxiety, depression, substance abuse, or eating disorders.

Studies of pharmacologic therapy for the treatment of trichotillomania have been limited. *N-acetylcysteine* (NAC) has shown reduction of hair pulling in adults in a 12-week double-blind, placebo-controlled study using a dose of 1200 mg/day for 6 weeks and 2400 mg/day for the remaining 6 weeks. However, this improvement in symptoms has not been demonstrated in a pediatric controlled trial. NAC is an ideal first-line pharmacologic therapy because its side effect profile is mild (e.g., flatulence and bloating). The tricyclic antidepressant *clomipramine*, indicated for obsessive-compulsive disorder, has been shown to reduce the frequency of hair-pulling urges. Clomipramine is started at a dose of 25 mg/day and is titrated up to 125–250 mg/day. Side effects include headache, orthostatic hypotension, anticholinergic effects, QT prolongation, and seizures.

High-dose *selective-serotonin reuptake inhibitors* (SSRIs), such as paroxetine, fluoxetine, or sertraline, can also be used to treat trichotillomania. Although SSRIs alone have not shown significant evidence to effectively treat trichotillomania, the combination of pharmacotherapy and habit-reversal training has been shown to be effective in decreasing the frequency of hair pulling. Paroxetine is typically started at 20 mg daily and then increased by 10 mg weekly to up to 50–60 mg/day. Fluoxetine is started at a dose of 10 mg/day and is titrated up to an effective dose, which usually ranges from 20 to 80 mg/day. The usual starting dose of sertraline is 50 mg/day, with an effective dose ranging typically from 50 to 200 mg/day. Side effects of SSRIs include gastrointestinal upset, headache, sexual dysfunction, and suicidality. Atypical antipsychotics such as olanzapine and aripiprazole have been reported to be successful in case reports.

Specific Investigations

- Hair microscopy
- Dermoscopy
- Scalp biopsy
- Laboratory testing (complete blood count, thyroid stimulating hormone, ferritin)

Trichotillomania. Grant JE, Chamberlain SR. *Am J Psychiatry* 2016; 9: 868–74.

A comprehensive and detailed review of trichotillomania.

First-Line Therapies

- Behavioral therapy/habit-reversal therapy **A**
- *N-acetylcysteine* **A**

Habit reversal therapy in obsessive compulsive related disorders: a systematic review of the evidence and CONSORT

evaluation of randomized controlled trials. Lee ML, Mpa-vaenda DN, Ledley DA, et al. *Front Behav Neurosci* 2019; 13: 79.

A systematic review of habit-reversal therapy in trichotillomania that shows evidence of improvement in symptoms.

Psychological treatments for trichotillomania. Rehm I, Moulding R, Nedelkovic M. *Australas Psychiatry* 2015; 23: 365–8.

Cognitive behavioral therapy has been shown to be the most effective treatment of OCD-related disorders. Further studies of treatment component efficacy and cognitive behavioral models are needed.

N-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: a double-blind, placebo-controlled study. Grant JE, Odlaug BL, Kim SWM. *Arch Gen Psychiatry* 2009; 66: 756–63.

N-acetylcysteine showed significant reduction in trichotillomania symptoms compared with controls.

Second-Line Therapies

- Clomipramine **B**
- SSRI **B**
- Combination of habit-reversal therapy and pharmacotherapy **C**

Pharmacotherapy of trichotillomania (hair pulling disorder): an updated systematic review. Rothbart R, Stein DJ. *Expert Opin Pharmacother* 2014; 15: 2709–19.

A systematic review of clinical trials of pharmacotherapeutic agents for the treatment of trichotillomania. Although limited, clinical trials have shown modest benefit from agents such as clomipramine and SSRIs.

Single modality versus dual modality treatment for trichotillomania. Dougherty D. *J Clin Psychiatry* 2006; 67: 1086–92.

Habit-reversal and SSRI-drug therapy together were better than either therapy alone.

Third-Line Therapy

- Antipsychotics **C**

Trichotillomania and trichophagia: modern diagnostic and therapeutic methods. Cisoń H, Kus A, Popowicz E, et al. *Dermatol Ther* 2018; 8: 389–98.

There are multiple case reports, case series, and a small, controlled trial reporting favorable response to antipsychotics as monotherapies and augmentation agents in the literature.

Tuberculosis (cutaneous) and tuberculids

Archana Singal, Shyam B. Verma



Cutaneous tuberculosis (CTB) is a chronic infection caused by *Mycobacterium tuberculosis* and occasionally by *M. bovis* and bacillus Calmette-Guérin (BCG), an attenuated strain of *M. bovis*. The spectrum of clinical manifestations varies depending on the host's immunity, route of infection, the infectious load, virulence factors, and prior contact with the bacilli. Treatment of CTB is the same as of systemic tuberculosis (TB) and consists of multidrug therapy.

The disease can occur following inoculation from an exogenous or endogenous source. Tuberculids are 'hypersensitivity' reactions to extracutaneous sources of *M. tuberculosis* (tuberculous antigen) in individuals with high immunity (Table 248.1).

CLINICAL FEATURES

Exogenous TB

Primary inoculation TB is rare and develops in previously unsensitized adults following local trauma as in tattooing, ear-piercing, ritual circumcision or exposure to unsterilized surgical instruments. A firm, painless reddish-brown papule/nodule forms after 1–3 weeks, evolving into a shallow ulcer with undermined bluish margins with regional lymphadenopathy. The chancre may heal spontaneously in 3–12 months. Tuberculosis verrucosa cutis (TVC) presents as solitary, slow growing, painless verrucous plaque over exposed sites in individuals with moderate-to-high immunity against *M. tuberculosis*. Lymphadenopathy is uncommon.

Table 248.1

Source of infection	Clinical types
Exogenous	Tuberculous chancre (primary inoculation tuberculosis) Tuberculosis verrucosa cutis (TVC)
Endogenous:	Scrofuloderma
a. by contiguity or autoinoculation	Orificial tuberculosis Lupus vulgaris (some cases)
b. by hematogenic dissemination	Lupus vulgaris Tuberculous gumma Acute miliary tuberculosis
Tuberculids	Papulonecrotic tuberculid (PNT) Lichen scrofulosorum (LS) Erythema induratum of Bazin (EIB)

Endogenous TB

Scrofuloderma (SCF), the most common variant worldwide, occurs as a result of contiguous spread from an underlying primary focus, usually a lymph node, bone, and/or joints. It presents as painless swellings and discharging sinuses with undermined bluish margins. There is the possibility of acid-fast bacilli (AFB) in stained cytology smears/biopsy samples as well as positive culture is higher.

Lupus vulgaris (LV) is the second most common variant and presents as single or multiple, well-defined, reddish-brown, irregular plaques that expand peripherally with prominent advancing margins and central atrophy/scarring. Untreated, chronic LV lesions may be complicated by gigantic size, deep tissue destruction, bony contractures, and malignancy.

Orificial TB is rare and generally seen in severely ill, immunodeficient patients. Lesions form around mouth, genital, or anal mucosae, following *M. tuberculosis* autoinoculation in patients with advanced intestinal or genitourinary tuberculosis.

Tuberculous gumma present as fluctuant non-tender subcutaneous nodules or abscesses forming ulcers with undermined margins in patients with poor immunity.

Acute military TB results from hematogenous dissemination of *M. tuberculosis* in severely ill immune-compromised patients (as in HIV/AIDS) with disseminated TB. Lesions are widespread erythematous to purplish papules, pustules, or vesicles that resolved spontaneously in 2–4 weeks.

Tuberculid

Tuberculid represent a cutaneous immunologic reaction to the presence of *M. tuberculosis* in patients with significant immunity. The diagnosis is based on evidence of an active or healed tubercular focus (lymph node, lungs, abdomen, etc.), tuberculoid histology on biopsy, negative culture, strongly positive tuberculin test, and response to antitubercular drugs.

Papulonecrotic tuberculid (PNT) is characterized by symmetrical, dusky red necrotizing papules and pustules over extremities, while lichen scrofulosorum (LS) is characterized by grouped, pin-head sized, skin-colored/erythematous, perifollicular papules over the trunk in children. Erythema induratum of Bazin (EIB) presents as slightly painful, erythematous to violaceous indurated plaques and nodules that tend to ulcerate over posterior and anterolateral aspects of the legs.

Box 248.1 List of diagnostic tests for cutaneous tuberculosis

- Mantoux test
- Histopathology
- Culture – tissue and sputum
- Interferon- γ release-based assays – QuantiFERON-TB Gold tests (QFT-G)
- Polymerase chain reaction (PCR)
- Screening tests for systemic involvement – X-ray chest, USG abdomen and pelvis, X-ray bone/joints
- HIV screen

MANAGEMENT STRATEGY**Diagnosis**

The diversity of clinical findings, relatively rare occurrence of cutaneous disease, and difficulty in demonstrating AFB on histologic specimens often lead to misdiagnosis or significant delays in correctly identifying CTB; therefore, a high index of suspicion is needed. The gold standard for TB diagnosis remains identification of *M. tuberculosis* in tissue culture; it often fails due to the paucibacillary nature of CTB. Often myriad tests are required (Box 248.1) to accrue evidence for diagnosis, thereby avoiding empirical treatment.

Mantoux test or tuberculin skin test (TST) is a widely used screening test. The TST can be false positive as a result of previous BCG vaccination or sensitization to non-tuberculous mycobacteria and false negative in patients with reduced cellular immunity.

Histology – shows characteristic dermal granuloma composed of epithelioid cells, lymphocytes, and Langhans giant cells with or without caseation necrosis.

Mycobacterial culture from tissue and sputum – culture of *M. tuberculosis* remains the most definitive test for the diagnosis with the added advantage of allowing drug susceptibility testing.

Interferon- γ release assays (IGRAs) such as T-SPOT Assay TB test (T-SPOT) and QuantiFERON-TB Gold test (QFT-G) have low false-positive rates, regardless of BCG vaccination, and high specificity for identification of *M. tuberculosis* infection. They require just one patient visit and are preferred over TST.

PCR is highly sensitive and specific, using the DNA *IS 6110* gene specific for the *M. tuberculosis* complex, either in the fresh tissue or paraffin block for amplification.

Systemic screen – a coexistent systemic focus of TB has been observed in about one-third of patients with CTB, making it mandatory to screen all patients for an associated TB focus.

Contact tracing is important for efficient management of TB.

Lichen scrofulosorum; a prospective study of thirty-nine patients. Singal A, Bhattacharya SN. Int J Dermatol 2005; 44: 489–93.

Of the 39 patients with LS, 72% had a coexistent focus of TB, commonest being TB lymphadenitis followed by pulmonary TB and skin TB.

Comparison of the radiometric BACTEC 460 TB culture system and Löwenstein–Jensen medium for the isolation of mycobacteria in cutaneous tuberculosis and their drug susceptibility pattern. Aggarwal P, Singal A, Bhattacharya SN, et al. Int J Dermatol 2008; 47(7): 681–7.

In total, 26 mycobacterial isolates were recovered from 35 patients. Nine isolates (25.7%) grew on Löwenstein–Jensen medium after a mean period of 31.5 days, and 22 (62.8%) on the BACTEC system in 17.3 days. All of the isolates were identified as

Mycobacterium tuberculosis. Drug susceptibility testing demonstrated 12 isolates to be resistant, and seven to be multidrug resistant.

Interferon- γ release assay and reverse blot hybridization assay: diagnostic role in cutaneous tuberculosis. Chung HC, Kim BK, Hong H, et al. Acta Derm Venereol 2016; 96: 126–7.

IGRAs and the reverse blot hybridization assay confirmed the diagnosis in seven patients, six of whom had been diagnostically challenging, with negative staining or culture from skin samples. These patients were successfully treated.

Detection of mycobacterial DNA in papulonecrotic tuberculid lesions by polymerase chain reaction. Quirós E, Bettinardi A, Quirós A, et al. J Clin Lab Anal 2000; 14(4): 133–5.

The PCR could detect mycobacterial DNA in 10 cases of PNT, suggesting a definite role of *M. tuberculosis* in its pathogenesis and providing a rational basis for antituberculous therapy in the management of tuberculid.

Role of Mantoux test in cutaneous tuberculosis. Verma P, Singal A. Int J Dermatol 2014; 53(2): e129–30.

Previous sensitization by BCG vaccination, age of the patient, and nutritional and immune status are a few of the parameters that may affect the Mantoux reading, so it has to be interpreted cautiously.

TREATMENT

The aims of treatment are to rapidly cure the patient, reduce its transmission to others, and prevent development and transmission of drug resistance. Patients with a past history of TB are more likely to be infected with a strain of drug-resistant *Mycobacterium*.

First-Line Therapy

- Antituberculous drugs

A

CTB is treated with conventional antituberculous therapy (ATT) recommended for pulmonary disease. The regimen comprises:

- **An intensive phase** – directed toward the rapid destruction of a large proportion of *M. tuberculosis* and resolution of symptoms; therapy is for 2 months with four drugs – 2 (HREZ)
- **Continuation phase** – to eliminate the remaining ‘dormant’ organisms; therapy is for 4 months with two drugs – 4 (HR)

The dosing schedule includes isoniazid (H) (5 mg/kg), rifampicin (R) (10 mg/kg), pyrazinamide (Z) (25 mg/kg), streptomycin (S) (15 mg/kg), and ethambutol (E) (15 mg/kg).

Daily dosing is preferred in fixed-dose combinations to reduce pill burden and to increase treatment compliance. Pyridoxine (10 mg/day) is added to the regimen to prevent isoniazid-related neuropathy, especially in alcoholics, malnourished persons, pregnant/lactating women, and patients of chronic renal failure, diabetes, and HIV infection/AIDS.

Guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update). World Health Organization 2017.**Second-Line Therapies**

• Recalcitrant TB lesion	Excision + ATT	D
• Drug-resistant TB:	Second-line ATT	A
• Isoniazid resistance		
• Isoniazid + rifampicin (MDR)		

Occasionally, localized and solitary lesions of LV and TVC may be surgically excised as an adjuvant measure with standard chemotherapy.

An unusual presentation of cutaneous tuberculosis for surgeons-review of literature. Banashankari GS, Rudresh HK, Harsha AH, Bharathi R, et al. Indian J Surg 2012; 74(4): 314–7.

Non-healing abscesses over the thigh in a 46-year-old diabetic woman resolved completely with 6 months' standard ATT combined with incision and drainage of infected wound from the most dependent area.

Drug Resistance in CTB

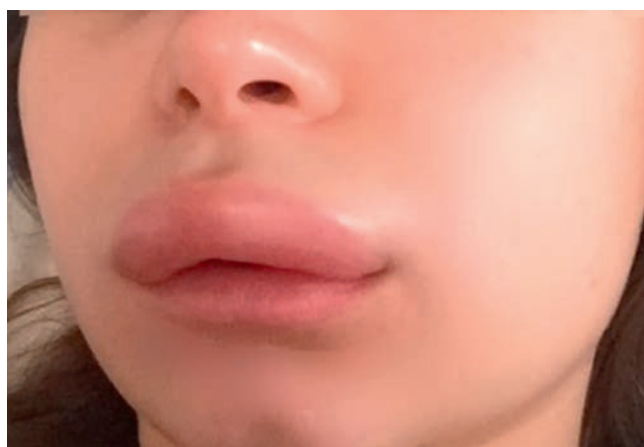
Though relatively uncommon, drug resistance in CTB may result from intermittent treatment, drug monotherapy, suboptimal drug dosing, and poor drug absorption.

Multidrug-resistant CTB should be managed at specialist centers.

WHO consolidated guidelines on drug-resistant tuberculosis treatment. World Health Organization 2019.

Urticaria and angioedema

Marcus Maurer, Torsten Zuberbier, Martin Metz



Urticaria is a frequent disease affecting up to 20% of us at least once during our lifetime. The hallmark feature of urticaria is the wheal, which is caused by mast cell–derived mediators such as histamine producing a transient increase in the permeability of cutaneous blood vessels, resulting in a short-lived superficial skin swelling. In addition to wheals (sometimes called hives), many urticaria patients also develop deep swellings of the dermis and subcutis, known as angioedema. Some urticaria patients exclusively experience angioedema, never having wheals. Wheals and angioedema as symptoms are not pathognomonic for urticaria; that is, patients with other diseases may experience whealing or angioedema. For example, angioedema without wheals can be mediated by bradykinin, independently of mast cell degranulation and histamine, and wheals also occur in patients with urticarial vasculitis or auto-inflammatory syndromes, which are mediated by interleukin-1 rather than mast cell–derived histamine or bradykinin.

URTICARIA

INTRODUCTION

The signs and symptoms of urticaria are brought about by the degranulation of cutaneous mast cells. Skin mast cells are preferentially localized in the vicinity of sensory nerves and small blood vessels. Their activation by certain signals, such as immunoglobulin E (IgE) crosslinking, can lead to their degranulation and release of *de novo* synthesized and preformed mediators, e.g., histamine. These mediators induce sensory nerve stimulation (itch, burning pain), vasodilatation (flare), edema (wheal, angioedema), and the recruitment of immune cells such as eosinophils, basophils, and neutrophils.

Clinically, urticaria is characterized by the rapid development of wheals, angioedema, or both. Wheals are associated with itching or burning as well as a flare reaction. They resolve spontaneously, usually within a few hours. In contrast, angioedema is a deeper, pronounced, and sometimes painful swelling of the lower dermis and subcutis and can also affect the mucous membranes. Swellings are of longer duration and slower resolution than wheals and can last for several hours to a few days. Angioedema, in patients with urticaria, can certainly be very debilitating and frightening. Patients need to be reassured that, unlike swelling attacks in patients with hereditary angioedema, urticaria-associated angioedema is not fatal.

Urticaria is either acute (less than 6 weeks' duration) or chronic. Urticaria patients develop wheals and/or angioedema spontaneously (spontaneous urticaria) or in response to a specific trigger (inducible urticaria). The specific triggers of whealing and angioedema formation in chronic inducible urticaria can be physical, e.g., contact with cold or heat (cold urticaria, heat urticaria), irradiation with ultraviolet (UV) light or visible light (solar urticaria), friction (symptomatic dermatographism), pressure (pressure urticaria), or vibration (vibratory angioedema). In contrast to these physical forms of inducible urticaria, the development of signs and symptoms in the other types of inducible urticaria is triggered by skin contact with urticariogenic substances (contact urticaria), water (aquagenic urticaria), or sweat (cholinergic urticaria).

In chronic spontaneous urticaria (CSU), both wheals and angioedema can occur anywhere on the body. However, wheals appear most often at the legs and arms and rarely in the face, whereas angioedema is most commonly localized in the face (e.g., the lips and eyes). In contrast, chronic inducible urticaria is usually characterized by whealing and/or angioedema formation at the skin sites that are exposed to the eliciting trigger. Disease activity and control in CSU urticaria is assessed using the urticaria activity score (UAS7) and the angioedema activity score (AAS), which rely on prospective patient documentation of daily wheal numbers and itch intensity (UAS7) and swellings (AAS), and the urticaria control test (UCT) and angioedema control test (AECT), respectively. The UCT and the AECT are validated and reliable 4-item retrospective tools, distinguishing patients with poorly or uncontrolled disease versus well or completely controlled disease. Disease activity in patients with inducible urticarias is measured by assessing trigger thresholds via provocation testing.

Important differential diagnoses of urticaria are severe allergic reactions (e.g., anaphylactic shock), where wheals and/or angioedema co-occur with systemic manifestations, urticarial vasculitis, autoinflammatory syndromes, and bradykinin-mediated angioedema (e.g., hereditary or acquired C1 inhibitor deficiency).

MANAGEMENT STRATEGY

The aim of the treatment of patients with urticaria is the elimination of signs and symptoms. This may be achieved by treating an underlying cause or condition, by the avoidance of eliciting triggers, by preventing mast cell degranulation, or by blocking the effects of histamine or other mast cell mediators. For the inducible urticarias, causes are largely unknown and their triggers of wheal and/or angioedema development may be difficult or impossible for patients to avoid. Urticaria is self-limiting but often lasts for several years and, in some cases, for decades. Effective and safe prophylactic therapy aimed at the prevention of signs and symptoms is, therefore, needed, and several treatment options are available. The prevention of recurring urticaria signs and symptoms by medication that protects patients from the effects of relevant mast cell degranulating signals or of the mediators released by mast cells is currently the most common approach for the management of urticaria.

Acute Urticaria

Acute urticaria in most patients can be managed with oral *second-generation H1-antihistamines* (sgAHs) (Table 249.1). Add-on oral glucocorticosteroids may be used for a few days for severe cases, and they can reduce disease activity and duration when given at the onset of the disease.

Chronic Spontaneous Urticaria

By taking a good history and asking the patient to keep a symptom diary, it is sometimes possible to identify exacerbating factors that increase disease activity, e.g., stress, infections, gastritis, or the intake of non-steroidal antiinflammatory drugs. Avoiding these triggers, where possible, can help to reduce disease activity.

Current guidelines recommend a step-up approach for the pharmacological treatment of patients with CSU, with standard-dosed (first-line therapy) and up to fourfold dosed sgAHs (second-line therapy) followed by add-on omalizumab (third-line therapy). In patients who do not respond to omalizumab, ciclosporin is recommended as fourth-line treatment. Based on the available evidence and experience, these treatment options work in most patients and should be explored before moving to other therapies.

The signs and symptoms of CSU are largely driven by mediators released from activated skin mast cells. The most prominent one is histamine, which exerts its action via H1-receptors on cutaneous blood vessels and nerves. The first-line pharmacological approach for the treatment of all patients with CSU is, therefore, the use of sgAHs at licensed doses. All sgAHs are inverse agonists that promote the inactivate state of the H1-receptor and prevent its binding of histamine. SgAHs should, therefore, be taken regularly, i.e., every day, to prevent histamine-mediated extravasation and to protect from the development of skin lesions, rather than as on-demand medication after skin lesions have already developed. SgAHs are highly selective for the H1-receptor and minimally or non-sedating because of their low penetration of the blood-brain barrier, an important difference to first-generation antihistamines. The use of standard-dosed sgAHs as first-line therapy of CSU is supported by a large body of high-quality evidence for their efficacy and safety from numerous randomized controlled trials. Current guidelines recommend against the routine use of first-generation H1-antihistamines (AHs) in the management of CSU, as they can have anticholinergic effects, cause

Table 249.1 Selection of second-generation H1 antihistamines used in the treatment of chronic urticaria

Second-generation antihistamine	Daily standard dose
Bilastine	20mg
Cetirizine	10mg
Desloratadine	5mg
Ebastine	10mg
Fexofenadine	180mg
Levocetirizine	5mg
Loratadine	10mg
Mizolastine	10mg
Rupatadine	10mg

sedation, impair the quality of sleep, affect cognitive and psychomotor functions, and exhibit interactions with other drugs.

In patients with CSU who continue to show signs and symptoms after 2–4 weeks of standard-dosed sgAH treatment (or earlier, if symptoms are intolerable) up dosing of the sgAH to up to fourfold the licensed dose is suggested. This second-line therapy, with one sgAH at a higher than standard dose, is preferable to combining different H1-antihistamines at the same time in the same patient. The recommendation to updose sgAHs in treatment-resistant patients is based on several randomized controlled trials, numerous real-life surveys, and longstanding and broad experience, all of which support the notion that up dosed sgAHs show higher efficacy in CSU as compared to standard dose sgAH treatment. In general, higher than standard doses of sgAHs are held to be safe and well tolerated, even with long-term use. Most modern sgAHs have been described to also have antiinflammatory effects, often only at high doses. However, individual sgAHs exhibit differences in the strength of the evidence in support of their safety and efficacy when used at higher than standard doses. Thus, responses to treatment, in terms of both disease control and sedation or other possible side effects, need to be monitored continuously.

Most patients with CSU benefit from sgAH treatment, but many do not show complete control. In patients who still have urticaria signs and symptoms after 2–4 weeks of high-dose sgAH therapy, or earlier, if symptoms are intolerable, add-on treatment with *omalizumab* should be considered. The long-term use of *systemic glucocorticosteroids* is to be avoided, but a short course may be tried to control acute exacerbation. Omalizumab is a humanized antibody against IgE licensed for the treatment of asthma and CSU. A meta-analysis of its use in seven randomized controlled trials found omalizumab to be very safe and effective in patients with CSU who were treatment-resistant to H1-antihistamine treatment in licensed doses or up to four times the licensed dose.¹ The first randomized controlled trial performed in CSU used the omalizumab dosing regimen established for severe asthma, but subsequent trials revealed that urticaria symptoms and quality of life improved significantly with a standard dose of 150 mg or 300 mg/4 weeks omalizumab, independent of body weight and IgE serum levels. The largest decrease of disease activity and the highest number of patients with complete response were found in the 300-mg group. Similar to antihistamines, omalizumab is a symptomatic rather than a curative treatment, and the adaptation of dosing and treatment intervals to fluctuations in disease activity should be considered, based on continued monitoring of disease activity, control, and impact on patients.

The treatment of patients with CSU with omalizumab during the past years confirms the good risk/benefit profile of this therapy seen in clinical trials. It also indicates that the onset of action of omalizumab in most patients is fast, often within a few days after the first administration, but that up to five treatments may be needed for some patients to respond. Most omalizumab-treated patients with CSU can stop all concomitant therapies and remain free of symptoms with omalizumab alone. Omalizumab appears to be effective in CSU patients with both wheals and angioedema, as well as those suffering from isolated angioedema.

The use of *ciclosporin* as a back-up treatment option in treatment-resistant patients is supported by the longstanding experience and evidence that this drug can be effective in patients with CSU. Ciclosporin is usually given over 3–4 months at a starting dose of 2–4 mg/kg/day with a fast onset of action, usually within a week, in most patients. When working with ciclosporin, its known side effects including hypertension, hypertrichosis, increase of creatinine levels up to renal failure, and dyslipidemia need to be considered, requiring careful monitoring.

Many other treatments have been used in CSU, but their effects have either not been studied in controlled settings or the strength of the evidence in support of their use is low. Treatments that may be used in CSU patients who are treatment-resistant to sgAHs, omalizumab, and/or ciclosporin include, but are not limited to, autologous whole blood or *serum therapy*, *azathioprine*, *benralizumab*, *cyclophosphamide*, *colchicine*, *dapsone*, *dupilumab*, *H2-antagonists*, *intravenous immunoglobulins*, *leukotriene antagonists*, *mepolizumab*, *methotrexate*, *mycophenolate mofetil*, and *reslizumab*.

Chronic Inducible Urticaria

The treatment approaches and medications used for chronic inducible urticarias are, by and large, very similar to those for CSU. Patients can benefit from knowing what triggers their urticaria and knowing their individual trigger threshold, as this can help them avoid situations that are associated with disease exacerbation. For many forms of chronic inducible urticaria, however, it is exceedingly difficult or impossible for patients to completely avoid any exposure to the eliciting trigger, for example, mechanical irritation of the skin in symptomatic dermatographism. Because of this, pharmacological treatment is very important and needed for most patients with chronic inducible urticaria.

SgAHs are the first-line treatment of choice, and doses should be increased up to fourfold in patients who do not respond. All sgAHs are licensed for the use in chronic inducible urticarias. Moreover, based on clinical experience and some studies, they are effective and safe in all forms of chronic inducible urticaria. However, for most forms of chronic inducible urticaria, no controlled studies have been performed with standard-dosed and/or higher than standard doses of sgAHs. Several case series and reports as well as a few randomized controlled trials and meta-analyses indicate that omalizumab is effective and safe for the treatment of patients with inducible forms of chronic urticaria, but it is not licensed for this use.²

Other treatments for patients with chronic inducible urticaria are, in general, backed only by weak evidence or no evidence and come with concerns regarding their risk/benefit profiles. For example, in some forms of chronic inducible urticaria such as cold urticaria, solar urticaria, and cholinergic urticaria, tolerance can be induced by *desensitization* protocols using repeated exposure to the relevant trigger with gradually increasing strength. However, this tolerance is transient, patients usually require daily maintenance exposure, and severe side effects have been described.

Specific Investigations

Acute urticaria

- None

Chronic spontaneous urticaria

- Exclude differential diagnoses, screen for comorbidities (e.g., chronic inducible urticaria, other autoimmune diseases, depression/anxiety)
- Check for systemic inflammation (CRP, ESR, and/or differential blood count)
- Assess disease activity, impact, and control, e.g., by use of the urticaria activity score (UAS7)/angioedema activity score, the chronic urticaria quality of life questionnaire (CU-Q2oL)/angioedema quality of life questionnaire (AE-QoL), and the UCT/AECT, respectively
- In patients with uncontrolled or longstanding disease, consider underlying causes based on history and physical examination (e.g., total IgE measurements, autologous serum skin testing, basophil activation assay [when available in cases of suspected autoimmunity])

Chronic inducible urticaria

- Exclude differential diagnoses
- Confirm relevance of trigger(s) by provocation testing
- Determine disease activity and control by assessing trigger threshold and use of the UCT, respectively

First-Line Therapy

- Second-generation H1 antihistamines

A

Second-Line Therapy

- Up to fourfold standard dose second-generation H1 antihistamines

A

Third-Line Therapy

- Omalizumab

A

Fourth-Line Therapy

- Ciclosporin³

A

The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Zuberbier T, Aberer W, Asero R, et al. *Allergy* 2018; 73(7): 1393–414.

The definition, diagnostic testing, and management of chronic inducible urticarias – the EAACI/GA(2) LEN/EDF/ UNEV consensus recommendations 2016 update and revision. Magerl M, Altrichter S, Borzova E, et al. *Allergy* 2016; 71(6): 780–802.

NON-MAST CELL-MEDIATED ANGIOEDEMA

INTRODUCTION

In contrast to mast cell-mediated angioedema, which is a frequent feature and sign of chronic urticaria, non-mast cell-mediated angioedema is a group of diseases. These include hereditary angioedema (HAE) (see Ch. 101) with or without C1 inhibitor (C1INH) deficiency, angioedema due to acquired C1INH deficiency, and drug-induced angioedema, such as angiotensin-converting enzyme inhibitor-associated angioedema. Patients with these angioedema diseases, all of which are held to be bradykinin-mediated, usually do not exhibit wheals.

Two major forms of HAE, both rare, have been described: HAE with C1INH deficiency, subclassified as type I and type II based on low antigenic and functional C1INH levels, respectively, and HAE with normal C1INH levels with or without known mutations, e.g., in Hageman factor (coagulation factor XII). Angioedema attacks in all type I and type II HAE patients are held to be due to the enhanced generation of bradykinin. The acquired forms of non-mast cell mediator-mediated angioedema include those that are due to acquired C1INH deficiency (e.g., increased catabolism of C1INH) and those that are due to certain drugs, mainly angiotensin-converting enzyme inhibitors (ACEI). Like in HAE, attacks of patients with these forms of angioedema are linked to bradykinin.

In patients with HAE due to C1INH deficiency, recurrent angioedema attacks primarily involve the hands and feet, the abdomen, the face, the oropharynx, or a combination of the above. Patients with HAE due to C1INH deficiency often experience prodromal symptoms (e.g., erythema marginatum). Typical attacks progress for several hours and then slowly resolve over many hours to several days. Attacks involving the extremities and abdomen are the most common, and attacks of the oropharynx are the most dangerous, with a significant risk of mortality due to suffocation. In comparison, HAE with normal C1INH is more likely to affect females, to first occur after puberty, and to come with fewer attacks. Triggers of attacks are common and similar in all forms of HAE and include trauma, increased estrogen levels, and stress.

Attacks in patients with angioedema due to acquired C1INH deficiency are similar to those of HAE patients, but the former show a later age of onset and no family history. Attacks in patients with ACEI-induced angioedema typically affect the face, especially the lips and tongue. The time to onset of angioedema attacks after the start of ACEI treatment is usually less than 1 month, but in one of four affected patients it is greater than 6 months, and up to 10 years in some patients.

The diagnosis of bradykinin-mediated angioedema requires a thorough history, exclusion of differential diagnoses (especially chronic urticaria), and laboratory testing for C1INH deficiency. Angioedema in patients taking an ACEI is due to the ACEI until or unless proven otherwise.

MANAGEMENT STRATEGY FOR BRADYKININ-MEDIATED ANGIOEDEMA

The management of HAE with C1INH deficiency consists of the avoidance of known triggers of attacks and pharmacotherapy, i.e., the use of on-demand treatment for attacks,

their prevention by prophylactic treatment, or both. Today, five highly effective and safe drugs are available for the on-demand treatment of attacks, three different C1 inhibitors (C1INHs, two plasma-derived and one recombinant) as well as *icatibant*, a selective bradykinin B2 receptor antagonist, and *ecallantide*, which inhibits plasma kallikrein, the protease that cleaves kininogen and generates bradykinin. Patients with HAE due to C1INH deficiency may also require prophylaxis. Preprocedural prophylaxis is usually done with C1INH with the aim to protect patients from attacks that occur in response to unavoidable triggers such as dental work or surgery. Long-term prophylaxis, i.e., the regular use of medication to prevent angioedema attacks, should be considered in all HAE patients with C1INH deficiency, especially in those with high attack frequency and severity or limited access or response to on-demand treatment. *Lanadelumab*, the oral kallikrein inhibitor *berotralstat*, a therapeutic antibody that inhibits plasma kallikrein, and C1INH are the preferred treatments for long-term prophylaxis. Patients with HAE and normal C1INH as well as patients with acquired bradykinin-mediated angioedema can also benefit from on-demand treatment with C1INH or *icatibant*. Importantly, the standard treatment for attacks in patients with mast cell mediator-mediated angioedema, such as glucocorticosteroids or H1-antihistamines, do not have any beneficial effect on HAE attacks and should not be used as on-demand medication for the treatment of bradykinin-mediated angioedema attacks.

Specific Investigation

- C4, C1INH level and function
Guideline for the management of hereditary angioedema: World Allergy Organization consensus document.⁴

First-Line Therapies

On-Demand

• C1INH	A
• Ecallantide	A
• Icatibant	A

Prophylaxis

• C1INH	A
• Lanadelumab	A
• Berotralstat	A

An evidence based therapeutic approach to hereditary and acquired angioedema. Bork K. Curr Opin Allergy Clin Immunol 2014; 14(4): 354–62.

Lanadelumab for the prevention of attacks in hereditary angioedema. Valeriewa A, Senter R, Wu MA, et al. Expert Rev Clin Immunol 2019; 15(12): 1239–48.

Lanadelumab, a human monoclonal antibody targeted against plasma kallikrein has been approved for prevention of symptoms in C1-INH-HAE.

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4. Maurer M, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. *Allergy*. 2018;73(8):1575–1596.

Varicella

Daniel Michalik, Johanna Goldfarb, Kenneth Tomecki



Varicella (chickenpox) is a self-limited viral exanthem caused by primary infection with varicella zoster virus (VZV), a double-stranded DNA herpesvirus. Varicella is a highly communicable disease transmitted through respiratory droplets and/or direct contact with vesicular fluid. The disease has an incubation period of 10–21 days and affected individuals are infectious 48 hours prior to the onset of the rash and until all vesicles have crusted. After primary infection, VZV travels to the dorsal root ganglion where it remains latent.

Varicella most commonly occurs in young children. Prior to the varicella vaccine, approximately 90% of children developed varicella by age 10. Most affected individuals are asymptomatic before onset of a rash, but a prodrome of fever, malaise, headache, arthralgias, and myalgias may occur. Individuals then develop pruritic macules and papules on the scalp and face, which spread to the trunk and extremities and rapidly evolve into vesicles on erythematous bases ('dew drops on a rose petal'), which then become crusted within several days. A distinctive feature of primary varicella zoster infection is the rash, which occurs in various stages simultaneously. Infection in adults is more severe and can be prolonged. Potential complications of varicella include bacterial superinfections (e.g., impetigo, otitis media, pneumonia), viral pneumonitis, otitis media, and corneal lesions. Rarer complications include encephalitis, especially a benign self-limited cerebellar ataxia; myocarditis, which can be severe; nephritis; hepatitis; arthritis; acute glomerulonephritis; vasculopathy; and disseminated intravascular coagulopathy. Reye syndrome may occur with salicylate ingestion, though now it is very uncommon with avoidance of aspirin in children. Delayed complications include herpes zoster (shingles), which is discussed in a separate chapter.

MANAGEMENT STRATEGY

All healthy individuals, especially children, without a definite history of varicella should be vaccinated. In the United States, a live attenuated monovalent vaccine (VARIVAX) and a quadrivalent

measles-mumps-rubella-varicella (MMRV) vaccine (ProQuad) are available, with the first dose administered at age 12 through 15 months and the second at age 4 through 6 years. For individuals who have only received a single dose of the vaccine, a second dose catch-up vaccination is recommended. Postexposure immunization may be effective for household contacts if given within 3 days of exposure, but should not be given to children with severe immune deficiency.

In **healthy children** younger than 12 years, *symptomatic treatment* is recommended. *Acetaminophen* (Tylenol) may be used in children with fever and pain, but aspirin should be avoided given the risk of Reye syndrome. Supportive *topical treatments* for pruritus include *oatmeal baths* and *calamine lotion*. Topical or oral antibiotics are appropriate for children with a secondary bacterial infection. Oral *aciclovir* and *valaciclovir* are US Food and Drug Administration (FDA) approved for children ages 2 through 17 years with varicella, but antiviral therapy is generally not recommended in otherwise healthy children.

In **healthy adolescents and adults**, it is recommended that oral *aciclovir*, *valaciclovir*, or *famciclovir* be initiated within 24 hours of onset of the rash as antiviral therapy can decrease disease severity and duration. These patients should also be treated symptomatically. Smokers and patients with chronic lung disease have greater risk of complications, particularly varicella pneumonia, which has a mortality of 10–30%.

Pregnant women with varicella have an increased risk of complications. Infections during the first 20 weeks of pregnancy may result in congenital varicella syndrome, which includes limb hypoplasia and developmental abnormalities of the eyes and central nervous system. This syndrome occurs in 2% of pregnancies complicated by varicella during the first 20 weeks of gestation. *Varicella zoster immune globulin* (VZIG) is recommended for non-immune pregnant women within 96 hours of exposure to varicella. VZIG offers protection for 3 weeks and decreases the risk of fetal transmission. If VZIG is unavailable, affected women should receive *intravenous immunoglobulin* (IVIG). Oral *aciclovir*, *valaciclovir*, or *famciclovir* should be initiated in pregnant women with varicella, especially in the second and third trimesters. Intravenous aciclovir is recommended in pregnant patients with serious complications of varicella, such as varicella pneumonia. Aciclovir, valaciclovir, and famciclovir are category B drugs in pregnancy, without significant risk of teratogenesis during pregnancy.

Neonates whose mothers develop varicella just before delivery (up to 5 days) or within 2 days after delivery should receive VZIG or IVIG prophylactically coupled with IV *aciclovir*.

Immunocompromised individuals exposed to varicella should receive VZIG or IVIG within 10 days of exposure. If the disease occurs despite administration of VZIG or IVIG, *intravenous aciclovir* should be given. Patients receiving high-dose corticosteroids (≥ 2 mg/kg/day or ≥ 20 mg/day prednisone or its equivalent) for more than 14 days are at risk of visceral involvement and death. *Valaciclovir* and *famciclovir* are often better alternatives given bioavailability and steadier plasma concentration. Resistance to aciclovir in immunocompromised individuals is rare. Patients requiring immunosuppressive therapy or solid organ transplantation should be screened for varicella zoster immunity and vaccinated at least 2 weeks prior to starting immunosuppressive treatment. Vaccination during immunosuppression is a complex decision requiring knowledge of a patient's relative immune competence.

Specific Investigations

- PCR
- Direct fluorescent antibody (DFA)

VZV can be identified by polymerase chain reaction (PCR) and DFA of skin scrapings from the base of a fresh vesicle. PCR is the preferred method given its rapidity and sensitivity. Viral culture has a poor yield and is not recommended. Tzanck smear is about 85% sensitive; it cannot differentiate between VZV and other herpesviruses.

First-Line Therapies

- Symptomatic treatment **D**
- Valaciclovir **D**
- Aciclovir **A**

Chickenpox: treatment. Cohen J, Breuer J. *BMJ Clin Evid* 2015; 2015: 0912.

Systematic review concluded that aciclovir, administered within 24 hours of rash onset, showed a therapeutic benefit in reducing duration of fever and the number of lesions in otherwise healthy children and adults. Valaciclovir and famciclovir are efficacious and acceptable therapies, but there have been no randomized control trials assessing these medications as treatment of chickenpox.

Varicella in a pediatric heart transplant population on non-steroid maintenance immunosuppression. Dodd DA, Burger J, Edwards KM, et al. *Pediatrics* 2001; 108: E80.

Six pediatric heart transplant patients with varicella received valaciclovir 500–750 mg three times daily for 7 days. Most experienced resolution of fever and absence of new lesions by day three of treatment.

Treatment of adult varicella with oral acyclovir: a randomized, placebo-controlled trial. Wallace MR, Bowler WA, Murray NB, et al. *Ann Intern Med* 1992; 117: 358–63.

A randomized trial of 148 adults hospitalized for varicella and treated with either aciclovir 800 mg orally five times per day for 7 days, or placebo. Patients treated within 24 hours of onset of the rash had fewer lesions and shorter time to crusting. Treatment after 24 hours had no effect.

Second-Line Therapy

- Famciclovir **D**

Pharmacokinetics and safety of famciclovir in children with herpes simplex or varicella-zoster virus infection. Sáez-Llorens X, Yogev R, Arguedas A, et al. *Antimicrob Agents Chemother* 2009; 53: 1912–20.

Fifty-four children with varicella received a 7-day course of famciclovir, with doses adjusted according to body weight (≈ 12.5 mg/kg daily for children <40 kg and 500 mg daily for children >40 kg). Resolution of symptoms occurred in 49 of 53 (92.5%) children.

Foscarnet therapy in five patients with AIDS and acyclovir resistant varicella zoster virus infection. Safrin S, Berger TG, Wolfe PR, et al. *Ann Intern Med* 1991; 115: 19–21.

Five adults with acquired immune deficiency syndrome (AIDS) and aciclovir-resistant VZV received foscarnet 40 mg/kg every 8 hours as therapy for 14–26 days, which resulted in clearance of lesions and cessation of viral shedding in four patients. The fifth patient failed therapy because of foscarnet resistance.

Prophylaxis

- Vaccines **A**
- Aciclovir **B**
- VZIG **B**
- IVIG **C**

SAGE working group on varicella and herpes zoster vaccines: background paper on varicella vaccine SAGE review 2015. http://www.who.int/immunization/sage/meetings/2014/april/1_SAGE_varicella_background_paper_FINAL.pdf.

A systematic review of efficacy of the varicella vaccine. The authors concluded, “There is strong scientific evidence that varicella vaccine is safe and effective in preventing varicella related morbidity and mortality in immunocompetent individuals.”

Varicella vaccination in the immunocompromised. Malaiya R, Patel S, Snowden N, et al. *Rheumatology* 2015; 54: 567–9.

Given the complications associated with varicella infection in immunocompromised individuals, the authors recommend that such individuals should be vaccinated 2 weeks before initiating immunosuppressive treatment.

Combination measles-mumps-rubella-varicella vaccine in healthy children: a systematic review and meta-analysis of immunogenicity and safety. Ma S, Li X, Xiong Y, et al. *Medicine* 2015; 94(44): e1721.

A meta-analysis comparing seroconversion rates between the monovalent varicella vaccine and the MMRV vaccine. There was no statistical difference in seroconversion rates between the varicella and MMRV groups.

Vaccines for postexposure prophylaxis against varicella (chickenpox) in children and adults. Macartney K, Heywood A, McIntyre P. *Cochrane Database Syst Rev* 2014; 6: CD001833.

Three studies involving 110 children demonstrated that the varicella vaccine, when administered within 3 days of household exposure, significantly reduced infection rates when compared with placebo.

Prophylactic role of long-term ultralow-dose acyclovir for varicella zoster virus disease after allogeneic hematopoietic stem cell transplantation. Kawamura K, Wada H, Yamasaki R, et al. *Int J Infect Dis* 2014; 19: 26–32.

A study of 141 immunosuppressed patients treated prophylactically with 200 mg of aciclovir daily for up to a year after stem cell transplantation. Discontinuation of the drug resulted in an increased frequency of varicella, demonstrating aciclovir’s efficacy in disease prevention.

Updated recommendations for use of VariZIG—United States, 2013. Centers for Disease Control and Prevention (CDC). *Morb Mortal Wkly Rep* 2013; 62: 574–6.

The CDC recommends administration of VZIG within 10 days of exposure to VZV, but ideally within 96 hours, for high-risk individuals without evidence of immunity to varicella and for whom varicella vaccination is contraindicated. High-risk groups include immunocompromised patients, newborn infants whose mothers have signs and symptoms of varicella at the time of delivery (i.e., 5 days before to 2 days after), hospitalized premature infants born at ≥ 28 weeks of gestation whose mothers do not have evidence of immunity to varicella, hospitalized premature infants

born at <28 weeks of gestation or who weigh ≤ 1000 g at birth, and pregnant women without evidence of immunity.

Management of varicella infection (chickenpox) in pregnancy. Shrim A, Koren G, Yudin MH, et al. *J Obstet Gynaecol Can* 2012; 34: 287–92.

Varicella immunization is recommended for all non-immune women as part of antenatal and postpartum care. Varicella vaccination should not be administered in pregnancy. The antenatal varicella immunity status of all pregnant women should be determined by history of previous infection, varicella vaccination, or serology. All non-immune pregnant women should be informed of the potential adverse maternal and fetal sequelae associated with varicella infection. With varicella exposure in a pregnant woman with unknown immune status, serum testing should be performed. If results are negative or unavailable within 96 hours of exposure, VZIG should be administered. Ultrasound is recommended for all women who develop varicella in pregnancy. IV aciclovir may be necessary for complications in pregnancy.

A varicella outbreak in a school with high one-dose vaccination coverage, Beijing, China. Lu L, Suo L, Li J, et al. *Vaccine* 2012; 30: 5094–8.

Of the 951 students, 916 had received one dose of varicella vaccine, and only two students had received two doses before the outbreak. In total, 87 cases occurred and 82 of them were mild (<50 lesions). Single-dose varicella vaccination was 89% effective in preventing varicella and 99% in preventing moderate/severe varicella.

Effectiveness of 2 doses of varicella vaccine in children. Shapiro ED, Vazquez M, Esposito D, et al. *J Infect Dis* 2011; 203(3): 312–5.

A case-control study of 71 children and 140 matched controls assessing the effectiveness of the two-dose varicella vaccine. The

one-dose vaccine was 86% effective, whereas the two-dose vaccine was 98.3% effective in preventing varicella.

Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). Marin M, Broder KR, Temte JL, et al. Centers for Disease Control and Prevention (CDC). *MMWR Recomm Rep* 2010; 59: 1–12.

Combined vaccination with MMRV vaccine is preferred over separate injections of its equivalent vaccines when used as a second dose in children ages ≥ 15 months or as a first dose in children ages ≥ 48 months. MMRV is not recommended for initial dosing before age 48 months as there appears to be a slightly increased risk of febrile seizures in this age group.

Postexposure prophylaxis of varicella in family contact by oral acyclovir. Asano Y, Yoshikawa T, Suga S, et al. *J Pediatr* 1993; 92: 219–22.

A group of 25 children received oral aciclovir, 40 or 80 mg/kg in four divided doses, for 7–9 days after household exposure to varicella. They were compared with 25 age-matched control subjects who had been exposed but did not receive treatment. Of the 25 children treated with aciclovir, four developed varicella, with seroconversion seen in 21 out of 25 children treated with aciclovir. All 25 controls developed varicella.

Intravenous immunoglobulin prophylaxis in children with acute leukemia following exposure to varicella. Chen SH, Liang DC. *Pediatr Hematol Oncol* 1992; 9: 347–51.

Five children with leukemia received a single dose of IVIG 200 mg/kg within 3 days of varicella exposure. None developed varicella. The authors concluded that IVIG was an effective and safe alternative therapy when VZIG is unavailable.

Viral exanthems: rubella, roseola, rubeola and enteroviruses

Paula C. Luna, Cindy P. Frare



RUBELLA

Rubella (German measles, 3-day measles) is caused by a member of the *Togaviridae* family; it is a usually benign infection characterized by a short prodrome of fever, cervical, suboccipital or postauricular lymphadenopathies and arthralgias, followed by a maculopapular erythematous rash that begins on the face and spreads centrifugally, lasting up to 5 days. A petechial enanthem called Forchheimer spots can be also seen. Thrombocytopenia and encephalitis are extremely rare complications.

MANAGEMENT STRATEGY

It is usually a benign disease; however, if the infection occurs in the first weeks of pregnancy, up to 85% of neonates might die in utero or be born with congenital rubella syndrome (CRS; growth restriction and major birth defects). CRS can lead to ocular involvement, auditive disorders, and cardiac and neurologic manifestations, as well as extramedullary hematopoiesis (blueberry muffin lesions; see figure). Those that survive the neonatal period may have an increased risk for developmental delay and endocrinopathies.

Differential diagnosis includes measles virus, parvovirus B19, and other rash etiologies. Suspected cases, especially during pregnancy, should be confirmed by laboratory testing.

The standard method for laboratory diagnosis is the detection of rubella-specific immunoglobulin M (IgM) in serum. These antibodies may not be detectable until 4 days after rash onset and persist for at least 8 weeks after infection and even more after vaccination. False-positive IgM results may be found. Seroconversion or a significant increase in rubella immunoglobulin G (IgG) titer in paired acute and convalescent phase sera tested in the same assay are also indicative of an acute infection. Distinguishing primary infections from persisting IgM antibodies is essential, especially during pregnancy.

The treatment is generally *supportive*.

Rubella vaccine is a live virus vaccine administered as a two-dose series in the United States as part of the measles-mumps-rubella (MMR) with or without varicella (MMRV) vaccine (MMR or MMRV at 12–15 months of age with a second dose at 4–6 years). Rubella is another vaccine-preventable viral disease, with life-long immunity after natural infection or vaccination. In the absence of vaccination, the mean age of rubella infection is 5–9 years of age.

According to the US guidelines, if a non-immune pregnant woman (in whom termination is not an option) is identified within 5 days of exposure, passive immunization with 20 mL intramuscular immune globulin (IMIG) within 72 h of exposure should be considered. This intervention has shown an excellent safety profile and it has proved to be of benefit for preventing rubella, although evidence directly in relation to the prevention of CRS is scarce.

Specific Investigations

- Viral culture
- Serology (acute IgM or acute and convalescent IgG)
- Polymerase chain reaction (PCR)

First-Line Therapies

• Antipyretics: acetaminophen (paracetamol), ibuprofen	E
• Analgesics: non-steroidal antiinflammatory drugs	E
• School avoidance for 7 days	A
• Immunization	A

Measles-mumps-rubella-varicella vaccine in healthy children. Ma SJ, Li X, Xiong YQ, et al. *Medicine (Baltimore)* 2015; 94: e1721.

MMRV had comparable immunogenicity and overall safety profiles to MMR administered with or without varicella vaccine.

Rubella Global Strategic Plan 2012–2020. Orenstein WA, Cairns L, Hinman A, et al. *Vaccine* 2018; 36 (Suppl 1): A35–42.

Although rubella is a vaccine-preventable viral disease, it is calculated that more than 100,000 babies with CRS were born globally in 2010.

Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome. Young MK, Cripps AW, Nimmo GR, et al. *Cochrane Database Syst Rev* 2015 Sep 9. <https://doi.org/10.1002/14651858.CD010586.pub2>.

Polyclonal immunoglobulins may prevent rubella up to 5 days after exposure, with dose-dependent effectiveness. Evidence of congenital rubella prevention with polyclonal immunoglobulins is inconclusive.

ROSEOLA

Roseola infantum (exanthem subitum, sixth disease) is a common disease caused by a primary infection with human herpesviruses HHV-6A, HHV-6B, or HHV-7. It mainly affects children aged 6–36 months. It consists of two phases: high fever for 3–7 days, followed by a fast defervescence and an exanthem starting on the neck and chest lasting for 2 days. It is a self-limiting illness and, as with other viruses belonging to the herpes family, it usually remains latent in immunocompetent patients with the possibility of reactivation.

Other dermatologic manifestations of these viruses are pityriasis rosea and HHV-7 and drug-induced hypersensitivity syndrome (DIHS/DRESS) with HHV-6B reactivations favored by certain drugs.

MANAGEMENT STRATEGY

Detecting genomic DNA by PCR is the technique of choice as it is specific, sensitive, and accessible. Other tests such as culture techniques and immunofluorescence for viral antigen detection can also be performed but are not recommended.

Detection of specific IgG and IgM antibodies by immunofluorescence is restricted due to cross-reactions between HHV-6A, HHV-6B, HHV-7, and cytomegalovirus (CMV) antibodies.

Ganciclovir, cidofovir, and foscarnet have shown to inhibit HHV-6 and -7 replication in vitro. Individual case reports have suggested benefit from these agents in immunocompetent patients with end-organ disease.

Specific Investigations

- No investigation is required routinely
- HHV-6 serology (acute IgM or acute and convalescent IgG)
- PCR

First-Line Therapy

- Antipyretics (acetaminophen, ibuprofen)

E

Second-Line Therapies

- Ganciclovir
- Foscarnet

D

D

Summary of the 11th International Conference on Human Herpesviruses-6A, -6B, and -7. Komaroff AL, Zerr DM, Flamand L. *J Med Virol* 2020; 92(1): 4–10.

Ganciclovir and foscarnet have shown antiviral activity against HHV-6B but are not approved to treat or prevent HHV-6A and -6B-associated diseases. Oral brincidofovir has in vitro activity against HHV-6B; it reduced cumulative incidence of HHV-6B viremia at high risk, but not low risk, patients. Several drugs labeled for other diseases (leflunomide, artesunate, sirolimus, and everolimus) have been found to have activity against HHV-6A and -6B.

Human herpesvirus types 6 and 7 infection in pediatric hematopoietic stem cell transplant recipients. Fule Robles JD, Cheuk DK, Ha SY, et al. *Ann Transplant* 2014; 19: 269–76.

Multiple studies have shown that ganciclovir and foscarnet resolve viremia but may not improve survival. If these medications fail in severe HHV-6 or -7 infections, cidofovir may be tried. However, cidofovir has poor cerebrospinal fluid (CSF) penetration and may not be effective in treating herpesvirus encephalopathy.

RUBEOLA

Measles (rubeola) is an acute viral disease caused by an RNA virus, which is a member of the morbillivirus genus in the family Paramyxoviridae.

MANAGEMENT STRATEGY

Measles starts with a prodromal phase of fever and at least one of the 'three Cs' (cough, coryza, and conjunctivitis). A morbilliform exanthem appears after 2–4 days of the onset of the fever, first on the face (along the hairline and behind the ears), and then spreads to the trunk and extremities. Koplik spots (small white plaques on the buccal mucosa), pathognomonic of measles, are present in up to 70% of cases. During the following 3–5 days the rash disappears, and full recovery occurs within 7 days.

Complications include otitis media, pneumonia, diarrhea, postinfectious encephalitis, and subacute sclerosing panencephalitis (a progressive degenerative disease with onset usually 5–10 years after infection). The risk of complications is increased among infants, adults, pregnant women, and immunocompromised or undernourished individuals, particularly children with vitamin A deficiency. During pregnancy it is associated with an increased risk of low birth weight, spontaneous abortion, intrauterine fetal death, and maternal death. Differential diagnosis includes rubella virus, human herpesvirus type 6, parvovirus B19, dengue fever, Kawasaki disease, and drug eruptions.

Measles virus is highly contagious; it spreads from person to person through respiratory droplets caused by coughing or sneezing, or through direct contact. Small-particle aerosols can float in the air for long periods. The usual contagious period is from 4 days before until 4 days after rash appearance. All cases of suspected measles should be reported immediately after suspicion to the local or state health department.

Diagnosis of measles is based on the clinical manifestations and is confirmed with laboratory testing.

The gold standard test with the highest sensitivity is the plaque reduction neutralization assay. Confirmation of measles infection is through the detection of specific anti-measles IgM blood antibodies by enzyme-linked, immunosorbent assay (ELISA; sensitivity 89%; specificity 99%). Dried blood spots or oral fluid is easier for collection and transportation. Twenty-five percent of patients might not show positive antibodies until the fourth day after the rash. Acute infection also can be confirmed serologically by measuring a fourfold or greater increase in measles virus-specific IgG antibody levels between acute and convalescent sera.

An RT-PCR assay for measles virus RNA in urine, blood, oral fluid, nose swabs, or nasopharyngeal aspirates can identify infection (sensitivity 94%; specificity 99%) before measles virus-specific IgM antibodies are detectable.

Other recently described methods for diagnosis of measles, such as automatable focus reduction neutralization tests (AFRNT), chemiluminescent immunosorbent assays (CLIA), or loop-mediated isothermal amplification (LAMP), are used by some laboratories.

Supportive measures to prevent dehydration and treating nutritional deficiencies when needed, as well as early detecting and

treating secondary bacterial infections, such as pneumonia and otitis media, are the interventions of choice.

If the patient is immunosuppressed, has clinical evidence of vitamin A deficiency, or has recently immigrated from areas with a high measles mortality, the World Health Organization recommends the use of oral vitamin A. The dose is given on two consecutive days and repeated at 4 weeks, and is age dependent: 200,000 IU for children 1 year or older, 100,000 IU for children 6 months to 1 year, and 50,000 IU for children younger than 6 months.

Although ribavirin and interferon have been used to treat severely affected and immunocompromised patients with measles with some positive response, randomized, controlled trials are lacking, and they are not licensed by the US Food and Drug Administration (FDA) for the treatment of measles, with the need for more studies to determine the benefits and risks in the treatment of severe cases.

Measles vaccines are routinely administered as combined MMR or MMRV live vaccines. For a correct population immunity, to assure interruption of measles transmission, two doses at 12–15 months and at 4–6 years of age are needed. With the second dose, 99% of patients develop immunity.

Patients at high risk might be treated with human immunoglobulins intramuscularly (IMIG) for infants aged less than 6 months and for infants aged 6–11 months in whom MMR cannot be administered within 72 h of exposure. The dose recommended is 0.5 mL/kg (maximum 15 mL). Intravenous immunoglobulins (IVIG) are recommended for immunocompromised, non-immune pregnant women, at a dose of 400 mg/kg. MMR can be administered within 72 h or IMIG within 6 days of exposure in non-immune contacts.

Specific Investigations

- Serology (acute IgM or acute and convalescent IgG)
- PCR

First-Line Therapies

- Antipyretics: acetaminophen, ibuprofen **E**
- Measles vaccine (prevention and after exposure) **A**

Second-Line Therapies

- Oral vitamin A **A**
- Immunoglobulin prophylaxis **A**
- Ribavirin and IFN- α **D**

Vitamin A supplementation. Imdad A, Mayo-Wilson E, Herzer K, et al. Cochrane Database Syst Rev 2017; 3: CD008524.

As vitamin A supplementation is associated with a clinically meaningful reduction in morbidity and mortality in children, universal supplementation for children under 5 years of age in populations at risk of vitamin A deficiency is recommended.

Challenges of measles laboratory diagnostic. Hübschen JM, Bork SM, Brown KE, et al. Clin Microbiol Infect 2017; 23: 511–15.

Cell cultures are no longer routinely used because they take longer and are less sensitive than RT-PCR. Newer methods for diagnosis, such as AFRNT, CLIA, or LAMP, are described.

Measles. Strebel PM, Orenstein WA. N Engl J Med 2019; 381: 349–57.

An extensive summary of recent findings regarding measles, highlighting the reemergence of this disease due to a reduction in the vaccination rate. It shows that in the first 6 months of 2019, 1077 cases were diagnosed in the United States, exceeding the numbers reported for whole years since 1992.

Measles. Moss WJ. Lancet 2017; 390: 2490–502.

This highlights important recent developments in measles. Estimated global measles deaths decreased 79% from 2000 to 2015 with measles outbreaks reported in populations with immunity gaps despite high overall vaccine coverage, including individuals who received two doses of measles vaccine. Only eight of the 24 known measles virus genotypes have been detected since 2009, suggesting that many genotypes are no longer circulating. The incidence of subacute sclerosing panencephalitis might be higher than previously estimated.

Measles and Rubella Global Strategic Plan 2012–2020. Orenstein WA, Cairns L, Hinman A, et al. Vaccine 2018; 36(Suppl 1): A35–42.

Measles is one of the most highly infectious diseases with a population immunity of 92%–95% necessary to interrupt measles transmission. Although a highly effective measles vaccine has existed since 1963, an estimated 134,200 measles deaths occurred globally in 2015.

Polyvalent immunoglobulin for post-exposure prophylaxis measles. Young MK. Hum Vaccin Immunother 2019; 15: 2060–5.

Polyvalent immunoglobulin administration within 6 days of exposure is recommended for infants aged less than 6 months and infants aged between 6 and 8 months who are household contacts of a measles case, and for non-immune pregnant women and immunocompromised contacts without evidence of ongoing protection from measles. Infant dose is 750 mg (5 mL) IM, pregnant dose is 2250 mg (15 mL) IM, and immunocompromised 0.15 g/kg IV.

ENTEROVIRUSES

Enteroviruses (EVs) are non-enveloped RNA viruses with more than 100 human enteroviruses identified and classified into four species (*Enterovirus A–D*) that include polioviruses, coxsackieviruses group A (CV-A, types 1–22, 24), coxsackieviruses group B (CV-B, types 1–6), enteroviruses (EV, type 68–71), and echoviruses.

These viruses are among the most common pathogens affecting children worldwide and show a broad spectrum of clinical manifestations ranging from asymptomatic or mild symptoms (herpangina), hand, foot, and mouth disease (HFMD), or severe neurologic complications (paralytic poliomyelitis, meningitis, encephalitis, acute flaccid paralysis), or neonatal sepsis-like systemic infections. EVs are transmitted via the fecal–oral or respiratory route and symptoms may develop after an incubation period of 3–21 days.

HFMD is an acute exanthem characterized by vesicles at the hands, feet, mouth, and occasionally buttocks associated with low-grade fever and malaise. Fever usually subsides within 48 h, and cutaneous and mucosal lesions disappear approximately in 10 days. It is caused mainly by enterovirus A71 (EV-A71) and coxsackievirus A16 (CV-A16). The disease is usually mild and self-limiting, but in recent years, they have been associated with severe clinical complications that have resulted in a major public health issue worldwide, especially in the Asia-Pacific region. It predominantly occurs in children under 10 years old, although

there have been cases involving adults reported particularly in contact with infected children.

CV-A10 and CV-A6 are the new serotypes associated with outbreaks with a high incidence of complications. EV-A71 is associated with the large majority of severe and fatal cases. EV-D68 is now being detected during respiratory disease outbreaks worldwide.

Although the clinical manifestations of HFMD caused by these enteroviruses are often indistinguishable from each other, infections caused by EV-A71 tend to be associated with neurological complications and even to fatalities.

The potential neurotropism of EVs and their ability to cause severe infections reinforces the need for the monitoring and characterization of EV types associated with these different clinical presentations.

A frequent non-severe dermatologic complication is onychomadesis. This loss of one or several nails usually happens around 40 days after the disease and is thought to be due to transient nail matrix arrest, and the isolation of EV in nail fragments seems to indicate that these lesions directly depend on viral replication.

MANAGEMENT STRATEGY

Sample collection should be performed according to clinical manifestations and as soon as possible after the onset of symptoms. Cell culture should be left for research purposes.

For the laboratory confirmation of acute EV infection, serological methods such as ELISA and neutralization tests are obsolete. Although specific IgM and IgG assays for EVs have been described and are available, their clinical utility is limited due to the cross-reactivity of the antigens used between the different serotypes. The 2-week interval between acute and convalescent samples makes diagnosis slow and often clinically irrelevant. However, when myocarditis, pericarditis, or cardiomyopathy is suspected and direct sampling impossible, antibody detection can be useful for diagnosis.

RT-PCR has been shown to be far more sensitive than cell culture for detection of EVs in clinical samples. In newborns and infants, the sensitivity of enterovirus PCR testing is higher in blood samples than in CSF specimens.

Treatment is supportive, focusing on the management of the most severe compromise. Mild cases are managed with symptomatic measures. Steroids should be avoided because they have been associated with an increased risk of severe HFMD development.

In cases of neonatal sepsis and meningitis, administration of immune globulin intravenous (IGIV) or hyperimmune plasma has been suggested.

Vaccine candidates for the prevention of hand, foot, and mouth disease. Fang CY, Liu CC. Expert Rev Vaccines 2018; 17: 819–31.

A monovalent EV-A71 vaccine was approved by China's FDA in December 2015. The vaccine had a good performance in the prevention and control of EV-A71 during the following 3 years. Monovalent CV-A16 vaccine and bivalent EV-A71 and CV-A16 are in the preclinical research stage.

Specific Investigations

- Viral culture
- Enteroviral PCR

First-Line Therapies

• Antipyretics such as acetaminophen or ibuprofen	E
• Analgesics	E
• Hydration	E

Second-Line Therapies

• Immunoglobulin	C
• Pleconaril	B

Recommendations for enterovirus diagnostics and characterization. Harvala H, Broberg E, Benschop K, et al. J Clin Virol 2018; 101: 11–7.

RT-PCR has been shown to be more sensitive than cell culture for detection of EVs in clinical samples.

New manifestations of enteroviruses. Lugo D, Krogstad P. Curr Opin Pediatr 2016; 28: 107–13.

Outbreaks of severe HFMD in the United States and other countries due to CV-A6. Hospitalization occurred in 19% of total cases and 24% of cases were seen in adults. Severe lesions were seen, especially in patients with a history of eczema, thus naming it 'eczema coxsackium'. Onychomadesis occurred in some individuals.

Serious hand, foot, and mouth disease associated with coxsackievirus A10. Bian L, Gao F, Mao Q, et al. Expert Rev Anti Infect Ther 2019; 17: 233–42.

Epidemiological studies have shown CV-A10 and CV-A6 as new and important agents associated with an increasing number of HFMD outbreaks and sporadic cases globally, especially in the Asia-Pacific region, where HFMD outbreaks were associated with a high incidence of fatal cardiopulmonary and neurologic complications.

Vitiligo

Nazgol-Sadat Haddadi, Mehdi Rashighi, John E. Harris



Vitiligo is a common autoimmune disease of the skin resulting from the destruction of epidermal melanocytes by cytotoxic CD8+ T cells. It presents with multiple white macules and patches, which can significantly affect patients' self-esteem and quality of life.

Vitiligo is estimated to affect about 1–2% of the population, regardless of gender and ethnicity (more than 3 million individuals in the United States). Existing treatments are non-targeted, time-consuming, and offer moderate efficacy. With the exception of *monobenzone cream* (monobenzyl ether of hydroquinone), which is used to permanently depigment unaffected skin in patients with widespread vitiligo, there are currently no Food and Drug Administration (FDA)-approved medical treatments, and so management of vitiligo is primarily through the use of off-label therapies.

MANAGEMENT STRATEGY

The mainstay of treatment in vitiligo is *topical immunosuppressives* and *phototherapy*. Multiple factors, including disease extent, activity, distribution, and the presence of normally pigmented hair in the lesions should be considered when developing a management strategy in each patient. In particular, lesions located in glabrous skin or that contain a large proportion of poliosis do not typically respond well to treatment, and patients' expectations should be set for this likely outcome. Treatments may be less effective in patients with the segmental variant of vitiligo because this variant typically involves the hair at a very early stage, causing poliosis. Segmental vitiligo is characterized by rapid progression

of depigmentation in a unilateral distribution, which then stabilizes and remains confined to this focal area.

Vitiligo is not a life-threatening condition; patients may therefore decline treatment. However, early and aggressive treatment is associated with better outcomes, which should be addressed with each patient. Regardless, education about the disease and psychological support should be offered to all patients. For treatment purposes, vitiligo patients are generally classified into two groups: patients with limited body surface area (BSA) involvement and patients with more widespread disease.

Segmental Vitiligo and Limited Vitiligo

First-line treatment in patients with limited body involvement, including segmental vitiligo, is treatment with *potent topical steroids* (clobetasol propionate 0.05%) and/or *calcineurin inhibitors* (tacrolimus 0.03–0.1% or pimecrolimus 1%). Weaker steroids have not demonstrated efficacy in clinical trials, and thus potent steroids are preferred. Steroids are slightly more effective than calcineurin inhibitors in head-to-head studies; however, the potential side effects limit prolonged use, especially in areas such as the face, genitals, axillae, and breasts. One common strategy is to use both steroids and topical calcineurin inhibitors in an alternating schedule. This can be achieved by application of steroids twice daily for 1 week, followed by calcineurin inhibitors twice daily for the next week, and continued in this way through an alternating weekly schedule. For sensitive areas like the face, genitals, axillae, and breasts, use of calcineurin inhibitors without steroids is preferred.

Targeted *phototherapy devices* (excimer laser or monochromatic lamp), which deliver light in the UVB range (peak at 308nm), can be considered a second-line option in patients who do not respond to topical treatments. Sessions are typically administered two or three times per week and continued for at least 3 months before deciding whether the patient is responsive to the treatment or not.

Surgical procedures can be considered in a minority of carefully selected patients with highly stable disease (at least 1 year, and preferably 2 years, without worsening of the existing lesions or development of new lesions) and have the best outcome in patients with the segmental variant. The main concept of this treatment is to transfer healthy melanocytes from non-lesional skin to the affected area within the same patient (autologous transplant). There are multiple different techniques to achieve this, including punch grafting, epidermal blister grafting, and cellular grafts, each with advantages and disadvantages. Epidermal cellular suspension transplant, however, is usually considered to provide the best outcome. Regardless of the technique being used, surgical procedures are contraindicated in patients with active disease, which is marked by the presence of confetti lesions, trichrome lesions, inflammatory lesions, or evidence of the Koebner phenomenon.

Widespread Disease (>3% BSA)

Phototherapy with *narrowband ultraviolet B* (NB-UVB) is considered the first-line treatment in patients with widespread disease and has largely replaced older phototherapy protocols. NB-UVB has been shown to be at least as effective as psoralen and ultraviolet A (PUVA) therapy with better color match, less risk of burning, and lower risk of skin cancer. Treatment should be delivered two or three sessions per week for at least 3 months and then continued for several additional months in patients who respond.

The decision to deliver two or three phototherapy sessions per week is usually based on patient compliance and personal

preference. A three-session-per-week schedule induces a more rapid response; however, there is probably no significant difference between the two schedules in terms of the extent of repigmentation achieved after a prolonged period. NB-UVB therapy can be combined with topical steroids or calcineurin inhibitors to improve the treatment efficacy, especially in limited areas that might be cosmetically more important to patients.

Systemic corticosteroids may be indicated to arrest disease activity in patients with highly progressive disease before other therapies have time to demonstrate efficacy. This is usually delivered as pulse therapy (e.g., 4 mg oral dexamethasone on Saturday and Sunday or alternate-day doses of 20 mg prednisone) to reduce the risk of side effects.

Surgical procedures may be considered to treat selected areas with high cosmetic impact that do not respond to medical treatment. However, this should be reserved for stable lesions, particularly in those with segmental vitiligo, and only in patients with no physical signs of disease activity as mentioned above.

Maintenance Therapy

Relapse of disease is common after discontinuation of treatment. Tacrolimus 0.1% ointment applied twice weekly may prevent relapse in patients and thus be a reasonable approach to maintenance therapy.

Emerging Treatments

Janus kinase (JAK) inhibitors comprise a new class of drugs that selectively inhibit enzymes involved in signal transduction of several cytokines, including IFN- γ . Recent studies have suggested promising results for oral and topical JAK inhibitors, tofacitinib and ruxolitinib. In addition, new investigational JAK inhibitors are currently being studied in early phase clinical trials. Combining NB-UVB phototherapy with JAK inhibitor treatment appears to improve efficacy.

Afamelanotide is a potent synthetic analog of α -melanocyte stimulating hormone (α -MSH), a naturally occurring neuropeptide that stimulates melanogenesis. Recently, a trial reported that afamelanotide boosts the effect of NB-UVB therapy.

Pseudocatalase is a cream that works as a topical oxygen radical scavenger. Consistent with a proposed role for elevated levels of melanocyte stress in vitiligo pathogenesis, studies have shown that there is an increased level of hydrogen peroxide (H_2O_2) in lesional skin of vitiligo patients. A small number of studies have reported that pseudocatalase may enhance repigmentation when combined with NB-UVB phototherapy; however, others have been unable to reproduce these results, and larger independent studies are needed to confirm these observations.

Specific Investigation

- Screening for associated autoimmune diseases

Vitiligo is a clinical diagnosis, and a skin biopsy is rarely necessary. Patients with vitiligo generally have a higher incidence of other autoimmune diseases, including thyroiditis, type 1 diabetes, lupus, alopecia areata, Addison disease, and pernicious anemia. However, the majority of patients do not have any accompanying autoimmune disease, and directed medical history and physical examination are sufficient to identify high-risk individuals who require further evaluation.

Increased risk of comorbid rheumatic disorders in vitiligo patients: a nationwide population-based study. Choi CW, Eun SH, Choi KH, Bae JM. *J Dermatol* 2017; 44: 909–13.

This cross-sectional study included 86,210 Korean patients with vitiligo and 172,420 age- and sex-matched healthy controls.

Vitiligo was found to be associated with increased risk of systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, and Sjögren syndrome, while there was no elevated risk of dermatomyositis/polymyositis, Behçet disease, or ankylosing spondylitis.

Low yield of routine screening for thyroid dysfunction in asymptomatic patients with vitiligo. Kroon MW, Joore IC, Wind BS, et al. *Br J Dermatol* 2012; 166: 532–8.

Thyroid function tests and anti-TPO antibody titers were assessed in 434 patients with non-segmental vitiligo. The overall prevalence of thyroid dysfunction was higher than reported in the general population. However, most patients had symptoms indicative of thyroid dysfunction and had been already diagnosed by their general practitioners. Moreover, in the majority of these patients, thyroid involvement preceded the onset of vitiligo. Thyroid disease was found mostly among older women and in subjects with a positive family history of thyroid disease. Thus, a thorough review of systems for signs of thyroid disease is sufficient, and routine screening is not necessary.

First-Line Therapies

Segmental vitiligo or limited vitiligo

- Topical corticosteroids and/or calcineurin inhibitors **A (B for segmental)**

Widespread vitiligo (>3% BSA)

- NB-UVB $\pm$ topical corticosteroids or calcineurin inhibitors **A**

The efficacy and safety of tacrolimus as mono- and adjunctive therapy for vitiligo: a systematic review of randomized clinical trials. Arora CJ, Rafiq M, Shumack S, et al. *Australas J Dermatol* 2020; 61: e1–9.

Meta-analysis of 19 studies including 814 patients reported that combination therapy with tacrolimus ointment and NB-UVB was better to achieve >75% repigmentation compared with NB-UVB alone. Tacrolimus and steroids had comparable efficacy in inducing >75% repigmentation. However, for the same result, the combination of fractional laser and tacrolimus was not superior to tacrolimus alone.

Treatment outcomes of topical calcineurin inhibitor therapy for patients with vitiligo: a systematic review and meta-analysis. Lee JH, Kwon HS, Jung HM, et al. *JAMA Dermatol* 2019; 155: 929–38.

In the 46 studies (1499 patients) selected, 2–7 months' application of topical calcineurin inhibitor alone (tacrolimus or pimecrolimus) caused at least mild ($\geq 25\%$), moderate ($\geq 50\%$), and marked ($\geq 75\%$) repigmentation in 55.0%, 38.5%, and 18.1% of patients, respectively. When used in combination with phototherapy, 47.5% of patients achieved a marked response.

Phototherapy for vitiligo: a systematic review and meta-analysis. Bae JM, Jung HM, Hong BY, et al. *JAMA Dermatol* 2017; 153: 666–74.

Findings from 35 prospective studies (1428 unique patients) were analyzed. The percentage of patients who achieved marked ($\geq 75\%$) repigmentation response to NB-UVB increased over time (from 13.0% at 3 months to 19.2% at 6 months and 35.7% at 12 months). The subgroup analysis revealed that the highest rate of marked response was achieved on the face and neck. In contrast, none of the patients experienced marked repigmentation on the hands and feet after 6 months of NB-UVB.

Evaluation for skin cancer and precancer in patients with vitiligo treated with long-term narrowband UV-B phototherapy. Bae JM, Ju HJ, Lee RW, et al. *JAMA Dermatol* 2020.

In this nationwide, population-based cohort study comprising 60,321 Korean patients with vitiligo, NB-UVB phototherapy was found to significantly increase the risk of actinic keratosis. However, it was not associated with an increased risk of Bowen disease, non-melanoma skin cancer, or melanoma.

Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. Hearn RMR, Kerr AC, Rahim KE, et al. *Br J Dermatol* 2008; 159(4): 931–5.

This retrospective study reviewed records from 4665 Scottish patients who had received NB-UVB (24,753 person-years of follow-up). The study found no significant association between NB-UVB treatment and BCC, SCC, or melanoma.

A cross-sectional analysis of skin cancer risk in patients receiving narrow-band ultraviolet B phototherapy: an evaluation of 100 patients. Karaosmanoglu N, Cetinkaya PO, Kutlu O, et al. *Arch Dermatol Res* 2020; 312(4): 249–53.

This cross-sectional study included 100 Turkish patients who had received whole-body NB-UVB treatment and 100 age- and sex-matched controls. This study did not provide evidence for an increased skin cancer risk in patients treated with NB-UVB phototherapy.

Second-Line Therapies

Segmental vitiligo or limited vitiligo

- Targeted phototherapy devices (handheld NB-UVB, excimer laser, monochromatic lamp) **A**

Widespread vitiligo (>3% BSA)

- Systemic corticosteroids (oral minipulse therapy) **B**

Efficacy and safety of 308-nm monochromatic excimer lamp versus other phototherapy devices for vitiligo: a systematic review with meta-analysis. Lopes C, Trevisani VE, Melnik T. *Am J Clin Dermatol* 2016; 17: 23–32.

Six randomized, controlled trials were analyzed, comprising a total of 411 patients/764 lesions. These studies compared the efficacy of monochromatic excimer lamp versus excimer laser and NB-UVB. All three modalities were found to be comparably safe and effective in treating vitiligo.

The efficacy of 308-nm excimer laser/light (EL) and topical agent combination therapy versus EL monotherapy for vitiligo: a systematic review and meta-analysis of randomized controlled trials (RCTs). Bae JM, Hong BY, Lee JH, et al. *J Am Acad Dermatol* 2016; 74: 907–15.

Eight RCTs including 425 patches/patients were analyzed. Topical calcineurin inhibitors in conjunction with EL was found to be more effective in treating vitiligo compared with EL alone. However, there was not sufficient evidence to support beneficial effects of topical vitamin-D3 analogs or corticosteroids.

A combination of excimer laser treatment and topical tacrolimus is more effective in treating vitiligo than either therapy alone for the initial 6 months, but not thereafter. Park OJ, Park GH, Choi JR, et al. *Clin Exp Dermatol* 2016; 41: 236–41.

In total, 276 non-segmental vitiligo patients were retrospectively assessed. The combination therapy with tacrolimus and excimer laser for up to 6 months was significantly more effective compared with either therapy alone. The continuation of this therapy for >6 months did not cause a better outcome than monotherapy.

A cross-sectional, comparative study of home vs in-office NB-UVB phototherapy for vitiligo. Liu B, Sun Y, Song J, et al. *Photodermatol Photoimmunol Photomed* 2020; 36: 14–20.

Nine pairs of patients with vitiligo receiving home or in-office NB-UVB phototherapy were included. Pairs were matched for skin phototype, distance from home to the clinic, and length of time they had received phototherapy prior to the start of the study. Home phototherapy was safe and provided a comparable repigmentation response. The annual out-of-pocket cost was significantly lower in patients who received home phototherapy.

Randomized, parallel group trial comparing home-based phototherapy with institution-based 308 excimer lamp for the treatment of focal vitiligo vulgaris. Tien Guan ST, Theng C, Chang A. *J Am Acad Dermatol* 2015; 72: 733–5.

Forty-four patients with stable focal vitiligo were randomized to receive either three-times-a-week home-based phototherapy or twice-a-week excimer laser in the clinic. Patients who received the home-based phototherapy were found to have a better response, primarily due to a higher compliance to the treatment.

Oral dexamethasone pulse treatment for vitiligo. Radakovic-Fijan S, Fürsinn-Friedl AM, Hönigsmann H, et al. *J Am Acad Dermatol* 2001; 44(5): 814–7.

Twenty-nine patients with vitiligo (25 with active progressive disease) were included in this prospective clinical trial. The patients were given weekly pulses of 10 mg dexamethasone each on 2 consecutive days followed by 5 days off treatment for a maximum period of 24 weeks. After a mean treatment period of 18.2 ± 5.2 weeks, the disease activity was arrested in 22 of 25 patients (88%). However, marked to moderate repigmentation only occurred in five patients (17.2%).

Oral mini-pulse therapy with betamethasone in vitiligo patients having extensive or fast-spreading disease. Pasricha JS, Khaitan BK. *Int J Dermatol* 1993; 32(10): 753–7.

This prospective clinical trial enrolled 40 patients with extensive and/or fast-spreading vitiligo. The patients were given 5 mg betamethasone/dexamethasone as a single oral dose after breakfast on 2 consecutive days per week. Within 1–3 months, progression of the disease was arrested in 89% of the 36 patients having active disease. Furthermore, 80% of the patients started having spontaneous repigmentation of the existing lesions within 2–4 months.

Third-Line Therapies

Segmental vitiligo or limited vitiligo

- Surgical treatment (autologous melanocyte transplant) **A**

Widespread vitiligo (>3% BSA)

- Surgical treatment (autologous melanocyte transplant) **A**
- Monobenzy ether of hydroquinone **C**

Efficacy of transplantation of combination of noncultured dermal and epidermal cell suspension vs epidermal cell suspension alone in vitiligo: a randomized clinical trial. Thakur V, Kumar S, Kumaran MS, et al. *JAMA Dermatol* 2019; 155: 204–10.

Forty patients with focal, segmental, or generalized vitiligo were randomly assigned to be treated with non-cultured epidermal suspension (NCES) or with the combination of NCES and non-cultured dermal cell suspension (NDCS). The physician assessing the outcomes was blinded to the treatment group. Combination of NCES and NDCS was found superior to NCES alone in patients with shorter duration of clinical stability (3–6 months). The authors concluded that the combination method may be used earlier in the course of stable disease without waiting for a period of 12 months or more.

Combination of follicular and epidermal cell suspension as a novel surgical approach in difficult-to-treat vitiligo: a randomized clinical trial. Razmi M, Kumar R, Rani S, et al. *JAMA Dermatol* 2018; 154: 301–8.

This prospective, observer-blinded, active-controlled, randomized clinical trial included 30 stable vitiligo patients. For each patient, a mixture of equal amounts of epidermal cell suspension (ECS) plus follicular cell suspension was applied to one lesion and ECS alone was applied to the anatomically paired lesion from the same patient. The combination therapy was found to have superior repigmentation outcomes in terms of repigmentation extent, rate of response, color match, and patient satisfaction.

A comparative study between suction blistering graft, mini punch graft and hair follicle transplant in treatment of patients with stable vitiligo. Ezz-Eldawla R, Abu El-Hamd M, Saied SM, et al. *J Dermatol Treat* 2019; 30: 492–7.

Thirty patients were assigned to a suction blistering group, mini-punch group, or hair follicle group. The percentage of repigmentation as well as the changes in quality of life were significantly higher in suction blister technique in comparison to the other two groups.

Comparison between autologous noncultured epidermal cell suspension and suction blister epidermal grafting in stable vitiligo: a randomized study. Budania A, Parsad D, Kanwar AJ, et al. *Br J Dermatol* 2012; 167: 1295–301.

Forty-one patients with 54 stable vitiligo lesions were randomized to receive either autologous non-cultured epidermal cell suspension (NCES) or blister epidermal grafting. The follow-up evaluation 16 weeks after surgery indicated that NCES was superior to blister epidermal grafting in terms of repigmentation and quality of life improvement.

A single-arm open-label clinical trial of autologous epidermal cell transplantation for stable vitiligo: a 30-month follow-up. Orouji Z, Bajouri A, Ghasemi M, et al. *J Dermatol Sci* 2018; 89: 52–9.

This prospective study included 1060 patches from 300 patients with stable vitiligo who underwent autologous epidermal cell transplantation. Repigmentation score continued to improve over the period of 9 months. The achieved repigmentation remained stable in 79.3% of lesions during the follow-up of 30 months.

Motorized 0.8-mm micropunch grafting for refractory vitiligo: a retrospective study of 230 cases. JM Bae, JH Lee, HS Kwon, et al. *J Am Acad Dermatol* 2018; 79: 720–7.

Motorized 0.8-mm micropunch grafting induced $\geq 75\%$ repigmentation in 181 of 230 lesions (78.7%) after a median of 6 months. The favorable prognostic factors were lesions on the face and neck, and disease stability of more than 12 months.

Long-term follow-up of patients undergoing autologous noncultured melanocyte-keratinocyte transplantation for vitiligo and other leukodermas. Silpa-Archa N, Griffith JL, Huggins RH, et al. *J Am Acad Dermatol* 2017; 77: 318–27.

A retrospective long-term follow-up (12–72 months; median = 24 months) of 63 patients who underwent 75 melanocyte-keratinocyte transplantation procedures (MKTP) at 157 anatomically based lesions showed long-term repigmentation. Skin phototype, age, and anatomic location of lesions had no significant effect on the outcome.

Topical monobenzyl ether of hydroquinone is an effective and safe treatment for depigmentation of extensive vitiligo in the medium term: a retrospective cohort study of 53 cases. Tan E S-T, Sarkany R. *Br J Dermatol* 2015; 172(6): 1662–4.

This retrospective study included 53 patients who had used monobenzyl ether of hydroquinone (MBEH) as depigmenting treatment. The most commonly treated anatomical locations were the face and limbs. The majority (58%) of cases achieved complete depigmentation of the treated areas after a mean treatment duration of 9.7 months. A further 34% developed significant but incomplete depigmentation of the treated sites. Diffuse depigmentation occurred in only one case and distant depigmentation away from treated areas was observed in another patient. Temporary skin irritation was the most common side effect reported in more than half of patients. Repigmentation in previously successfully depigmented areas after discontinuing MBEH was observed in up to 78% of patients. Sun exposure was identified as the main trigger for repigmentation in all those cases.

EMERGING TREATMENTS

Ruxolitinib cream for treatment of vitiligo: a randomised, controlled, phase 2 trial. Rosmarin D, Pandya AG, Lebwohl M, et al. *The Lancet* 2020; 396(10244): 110–20.

This multicenter, randomized, double-blind, dose-ranging, phase 2 study enrolled 157 patients with vitiligo with at least 0.5% facial and 3% non-facial BSA. The subjects were equally randomized to receive ruxolitinib cream (1.5% twice daily [BID], 1.5% once daily [QD], 0.5% QD, or 0.15% QD) or vehicle BID on lesions constituting $\leq 20\%$ total BSA for 24 weeks.

The primary end point was the proportion of patients achieving $\geq 50\%$ improvement from baseline in the facial Vitiligo Area Scoring Index [F-VASI] at week 24. An intent-to-treat analysis revealed that a significantly higher number of patients treated with ruxolitinib cream achieved F-VASI50 compared with the vehicle group (25.8–50.0% across ruxolitinib doses vs. 3.1% vehicle).

There were no serious treatment-related adverse events or clinically relevant changes in laboratory values in patients who received ruxolitinib cream.

Repigmentation in vitiligo using janus kinase (JAK) inhibitors with phototherapy: systematic review and meta-analysis. Phan K, Phan S, Shumack S, et al. *J Dermatolog Treat* 2020; 1–5. PMID: 32096671 [Epub ahead of print].

Nine studies including 45 cases were included. Repigmentation of >50% was seen in 57.8%, while 20% of cases had no response or minimal response to JAK1/3 inhibitors, including tofacitinib and ruxolitinib. Facial vitiligo had the highest response rate (70%), compared to extremities (27.3%) or torso/non-sun exposed areas (13.6%). Concurrent UVB phototherapy seems to potentiate the efficacy of JAK inhibitors.

Afamelanotide and narrowband UV-B phototherapy for the treatment of vitiligo: a randomized multicenter trial. Lim HW, Grimes PE, Agbai O, et al. *JAMA Dermatol* 2015; 151: 42–50.

Fifty-five patients with generalized vitiligo were randomized to NB-UVB therapy or NB-UVB in combination with afamelanotide, an analog of α -MSH. Monthly subcutaneous implantation of 16 mg of afamelanotide resulted in a significantly superior and faster repigmentation compared with NB-UVB monotherapy, especially in patients with darker skin type.

Vulvodynia

Lisa Kirby, David Nunns



INTRODUCTION

Vulvodynia has been defined by the International Society for the Study of Vulvovaginal Disease (ISSVD) as vulval discomfort, most often described as a burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable neurologic disorder.

The ISSVD classifies vulvodynia according to site (generalized or localized), requirement of stimulus (provoked, unprovoked, or mixed) and onset (primary or secondary). Patients with provoked pain were formerly diagnosed as having 'vestibulitis', which is incorrect as there is no inflammatory component to the condition. The most common types of vulvodynia are localized, provoked vulval pain (vestibulodynia) and generalized, unprovoked vulval pain. It is worth mentioning that in clinical practice some patients will have a combination of both unprovoked and provoked pain, which is not reflected in the literature.

The etiology of vulvodynia remains unclear, but recurrent vulval inflammation may have a role. One laboratory study showed a neuronal proliferation and allodynia in the vulva following repeated attacks of thrush in mice. Vestibular neuronal proliferation has also been demonstrated in patients with vestibulodynia, so it is possible that vulvodynia is a chronic pain syndrome where there is an excess of dysfunctional vulval skin nociceptors. There is likely to be overlap with other pain syndromes such as irritable bowel syndrome and painful bladder syndromes.

MANAGEMENT STRATEGY

Vulvodynia is a diagnosis of exclusion and a thorough history and examination are essential to confidently exclude subtle skin disease. A pain history should include nature, severity, site, and aggravating or relieving factors. One important differential is pudendal neuralgia, which is a nerve entrapment syndrome of the pudendal nerve. These patients usually experience pain on sitting, relieved by lying down or standing. They also might complain of the sensation of a 'lump or egg' being present in the vagina. An assessment of the impact of pain on function is important and a psychosexual history should be explored if appropriate. For women with provoked pain, dyspareunia is the main complaint and can often be missed in the initial referral. Vulvodynia can lead to secondary psychosexual problems such as avoidance, phobia of touch, loss of libido, and vaginismus. Recognition of this as the main problem for the patient is crucial so that treatment can focus on sexual rehabilitation either through self-management (increasing communication with partners, use of lubricants and vaginal dilators) or more formal treatment with a psychosexual counselor.

Clinical examination of the patient with vulvodynia is often unremarkable as demonstrated in the image. Examination is essential in order to exclude vulval conditions that can produce pain. Examples include subtle vulval fissures, infection, inflammatory vulval disease (e.g., eczema, lichen sclerosus, lichen planus), and malignancy (e.g., vulval intraepithelial neoplasia, Paget disease). Patients with vestibulodynia can have tenderness on light cotton-stick touch over the vestibule (the reported Q-tip swab test); however, labial skin should be non-tender. Erythema of the vulva and vestibule can be a normal finding in healthy women and may be mistaken for a disease process.

The heterogeneity of vulvodynia poses a significant challenge to identifying any kind of 'gold standard' treatment and patients require individualized, combination treatment strategies. As with many chronic pain conditions, good quality evidence for management is limited. It is important that a 'one size fits all' approach is avoided. Not every treatment will be suitable for every woman and certain interventions may be more suited to a particular type of vulvodynia; e.g., topical lidocaine for localized, provoked pain (vestibulodynia).

The outcomes of effective treatment should include (1) reduction in pain level with improved function; (2) confidence in self-managing symptoms through education and self-empowerment; and, if relevant, (3) reduction in pain experienced with sex with an improvement in sexual function and satisfaction. Many patients respond to simple measures, many of which involve self-help and patient education.

SPECIFIC INVESTIGATIONS

Vulvodynia is a clinical diagnosis and routine investigations are invariably unhelpful. Knowledge that vulvovaginal swabs are negative will be helpful for patients to support their understanding that infection is not a cause. There is no evidence that routine vulval biopsies are useful.

General Reading

Guidelines for the management of vulvodynia. Nunns D, Mandal D, Byrne M, et al. *Br J Dermatol* 2010; 162: 1180–5.

2013 Vulvodynia guideline update. Stockdale CK, Lawson HW. *J Low Genit Tract Dis* 2014; 18(2): 93–100.

Women with provoked vestibulodynia experience clinically significant reductions in pain regardless of treatment: results from a 2-year follow-up study. Davis SN, Bergeron S, Binik YM, et al. *J Sex Med* 2013; 10: 3080–7.

In this secondary analysis of a prospective study, 239 women completed a questionnaire at study initiation and after 2 years. Patients had received various therapies, although 41% did not undergo any treatment. At 2 years, there was significant improvement in pain, sexual function, and depression for the group as a whole. Women not receiving any treatment also improved significantly. The authors conclude that no single treatment is superior, and that spontaneous resolution may occur.

First-Line Therapies

• Pelvic floor physical therapy	B
• Psychological therapy	B
• Topical lidocaine	B

Pelvic floor muscle functioning in women with vulvar vestibulitis syndrome. Reissing ED, Brown C, Lord MJ, et al. *J Psychosom Obstet Gynaecol* 2005; 26(2): 107–13.

A review involving 43 studies (7 RCTs) demonstrated that physical therapy modalities such as biofeedback, dilators, electrical stimulation, education, multimodal physical therapy, and multidisciplinary approaches were effective for decreasing pain during intercourse and improving sexual function.

A randomized comparison of group cognitive-behavioral therapy, surface electromyographic biofeedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. Bergeron S, Binik YM, Khalifé S, et al. *Pain* 2001; 91: 297–306.

A total of 78 women were randomized to surgical vestibulectomy, biofeedback, or group cognitive-behavioral therapy (CBT). At 6-month postintervention follow-up, those who received CBT reported significant improvements in their pain during intercourse. Importantly, women who received CBT had a lower attrition rate than those who underwent vestibulectomy and were more satisfied with their treatment than women who received biofeedback.

A randomized clinical trial comparing group cognitive-behavioral therapy and a topical steroid for women with dyspareunia. Bergeron S, Khalifé S, Dupuis MJ, et al. *Consult Clin Psychol* 2016; 84: 259–68.

Ninety-seven women with provoked vulvodynia were randomized to 13 weeks of group CBT or treatment with a topical steroid. Both groups reported statistically significant reductions in pain at 6-month follow-up and significant improvement on measures of psychological adjustment, and the CBT group had significantly greater reduction in pain catastrophizing at posttreatment. Both groups' sexual function significantly improved from baseline to posttreatment and 6-month follow-up, and the CBT group was doing significantly better at the 6-month follow-up. Treatment satisfaction was significantly higher in the CBT group, as were self-reported improvements in pain and sexuality.

Overnight 5% lidocaine ointment for treatment of vulvar vestibulitis. Zolnoun DA, Hartmann KE, Steege JF. *Obstet Gynecol* 2003; 102: 84–7.

Long-term nightly lidocaine 5% ointment left in place overnight on a cotton ball improved daily pain scores in an open-label

trial involving 61 women with provoked pain. Ability to have intercourse also improved from 36% to 76% after treatment.

Second-Line Therapies

• Tricyclic antidepressants (TCA) (oral amitriptyline, oral desipramine, other TCA)	B
• Electromyographic (EMG) biofeedback	B
• Anticonvulsants (oral gabapentin, oral pregabalin, oral lamotrigine)	C

Treatment of vulvodynia with tricyclic antidepressants: efficacy and associated factors. Reed BD, Caron AM, Gorenflo DW, et al. *J Low Genit Tract Dis* 2006; 10: 245–51.

In a prospective study of 209 women with vulvodynia, 183 were treated with a TCA (amitriptyline, desipramine or other TCA), regardless of generalized vulvodynia or vestibulodynia. Of the 78 women taking a TCA at first follow-up, 59.3% had more than 50% improvement in pain score compared with 38% of the patients who were either not prescribed a TCA or stopped the TCA prior to follow-up ($p=0.007$; OR=2.35; 95% CI 1.23–4.42).

Oral desipramine and topical lidocaine for vulvodynia: a randomized controlled trial. Foster DC, Kotok MB, Huang LS, et al. *Obstet Gynecol* 2010; 116: 583–93.

This study consisted of four treatment arms: 133 women with vulvodynia were randomly assigned to 12 weeks of oral desipramine, topical lidocaine, oral desipramine plus topical lidocaine, or placebo. There was no statistically significant benefit in pain reduction of the treatment arms compared with placebo.

Systematic review and meta-analysis of the effects of treatment modalities for vestibulodynia in women. Pérez-López FR, Bueno-Notivol J, Hernandez AV, et al. *Eur J Contracept Reprod Health Care* 2019; 24(5): 337–46.

A systematic review and meta-analysis compared any intervention with placebo in women with vestibulodynia. Four randomized, controlled trials (RCTs) involving six interventions were included. Interventions consisted of conjugated estrogens cream, oral desipramine with or without topical lidocaine, topical lidocaine cream alone, low-level laser therapy, and transcranial direct current stimulation. Compared with placebo or no treatment, six different treatment modalities did not produce reduction of dyspareunia in six interventions as assessed with pain scores. In network meta-analysis, sexual satisfaction scores were significantly improved in women receiving oral desipramine alone or associated with topical lidocaine (mean difference 5.14; 95% CI –9.52 to –0.75; $p=0.02$).

Treating vulvar vestibulitis with electromyographic biofeedback of pelvic floor musculature. McKay E, Kaufman RH, Doctor U, et al. *J Reprod Med* 2001; 46(4): 337–42.

Twenty-nine patients with moderate-to-severe vulvar vestibulitis syndrome had computerized EMG assessment of pelvic floor muscles and were then provided with a portable EMG home trainer device for performing biofeedback-assisted pelvic floor muscle rehabilitation exercises. Of the group, 51.7% demonstrated markedly decreased introital tenderness, and 93.3% were able to resume sexual activity without discomfort. Within 6 months of the start of therapy, 90% ultimately resuming sexual activity had done so.

Open-label trial of lamotrigine focusing on efficacy in vulvodynia. Meltzer-Brody SE, Zolnoun D, Steege JF, et al. *J Reprod Med* 2009; 54: 171–8.

This case series pilot study investigated the effect of lamotrigine in chronic pelvic pain over a 12-week course in 17 patients with vulvodynia. They reported statistically significant decreases in all pain scores in the vulvodynia group. The study is limited by low power and high drop-out rate.

A systematic review of the utility of anticonvulsant pharmacotherapy in the treatment of vulvodynia pain. Leo RJ. *J Sex Med* 2013; 10(8): 2000–8.

A systematic review including one open-label trial and six studies found insufficient evidence for the role of anticonvulsants in treatment of vulvodynia, although it acknowledges some patients may find them helpful. The majority of studies employed gabapentin. RCTs are needed.

Gabapentin for the treatment of vulvodynia: a randomized controlled trial. Brown CS, Bachmann GA, Wan J, et al.; Gabapentin (GABA) Study Group. *Obstet Gynaecol* 2018; 131(6): 1000–7.

This multicentre, double-blind, placebo-controlled randomized crossover trial compared oral gabapentin with a placebo in 53 patients with vulvodynia. The primary outcome measure was the tampon test, which serves as a marker for dyspareunia. Secondary outcomes were sexual intercourse pain and daily pain. Gabapentin was not different compared with the placebo (adjusted mean 4.0, 95% CI 3.0–4.9 vs. 4.3, 95% CI 3.4–5.2, difference –0.3, 95% CI –0.7–0.0; $p=.007$). Gabapentin also did not improve pain over placebo for sexual intercourse pain and daily pain.

Third-Line Therapies

• Transcutaneous electrical nerve stimulation (TENS)	A
• Enoxaparin (subcutaneous injection)	A
• Cultured fibroblasts	B
• Botulinum toxin type A injections	B
• Surgery	B
• Topical diazepam	B
• Multilevel local anesthetic nerve blockade	C
• Nitroglycerin cream	C
• Acupuncture	C
• LASER	C
• Topical amitriptyline	C
• Spinal cord stimulator	E
• Intralesional infiltration of betamethasone and lidocaine	E

Transcutaneous electrical nerve stimulation to treat vestibulodynia: a randomised controlled trial. Murina F, Bianco V, Radici G, et al. *BJOG* 2008; 115(9): 1165–70.

A randomized, placebo-controlled trial involving 40 women showed twice weekly TENS significantly improved pain scores in the TENS group but not in the placebo group (2.1 ± 2.7 , $p=0.004$ and 8.5 ± 10.7 , $p=0.001$, respectively).

Enoxaparin treatment for vulvodynia: a randomized controlled trial. Farajun Y, Zarfati D, Abramov L, et al. *Obstet Gynecol* 2012; 130(3): 565–72.

The hypothesis for this study is that proliferation of nerve fibers in the perineal epithelium increases sensitivity in patients with vulvodynia. Enoxaparin inhibits heparanase, theoretically preventing neuroproliferation. Forty women with severe vestibulodynia received daily subcutaneous (SC) injections of enoxaparin or placebo. Biopsies were taken to evaluate localization of nerve

fibers and presence of heparanase. Outcomes were sex pain scores and clinically evaluated pain scores. The study considered a 30% reduction in pain intensity to be significant. Differences in number of nerve fibers were not significant. Of the enoxaparin group, 75% reported more than 20% reduction in symptoms compared with 27.8% in the placebo group ($p=0.04$).

Cream with cutaneous fibroblast lysate for the treatment of provoked vestibulodynia: a double-blind randomized placebo-controlled crossover study. Donders GG, Bellen G. *J Low Genit Tract Dis* 2012; 16: 427–36.

In this crossover study, 30 patients were randomized to a topical lysate of cultured human fibroblasts or placebo. There was a statistically significant reduction in dyspareunia with treatment, with no improvement with placebo use.

Subcutaneous botulinum toxin type A injections for provoked vestibulodynia: a randomized placebo-controlled trial and exploratory subanalysis. Diomande I, Gabriel N, Kashiwagi M, et al. *Arch Gynecol Obstet* 2019; 299(4): 993–1000.

This double-blind, randomized, placebo-controlled study randomized 33 patients to three groups: high-dose single injections of botulinum toxin (BT) (50 or 100 units) versus placebo, and then repeat BT 100 U injections over 6 months for symptomatic patients. Symptoms were measured at 3 months and successful treatment was defined as ≥ 2 -point improvement on the cotton swab-provoked pain assessment or symptom-free patients. There were no significant differences in pain levels when comparing treatment arms at 3 months, after a single BT injection. In the analysis with repeat injections of 100 units BT ($n=10$), a significant reduction of the cotton swab-provoked pain score could be shown ($p=0.029$). However, this effect could not be compared with an exclusively placebo study arm.

Surgical treatment of vulvar vestibulitis: a review. Tommola P, Unkila-Kallio L, Paavonen J. *Acta Obstet Gynecol Scand* 2010; 89(11): 1385–95.

This systematic review, including 33 studies, reports fair evidence of effect of vestibulectomy for patients with provoked pain. Vestibulectomy resulted in significant self-reported relief of dyspareunia in 79% of patients, some relief in 89% of patients, and no relief in 12% of patients. Significant improvements in sexual functioning were also reported. There was insufficient evidence to describe the size of the effect with certainty, due to risk of bias in pain interventions without placebo controls.

A randomized comparison of group cognitive-behavioral therapy, surface electromyographic biofeedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. Bergeron S, Binik YM, Khalifé S, et al. *Pain* 2001; 91: 297–306.

This study compared group cognitive-behavioral therapy surface electromyographic biofeedback and vestibulectomy. Subjects were 78 women randomly assigned to one of three treatments and assessed at pretreatment, posttreatment, and 6-month follow-up via examination, structured interviews, and pain questionnaires.

As compared with pretreatment, all treatment groups reported statistically significant reductions on pain measures at posttreatment and 6-month follow-up, although the vestibulectomy group was significantly more successful than the two other groups. This needs to be interpreted with caution since seven women who had been assigned to the vestibulectomy group did not go ahead with the intervention.

Vaginal diazepam plus transcutaneous electrical nerve stimulation to treat vestibulodynia: a randomized controlled trial. Murina F, Felice R, Di Francesco S, et al. *Eur J Obstet Gynecol Reprod Biol* 2018; 228: 148–53.

Forty-two patients with vestibulodynia were randomized to vaginal diazepam plus TENS or placebo plus TENS. Patient reported pain outcomes and objective measurements of pelvic floor muscle relaxation were recorded. There was no difference in visual analog score between the groups, but there was a significant improvement in dyspareunia scores in the treatment group.

Multilevel local anesthetic nerve blockade for the treatment of vulvar vestibulitis syndrome. Rapkin AJ, McDonald JS, Morgan M. *Am J Obstet Gynecol* 2008; 198(1): 41.

A prospective pilot study of 27 patients showed that multilevel nerve block involving the pudendal nerve and its dorsal root ganglia, along with vestibular local anesthetic infiltration, produced significant improvements in pain. Pain was measured by vulvagesiometer, pain scores, sexual function scores, and self-reported symptoms.

Safety and efficacy of topical nitroglycerin for treatment of vulvar pain in women with vulvodynia: a pilot study. Walsh KE, Berman JR, Berman LA, et al. *J Gend Specif Med* 2002; 5: 21–7.

This is the only report of the use of topical nitroglycerin 0.2% for the management of vulvodynia. The majority of the 21 women, who applied the cream before intercourse and completed all questionnaires, reported significant pain reduction.

Acupuncture for the treatment of vulvodynia: a randomized wait-list controlled pilot. Schlaeger JM, Xu N, Mejta CL, et al. *J Sex Med* 2015; 12: 1019–27.

This small feasibility study included 36 women. It found that acupuncture appeared to reduce vulvar pain and dyspareunia with an increase in overall sexual function for women with vulvodynia. This study should be replicated in larger double-blinded RCTs.

The clinical role of LASER for vulvar and vaginal treatments in gynecology and female urology: an ICS/ISSVD best practice consensus document. Preti M, Vieira-Baptista P, Digesu GA, et al. *J Low Genit Tract Dis* 2019; 23(2): 151–60.

The ISSVD does not support the use of LASER in routine clinical practice for the treatment of vulval conditions and its use should be limited to RCTs.

Low-level laser therapy for the treatment of provoked vestibulodynia – a randomized, placebo-controlled pilot trial. Lev-Sagie A, Kopitman A, Brzezinski A. *J Sex Med* 2017; 14: 1403–11.

This placebo-controlled, double-blinded RCT randomized 34 women to treatment with low-level LASER therapy (LLLT) versus placebo. There was improvement in reported pain improvement in 78% in the LLLT group and 44% in the placebo group. There was no improvement in measurable parameters (tampon test, Q-tip test, intercourse pain visual analog score, daily activity reported pain). Although none of the patients reported side effects during the study, recurrence of pain occurred in 33% of the LLLT group.

Use of amitriptyline cream in the management of entry dyspareunia due to provoked vestibulodynia. Pagano R, Wong S. *J Low Genit Tract Dis* 2012; 16(4): 39–397.

A prospective study of 150 patients treated with amitriptyline 2% cream twice daily for 3 months. Based on pain scores, 56% reported symptom reduction and 10% were completely pain free; 44% had no response at all.

Spinal cord stimulator for the treatment of a woman with vulvovaginal burning and deep pelvic pain. Nair AR, Klapper A, Kushnerik V, et al. *Obstet Gynecol* 2008; 111: 545–7.

The use of spinal cord stimulation was successful in a patient with vulvodynia and unsuccessful multiple prior therapies and whose symptoms were diffuse in nature.

Successful treatment of persistent vulvodynia with submucous infiltration of betamethasone and lidocaine. Dede M, Yenen MC, Yilmaz A, et al. *Eur J Obstet Gynecol Reprod Biol* 2006; 124: 258–9.

Single case report on the use of subcutaneous infiltration of betamethasone 6 mg plus lidocaine 1% to a previous surgical site on the vulva at several different points once a week for 6 weeks. At follow-up there was no complaint of itching, pain or hyperesthesia.

Warts

Rabia S. Rashid



Warts are a common disease caused by infection with various strains of the human papillomavirus (HPV). They appear on different sites of the body and in various forms, including common, flat, filiform, periungual, plantar, mosaic, and genital warts. Children most commonly present with common or periungual warts on hands and feet, whereas adults often present with common warts on the back of hands or filiform warts on the face and neck. Genital warts are discussed in another chapter.

MANAGEMENT STRATEGY

Most warts resolve spontaneously with time. However, patients and children's parents often ask for treatment because of pain, social stigma, or concern over infectivity. In some cases warts cause ridicule, distorted self-image, impaired dexterity, worry over loss of employment, or a health and safety issue. Immunosuppressed patients may have extensive and resistant warts.

Most patients will treat themselves with over-the-counter preparations containing *keratolytics* before presenting to the dermatologist. Salicylic acid has the best evidence base and is the most commonly used therapy. It can be applied in various concentrations, with or without occlusion, and is suitable for any cutaneous site except the face. However, it requires frequent application, and it may cause irritation of the surrounding skin. *Cryotherapy* with dimethyl ether and propane applicator, silver nitrate pencils, and occlusive 'duct tape' are also available over the counter.

When a dermatologist sees patients with warts, the diagnosis and the possibility of *spontaneous resolution* and watchful waiting should be explained. The patient should be educated on how to apply topical preparations accurately. Keeping the warts well pared down with the use of a file or pumice stone after soaking is especially important for plantar warts. Young

and healthy individuals with short duration of infection have the highest clearance rate. Cryotherapy with liquid nitrogen is one of the most common treatments used by the dermatologist. Liquid nitrogen is applied with a cryospray or a cotton bud. The wart should be frozen outward from the center to include a 2-mm rim of normal skin and the freeze maintained for 5 seconds. Cryotherapy is best repeated at 2- to 3-week intervals. Hyperkeratotic warts should be pared before cryotherapy and plantar warts treated with two freeze-thaw cycles. This treatment is painful and not always well tolerated by young children. The treated warts are sore and may blister. In pigmented skin, posttreatment hypopigmentation and hyperpigmentation can be a problem. Cryotherapy with liquid nitrogen can be combined with other topical preparations such as salicylic acid. Cryotherapy with carbon dioxide snow or dimethyl ether applicators does not produce temperatures as low as liquid nitrogen and is less effective.

If cryotherapy is not successful, then various other options are available, including *immunotherapy* with diphenylprone (DCP) or squaric acid, or intralesional therapy with *Mycobacterium w* vaccine, Bacillus Calmette-Guérin (BCG), purified protein derivative (PPD) of tuberculin antigen, or mumps or *Candida* antigen. Intralesional bleomycin may be injected into the wart or the solution applied to the wart and then repeatedly pricked through with a lancet. Laser ablation, hyperthermia, curettage and cautery, or even surgical excision of troublesome and resistant warts can be attempted, but the risk of scarring and recurrence of the warts in the scar can be a problem. The *pulsed dye laser* (PDL), thought to target the rich capillary network in warts, can be effective. *Photodynamic therapy* (PDT) is another option; however, pain during and after ALA (aminolevulinic acid)-PDT is well recognized. Other treatments used occasionally include 5-fluorouracil, zinc, levamisole, cimetidine, topical and oral retinoids, and imiquimod. Novel treatments included in this chapter include intralesional vitamin D₃, microwave therapy, topical hydrogen peroxide, digoxin and furosemide gel, topical sandalwood oil, and green tea sinecatechins.

First-Line Therapies

• Salicylic acid preparations	A
• Silver nitrate	B
• Cryotherapy with dimethyl ether and propane	C

Topical treatments for cutaneous warts. Kwok CS, Gibbs S, Bennett C, et al. Syst Rev 2013; 9: CD001781.

This updated review contained 26 new studies. According to 85 trials meeting the criteria for inclusion, the best evidenced therapy for cutaneous warts is for salicylic acid. Data pooled from six placebo-controlled trials showed a statistically significant result favoring the topical application of salicylic acid for warts at all sites (response rate [RR] 1.56, 95% confidence interval, 1.20–2.03). On the contrary, no benefit was found between cryotherapy and placebo in three studies.

Efficacy of 10% silver nitrate solution in the treatment of common warts: a placebo-controlled, randomized, clinical trial. Ebrahimi S, Dabiri N, Jamshidnejad E, et al. Int J Dermatol 2007; 46: 215–7.

A topical solution of 10% silver nitrate applied to the warts on alternate days for 3 weeks in 30 patients resulted in complete

clearance in 63% of patients after 6 weeks in the treatment group versus no healing in the placebo group.

Cryosurgical treatment of warts: dimethyl ether and propane versus liquid nitrogen: case report and review of the literature. Nguyen NV, Burkhart CG. J Drugs Dermatol 2011; 10: 1174–6.

Other coolants are probably less effective than liquid nitrogen.

Second-Line Therapies

- Cryotherapy with liquid nitrogen **B**
- Cryotherapy in combination with salicylic acid **B**

Cryotherapy versus salicylic acid for the treatment of plantar warts: a randomised controlled trial. Cockayne S, Hewitt C, Hicks K, et al. BMJ 2011; 342: d3271.

A study of 240 patients treated by healthcare professionals with liquid nitrogen, for up to four treatments, 2–3 weeks apart, was compared with patient self-treatment with 50% salicylic acid daily, for up to 8 weeks. Overall, 14% had complete clearance at 12 weeks, with no significant difference between the two groups.

A two-week interval is better than a three-week interval for reducing the recurrence rate of hand–foot viral warts after cryotherapy: a retrospective review of 560 hand–foot viral warts patients. Youn SH, Kwon IH, Park EJ, et al. Ann Dermatol 2011; 23: 53–60.

In a retrospective study with 560 patients, a 2-week interval was compared with a 3-week interval between cryotherapy with liquid nitrogen. For the 2- and 3-week groups, cure rates were 77% and 75%, respectively. Recurrence rates were 13% and 25%, and mean time to recurrence was 9.8 months and 6.9 months, respectively.

Two-week cryotherapy is optimal not only because of the rapid cure but also because of the lower recurrence rate.

Value of a second freeze–thaw cycle in cryotherapy of common warts. Berth-Jones J, Bourke J, Eglitis H, et al. Br J Dermatol 1994; 131: 883–6.

In a randomized trial 300 patients received cryotherapy with either one or two freeze–thaw cycles at a 3-week interval. In addition, all subjects used keratolytic wart paints, and plantar warts were pared before freezing. At 3 months, the cure rate was 57% from the single freeze technique versus 62% from the double freeze technique. In plantar warts, the cure rate was 41% from single freezing and 65% for double freezing, whereas in the hand warts there was no additional benefit from the second freeze.

Liquid nitrogen and salicylic/lactic acid paint in the treatment of cutaneous warts in general practice. Steele K, Irwin WG. J R Coll Gen Pract 1988; 38: 256–8.

In this randomized study, 207 patients with common hand warts and simple plantar warts were assigned to one of three treatment groups: cotton wool bud cryotherapy applied weekly, daily application of wart paint (lactic acid one part, salicylic acid one part, collodion four parts), or a combination of the two. Combination therapy cured 87% of common hand warts over a 6-week period and was significantly more effective than either agent used separately ($p < 0.05$). The results for simple plantar warts were disappointing, and no treatment regimen proved to be significantly better than any other.

Third-Line Therapies

Immunologic therapy

- Imiquimod **B**
- Contact immunotherapy **B**
- Diphenycprone **D**
- Squaric acid **D**
- Topical BCG **D**
- Intralesional immunotherapy **B**
- Intralesional BCG **D**
- Candida **D**
- MMR **D**
- *Mycobacterium w* vaccine **A**
- Purified protein derivative (PPD) of tuberculin antigen **A**
- Cimetidine **D**
- Zinc **A**
- Zinc oxide (topical) **B**
- Zinc sulfate (intralesional) **B**
- Zinc (oral) **B**
- Interferon **E**
- Human papillomavirus vaccine **E**

Destructive therapies

- Cantharidin **D**
- Glycolic acid **D**
- Hydrogen peroxide **A**
- Formic acid **B**
- Monochloroacetic acid **B**
- Trichloroacetic acid **B**
- Hyperthermia **B**
- Electrosurgery **C**
- Surgery **B**
- Pulsed dye laser **D**
- Photodynamic therapy **D**
- CO₂ laser **D**
- Nd:YAG laser **D**
- Er:YAG laser **D**

Virucidal agents

- Glutaraldehyde **B**

Antiproliferative therapies

- Dithranol **B**
- Podophyllin **D**
- 5-Fluorouracil **A**
- Bleomycin **B**
- Cidofovir **D**
- Intralesional vitamin D **B**
- Occlusotherapy **B**
- Digoxin and furosemide gel **A**
- Topical retinoids **D**
- Systemic retinoids **E**
- Acitretin **A**
- Isotretinoin **A**

Complementary and alternative therapies

- Hypnosis **B**
- Acupuncture **B**
- Echinacea **B**
- Topical sandalwood oil **D**
- Sinecatechins **E**

Immunologic Therapy

Topical 5% imiquimod long-term treatment of cutaneous warts resistant to standard therapy modalities. Grussendorf-Conen EI, Jacobs S, Rübber A, et al. *Dermatology* 2002; 205: 139–45.

In this study, 10 of 37 (27%) patients cleared with imiquimod self-applied twice daily with mean duration of 19 weeks.

Investigations of the efficacy of diphenylcyclopropenone immunotherapy for the treatment of warts. Suh DW, Lew BL, Sim WY. *Int J Dermatol* 2014; 53: e567–71.

Patients were sensitized with 0.1% diphenylcyclopropenone (DPCP), and 2 weeks after sensitization, DPCP was applied to warts weekly. High clearance rates of 141/170 patients (82.9%) were achieved in 434/511 lesions (84.9%). Immunotherapy proved more effective in patients <20 years of age and for hand warts. The mean $\pm$ standard deviation number of applications was 9.02 ± 2.59 . Side effects occurred in 36 patients, with blistering at the sensitized site being the most common. No serious adverse events occurred.

Does immunotherapy of viral warts provide beneficial effects when it is combined with conventional therapy? Choi JW, Cho S, Lee JH. *Ann Dermatol* 2011; 23: 282–7.

This study assessed the efficacy of DCP as an adjunctive to cryotherapy. Retrospective chart review of 124 patients with warts showed that DCP may be a successful adjuvant to cryotherapy in reducing the number of cryotherapy sessions.

Clinical efficacy of diphenylcyclopropenone immunotherapy as monotherapy for multiple viral warts. Park JY, Park BW, Cho EB, et al. *J Cutan Med Surg* 2018; 22(3): 285–9.

The records of 250 patients with multiple viral warts was analyzed retrospectively, evaluating clinical efficacy of DPCP monotherapy compared with cryotherapy and PDL therapy. The DPCP-only group ($n=43$) showed a lower clinical response (75.6%) than the cryotherapy-only group ($n=171$, 89.8%, $p<0.01$) and PDL-only group ($n=36$, 90.3%, $p<0.01$).

Squaric acid immunotherapy for warts in children. Silverberg NB, Lim JK, Paller AS, et al. *J Am Acad Dermatol* 2000; 42: 803–8.

In this retrospective study, 61 children had their warts treated with home application of 0.2% squaric acid, 3–7 nights per week, for at least 3 months, after initial sensitization with 2% squaric acid on the forearm. Complete clearance after 7 weeks of this treatment occurred in 58% of patients, partial clearance occurred in 18%, and no response occurred in 24%.

Treatment of common and plane warts in children with topical viable bacillus Calmette–Guerin. Salem A, Nofal A, Hosny D. *Pediatr Dermatol* 2013; 30: 60–3.

Topical BCG paste (containing 3 mg of salicylic acid, dissolved in 3 mL of glycerin) was applied to all warts in 40 children weekly for a maximum of 12 weeks. A control group of 40 children were treated with saline once weekly for same duration. Complete response occurred in 65% of children with common warts and 45% of plane warts with no response in the control group. A statistically significant difference was found between the active and control groups.

Immunotherapy in viral warts with intradermal *Bacillus Calmette–Guerin* vaccine versus intradermal tuberculin

purified protein derivative: a double-blind, randomized controlled trial comparing effectiveness and safety in a tertiary care center in Eastern India. Podder I, Bhattacharya S, Mishra V, et al. *Indian J Dermatol Venereol Leprol* 2017; 83(3): 411.

Sixty patients received three doses of 0.1 mL of *Bacillus Calmette–Guerin* vaccine or tuberculin purified protein derivative (PPD) intradermally in the deltoid region at 4-weekly intervals. They were followed up for another month. Complete clearance was noted in 48.5% and in 18.5% of the tuberculin PPD group. The number of lesions reduced significantly from baseline in both the groups from the first follow-up visit onward.

Intralesional *Candida* antigen immunotherapy for the treatment of recalcitrant and multiple warts in children. Muñoz Garza FZ, Roé Crespo E, Torres Pradilla M, et al. *Pediatr Dermatol* 2015; 32: 797–801.

In this retrospective review, 220 children with refractory warts received three intralesional injections of 0.2 mL of *Candida albicans* antigen, one per visit, at 3-week intervals. Results showed that 156 (70.9%) had a complete response, 37 (16.8%) had a partial response, and 27 (12.2%) had no response. An average of 2.7 injections were required.

Two-year experience of using the measles, mumps and rubella vaccine as intralesional immunotherapy for warts. Na CH, Choi H, Song SH, et al. *Clin Exp Dermatol* 2014; 39: 583–9.

A retrospective study of 136 patients with various types of warts who were treated for a total of six times at 2-week intervals. Thirty-six patients (26.5%) experienced complete resolution with an average of five treatments; 51.5% experienced >50% reduction in size and number of warts. Common warts showed statistically higher treatment response than other types of warts.

Intralesional *Mycobacterium w* vaccine versus cryotherapy in treatment of refractory extragenital warts: a randomized, open-label, comparative study. Dhakar AK, Dogra S, Vinay K, et al. *J Cutan Med Surg* 2016; 20(2): 123–9.

In this prospective, comparative study of 66 patients, 33 patients were randomized to receive 0.1 mL *Mycobacterium w* (Mw) vaccine weekly and the other 33 received cryotherapy every 2 weeks. Both groups were treated until resolution of lesions or for a maximum of 12 doses. Complete clearance of treated warts was seen in 66.7% and 65.5% of patients in the Mw and cryotherapy groups, respectively. Mw vaccine and cryotherapy were found to be equally efficacious.

A double-blind, randomized controlled trial to compare the effectiveness and safety of purified protein derivative of tuberculin antigen with *Mycobacterium w* vaccine in the treatment of multiple viral warts. Chandra S, Sil A, Datta A, et al. *Indian J Dermatol Venereol Leprol* 2019; 85(4): 355–66.

Sixty-four patients with multiple warts were randomized (1:1) to receive either PPD or Mw vaccine, via intradermal injections of 0.1 mL of either drug administered fortnightly over the deltoid region, until complete resolution or a maximum of six doses. Patients were followed up for another 3 months for recurrence. The number of warts reduced significantly with treatment in both groups. Complete remission was seen in 68.8% of the Mw group and 50% of the PPD group. Adverse events were significantly more with Mw compared to PPD of tuberculin antigen in patients with warts.

Cimetidine therapy for recalcitrant warts in adults: is it any better than placebo? Rogers CJ, Gibney MD, Siegfried EC, et al. *J Am Acad Dermatol* 1999; 41: 123–7.

In this double-blind, placebo-controlled study, 70 patients with multiple viral warts were randomized to cimetidine 25–40 mg/kg daily or placebo for 3 months. Cimetidine was found to be no more effective than placebo.

Cimetidine therapy for recalcitrant warts in adults. Glass AT, Solomon BA. *Arch Dermatol* 1996; 132: 680–2.

In this prospective study, 20 patients received cimetidine 30–40 mg/kg/day. Complete resolution or a dramatic improvement was achieved in 84% of the 18 patients after 3 months.

Topical zinc oxide vs. salicylic acid–lactic acid combination in the treatment of warts. Khattar JA, Musharrafieh UM, Tamim H, et al. *Int J Dermatol* 2007; 46: 427–30.

In this double-blind trial, 44 patients were treated with either 20% zinc oxide ointment or 15% salicylic acid ointment + 15% lactic acid ointment combination, twice daily for 3 months. In the zinc oxide group, 50% patients were cured versus 42% with salicylic acid–lactic acid.

Topical zinc sulfate solution for treatment of viral warts. Sharqie KE, Khorhseed AA, Al-Nuaimy AA. *Saudi Med J* 2007; 28: 1418–21.

Topical zinc sulfate solution used three times daily for 4 weeks led to a higher cure rate than water placebo in a double-blind trial of 40 patients with plane warts and 50 patients with common warts. The cure rate appeared to be dependent on the concentration of zinc solution used and was better for plane than common warts. For plane warts, cure rates were 85.7% for 10% zinc sulfate (6/7 patients), 42.8% for 5% zinc sulfate (3/7 patients), and 10% for placebo 10% (1/10 patients). For common warts, cure rates were 11%, 5%, and 0%, respectively.

Treatment of viral warts by intralesional injection of zinc sulphate. Sharquie KA, Al-Nuaimy AA. *Ann Saudi Med* 2002; 22: 26–8.

One hundred patients with 623 warts were divided into two groups. In the treatment group, 53 patients had 173 warts treated with 2% zinc sulfate intralesionally, whereas 176 warts were left untreated as control. Within 6 weeks in the treatment group 98% of the warts cleared versus none in the control group.

Evaluation of oral zinc sulfate effect on recalcitrant multiple viral warts: a randomized placebo-controlled clinical trial. Yeghoobi R, Sadighha A, Baktash D. *J Am Acad Dermatol* 2009; 60: 706–8.

After 2 months of treatment with oral zinc sulfate (10 mg/kg to a maximum of 600 mg daily), 78% of patients cleared their warts (25/32) compared with 13% in the placebo group (3/23). The baseline serum zinc levels did not differ significantly between the two groups, but mean levels in both groups were low pretreatment.

Oral zinc sulfate for unresponsive cutaneous viral warts: too good to be true? A double-blind, randomized, placebo-controlled trial. López-García DR, Gómez-Flores M, Arc-Mendoza AY, et al. *Clin Exp Dermatol* 2009; 34: e984–5.

This double-blind, randomized controlled trial (RCT) showed no difference between oral zinc sulfate and placebo.

Successful treatment of verruca plantaris with a single sublesional injection of interferon- α 2a. Aksakal AA, Ozden MG, Atahan C, et al. *Clin Exp Dermatol* 2009; 34: 16–9.

In this placebo-controlled, single-blind study, 45 patients with a variety of hand or foot warts were treated with single-dose

4.5 MU interferon (IFN)- α 2a (three study arms) versus eight controls treated with normal saline. As local anesthesia, liquid nitrogen was sprayed onto the injection site of the IFN group for 3–4 seconds. At 12-month follow-up 19/24 patients (79.2%) with single verruca plantaris cleared completely, whereas only 2/8 patients (25%) had partial response in the control group.

Complete resolution of chronic multiple verruca vulgaris treated with quadrivalent human papillomavirus vaccine. Daniel BS, Murrell DF. *JAMA Dermatol* 2013; 149: 370–2.

The quadrivalent HPV vaccine was used in four patients with chronic verruca vulgaris resulting in resolution of all warts. Further studies are warranted.

Destructive Therapies

Cantharidin treatment for recalcitrant facial flat warts: a preliminary study. Kartal Durmazlar SP, Atacan D, Eskioğlu F. *J Dermatolog Treat* 2009; 20: 114–9.

A study of 15 patients with plane facial warts who were treated with cantharidin 0.7% solution applied for 4–6 hours, washed off, and repeated every 3 weeks. All 15 patients achieved clearance within 16 weeks with one to four treatments.

Glycolic acid 15% plus salicylic acid 2%: a new therapeutic pearl for facial flat warts. Rodríguez-Cerdeira C, Sánchez-Blanco E. *Clin Aesthet Dermatol* 2011; 4: 62–4.

All 20 patients who applied a fine layer of glycolic acid 15% and salicylic acid 2% gel to their warts once daily clinically were cured within 8 weeks.

Evaluation of different concentrations of hydrogen peroxide solution (3% and 6%) as a potential new therapeutic option of nongenital warts: a randomized controlled triple-blinded clinical trial. Mahran AM, Twisy HO, Elghazally SA, et al. *J Cosmet Dermatol* 2020; 19(2): 416–22.

In this prospective, randomized controlled study, 145 patients were divided into three groups. Group 1 used topical hydrogen peroxide 6% solution under occlusion with a plastic tape for 1 hour daily for 6 weeks; group 2 used hydrogen peroxide 3% solution; and group 3 used normal saline 0.9% as a placebo. After 6 weeks of treatment, 46.6% of patients in group 1 had complete response, 48.3% in group 2, and only one patient (3.4%) in group 3. Treatment responses were significantly better in the hydrogen peroxide-treated groups, with a better overall response for the 6% concentration. The authors suggested using hydrogen peroxide 6% solution as a once-daily application under occlusion for 1 hour for 6 weeks.

A double blind, randomized trial of local formic acid puncture technique in the treatment of common warts. Faghihi G, Vali A, Radan M, et al. *Skinmed* 2010; 8: 70–1.

In this trial, 34 patients applied 85% formic acid in distilled water solution on their warts on one side of the body and distilled water as placebo on the other side of the body every other day using a needle puncture technique. Follow-up occurred every 2 weeks for 3 months. Complete clearance was achieved in 91% of patients who received formic acid versus 10% in the placebo group.

Monochloroacetic acid application is an effective alternative to cryotherapy for common and plantar warts in primary care: a randomized controlled trial. Bruggink SC, Gussekloo J, Egberts PF, et al. *J Invest Dermatol* 2015; 135: 1261–7.

Patients were randomly allocated to monochloroacetic acid (MCA) versus liquid nitrogen cryotherapy every 2 weeks for common warts ($n=188$) and MCA versus cryotherapy combined with daily salicylic acid (SA) self-application for patients with plantar warts ($n=227$). MCA was found to be an effective alternative to cryotherapy for both types of warts with cure rates at 13 weeks comparable in all treatment groups. In the common wart group, cure rates were 43% for MCA and 54% for cryotherapy, and in the plantar wart group, cure rates were 46% for MCA and 39% for cryotherapy combined with SA.

Comparative study of topical 80% trichloroacetic acid with 35% trichloroacetic acid in the treatment of the common wart. Pezeshkpoor F, Banihashemi M, Yazdanpanah MJ, et al. *J Drugs Dermatol* 2012; 11: e66–9.

In this single-blind study, 62 patients were randomly assigned to weekly treatment with trichloroacetic acid (TCA) in two different concentrations until complete clearance for a maximum of 6 weeks. Fifty-five patients were included in the final analysis. With the higher concentration of TCA, 46.7% of patients cleared >75% warts versus 12% for the lower concentration.

Microwave therapy for cutaneous human papilloma virus infection. Bristow I, Lim WC, Lee A, et al. *Eur J Dermatol* 2017; 27(5): 511–8.

In this pilot study, 32 consecutive individuals with 54 recalcitrant plantar warts were treated with microwave therapy. Treatment was administered via a handheld device over 5 seconds. If the wart persisted, treatment was repeated at 1 week, 1 month, and 3 and 12 months. Tissue inflammation was minimal and 75.9% of lesions were cleared. The mean number of days to resolution was 79.49 days.

Local hyperthermia at 44°C for the treatment of plantar warts: a randomized, patient-blinded, placebo-controlled trial. Huo W, Gao XH, Sun XP, et al. *J Infect Dis* 2010; 201: 1169–72.

In this study, 54 patients had their warts treated with local hyperthermia of 44°C with an infrared-emitting source for 30 min a day for three consecutive days plus two additional days 2 weeks later. Within 3 months, 54% of patients in the treatment group were cured versus 12% in the control group.

Controlled localized heat therapy in cutaneous warts. Stern P, Levine N. *Arch Dermatol* 1992; 128: 945–8.

In this placebo-controlled, randomized trial, 13 patients had their 29 warts treated by a handheld radiofrequency heat generator device between one and four times for 30–60 seconds so that a temperature of 50°C was achieved in the warts. Complete clearance was achieved in 86% in the heat therapy group versus 41% in the control group.

Treatment of plantar warts by blunt dissection. Pringle WM, Helms DC. *Arch Dermatol* 1973; 108(1): 79–82.

Sixty patients had one or more plantar warts treated with a blunt dissecting instrument, which allowed complete removal of warty tissue with minimal bleeding. The cure rate with one treatment was 85%, with follow-up periods averaging 10 months (minimum of 6 months).

Efficacy of punch reduction prior to cryotherapy in patients with viral warts: a case-control study in a single tertiary center. Choi JY, Park JH, Oh SH, et al. *Ann Dermatol* 2017; 29(2): 200–5.

Thirty-nine patients who received a 3–5-mm punch biopsy for warts were reviewed through charts and photos. Among them, 15 were matched with cryotherapy-only controls in terms of size and location of the wart. The average number of treatments was 4.1 ± 3.3 (mean $\pm$ standard deviation) in the control group. The number of treatments and total cost in the punch biopsy group was statistically less than that in control group ($p=0.008$). The authors concluded that punch reduction can decrease the number and cost of treatments for patients with warts.

Electrosurgery vs. 40% salicylic acid in the treatment of warts. Sudhakar Rao KM, Ankad BS, Naidu V, et al. *J Clin Diagn Res* 2012; 6: 81–4.

In this prospective randomized comparative study, 60 patients with viral warts received either electrosurgery or 40% SA (protocol or equipment not specified) and were followed up monthly for 6 months. Clearance rate with electrosurgery was 90% (27 out of 30 patients) versus 16.7% with SA (5 out of 30 patients).

Pulsed dye laser treatment for facial flat warts. Grilo W, Boixeda P, Ballester A, et al. *Dermatol Ther* 2014; 27: 31–5.

In this prospective study, 32 patients were treated with PDL at 595-nm wavelength, a laser energy density of 9 or 14 J/cm² with a spot size of 7 or 5 mm, respectively, with air cooling and a pulse duration of 0.5 millisecond. Patients were treated in one to two sessions, 3 weeks apart, with one to three passes for each session. A complete response was noted in 14 patients (44%) and an excellent response in 18 patients (56%). There were only four recurrences at 1-year follow-up.

Pulsed-dye laser for recalcitrant viral warts: a retrospective case series of 227 patients. Sparreboom EE, Luijck HG, Luiting-Welkenhuyzen HA, et al. *Br J Dermatol* 2014; 171: 1270–3.

A retrospective study of 227 consecutive patients with recalcitrant warts (those that failed all available topical therapy and repetitive cryotherapy). Overall efficacy for PDL treatment was 86%. This was achieved with generally more powerful laser settings than in the previous literature. Up to six treatments with fluences of 12.5–15.0 J/cm² and treatment intervals of 3–4 weeks were recommended to achieve maximal treatment success.

Photodynamic therapy with 5-aminolaevulinic acid or placebo for recalcitrant foot and hand warts: randomized double-blind trial. Stender IM, Na R, Fogh H, Gluud C, et al. *Lancet* 2000; 335: 963–6.

Forty-five adults with refractory warts received ALA-PDT or placebo PDT and showed cure rates of 64/114 (56% of warts) and 47/113 (42% of warts), respectively, which was statistically significant ($p < 0.05$). All warts were also treated with paring and topical SA (Verucid).

Is the step-up therapy of topical 5-aminolevulinic acid photodynamic therapy effective and safe for the patients with recalcitrant facial flat wart? Quian G, Wang S, Deng D, et al. *Dermatol Ther* 2014; 27: 83–8.

Step-up therapy of ALA-PDT was used on 30 patients in a maximum of three treatment sessions. Concentrations of ALA used were 5%, 10%, and 20%, and the treatment was increased at 2-weekly intervals if clearance was not achieved, to a maximum of three treatment sessions. The treatment response was good with 12 patients clearing completely after one session, three by two sessions, and 10 by the third session. Tolerance to ALA-PDT could improve with step-up therapy.

Recalcitrant viral warts treated with photodynamic therapy methyl aminolevulinate and red light (630nm): a case series of 51 patients. Alcántara-González J, Calzado-Villarreal L, Sánchez-Largo ME, et al. *Lasers Med Sci* 2020; 35(1): 229–31.

In this retrospective study, 51 patients were treated with PDT with methyl-aminolevulinate (MAL). Treatment was carried out every 2 weeks, until complete resolution of the warts or a maximum of six sessions. All patients were reviewed 3 months after their last treatment session. Complete resolution of the lesions was seen in 49.02% and failure of the treatment in 50.98%.

Enhanced efficacy of photodynamic therapy with methyl 5-aminolevulinic acid in recalcitrant periungual warts after ablative carbon dioxide fractional laser: a pilot study. Yoo KH, Kim BJ, Kim MN. *Dermatol Surg* 2009 Dec; 35(12): 1927–32.

Twelve patients with a total of 40 periungual warts were treated using an ablative CO₂ fractional laser. Immediately after each fractional treatment, MAL was applied on the periungual warts, and 3 hours later, the areas were illuminated with a red light at a dose of 50 J/cm² for 15 minutes. A mean clearance of 100% was achieved in 36 (90%) warts after a mean of 2.2 treatments per wart. There were no recurrences of the warts that had achieved 100% clearance during the follow-up period of 6 months.

A comparative study: superficial shaving combined with photodynamic therapy versus cryotherapy in the treatment of recalcitrant plantar warts. Huang K, Xie Y, Li M, et al. *Lasers Surg Med* 2020. doi: 10.1002/lsm.23212 [Epub ahead of print].

In this study, 46 patients with 271 warts received SS-PDT, and 26 patients with 147 warts received cryotherapy. After injection with 2% lidocaine and epinephrine, lesions were shaved in situ for the SS-PDT group, and PDT was performed immediately. The ALA-PDT procedure was repeated for three sessions at 1-week intervals for each patient. For the cryotherapy group, a freezing rod with direct contact was used and three freeze–thaw cycles were administered; after 7–15 days treatment was repeated if appropriate. After 6 months, the clearance rate (defined as >50%) was 91.3% in the SS-PDT group and 23.1% in the cryotherapy group. The recurrence rate in the SS-PDT group was significantly lower than that in the cryotherapy group (8.7% vs. 76.9%, $p < 0.001$) after 6 months of follow-up.

Successful treatment of recalcitrant warts in pediatric patients with carbon dioxide laser. Serour F, Somekh E. *Eur J Pediatr Surg* 2003; 13: 219–23.

In this case series, 40 children with 54 warts were treated with CO₂ laser ablation under local anesthesia. Healing time was 4–5 weeks, and there was no recurrence at 12 months. Hypopigmentation was noticed in 11 cases.

Combination of carbon dioxide laser therapy and artificial dermis application in plantar warts: human papilloma virus DNA analysis after treatment. Mitsuishi T, Sasagawa T, Kato T, et al. *Dermatol Surg* 2010; 36: 1401–5.

In 31 patients, CO₂ laser was used for ablation of 35 warts, and the defects were covered with artificial dermis. Follow-up periods ranged from 3 to 12 months. Complete clearance was achieved in 31/35 warts after one treatment. After complete remission, HPV DNA was not detected in the upper epidermis of the postoperative site.

Long-pulsed Nd:YAG laser treatment of warts: report on a series of 369 cases. Han TY, Lee JH, Lee CK, et al. *J Korean Med Sci* 2009; 24: 889–93.

A 96% clearance rate of recalcitrant common, palmoplantar, and periungual warts was achieved in 369 patients treated with Nd:YAG laser over the course of a year.

Pulsed dye laser versus Nd:YAG in the treatment of plantar warts: a comparative study. El-Mohamady Ael-S, Mearag I, El-Khalawany M, et al. *Lasers Med Sci* 2014; 29: 1111–6.

The study included 46 subjects with multiple plantar warts. In each patient, half the lesions were treated with Nd:YAG laser and half with PDL fortnightly for a maximum of six sessions. There was no significant difference between cure rates for PDL (73.9%) and Nd:YAG (78.3%), but Nd:YAG was more painful and associated with more complications.

Er:YAG laser followed by topical podophyllotoxin for hard to treat palmoplantar warts. Wollina U. *J Cosmet Laser Ther* 2003; 5: 35–7.

Complete resolution of warts was observed in 31/35 patients after treatment with Er:YAG laser, followed with topical podophyllotoxin for 3 days on, 4 days off, for up to six cycles.

Virucidal Treatments

Topical treatment of resistant warts with glutaraldehyde. Hirose R, Hiro M, Shakuwa T, et al. *J Dermatol* 1994; 21: 248–53.

A cure rate of 72% was achieved in 25 patients treated topically with 20% glutaraldehyde solution. The treatment did not cause pain or permanent pigmented change.

Glutaraldehyde is suitable for home treatment, as there is no need for special instruments or special technique, and the cure rates are almost equal to those with cryotherapy.

Cutaneous necrosis secondary to topical treatment of wart with 20 p. 100 glutaraldehyde solution. Prigent F, Iborra C, Meslay C. *Ann Dermatol Venereol* 1996; 123: 644–6.

Case reports like this led to the withdrawal of a glutaraldehyde product from the market in France in December 1995.

Antiproliferative Agents

Wart treatment with anthralin. Flindt-Hansen H, Tikjob G, Brandrup F. *Acta Derm Venereol* 1984; 64: 177–9.

An RCT of dithranol 2% cream versus Verucid (11% SA, 4% lactic acid with copper) showed a higher cure rate for dithranol: 56% (15/27) versus 26% (8/31).

Treatment of plantar warts with Elastoplast and podophyllin. Duthie DA, McCallum DI. *BMJ* 1951; 2: 216–8.

Forty patients with plantar warts were treated with podophyllin 25% in liquid paraffin under prolonged adhesive plaster occlusion, repeated at intervals of 1–2 weeks, and reported a clearance rate of 72.5% at 3 months.

Topical 5% 5-fluorouracil cream in the treatment of plantar warts: a prospective randomized and controlled clinical study. Salk RS, Grogan KA, Chang TJ. *J Drugs Dermatol* 2006; 5: 418–24.

In this study, 40 patients were treated either with 5-fluorouracil 5% with tape occlusion or tape occlusion alone with regular debridement for 12 weeks. In the active group 19/20 patients achieved complete cure versus 2/20 in the tape occlusion group.

Treatment of common warts with an intralesional mixture of 5-fluorouracil, lidocaine, and epinephrine: a prospective

placebo-controlled, double-blind randomized trial. Yazdanafar A, Farshchian M, Fereydoonnejad M. *Dermatol Surg* 2008; 34: 656–9.

This study included 40 patients. A pair of warts on each subject was randomized to receive weekly intralesional 5-fluorouracil 4% (in combination with 2% lidocaine and 0.0125 mg/mL of epinephrine) or normal saline placebo. After four injections 65% of warts cleared up compared with 35% in the placebo group.

Efficacy of intralesional bleomycin in palmo-plantar and periungual warts. Soni P, Khandelwal K, Aara N, et al. *J Cutan Aesthet Surg* 2011; 4: 188–91.

Twenty-five patients were allocated to 0.1% intralesional bleomycin (1-mg/mL solution) or normal saline placebo fortnightly for a maximum of two injections; 96% (82/85) of warts treated with bleomycin cleared, whereas only 11% of warts (8/72) treated with placebo showed clearance at 3 months. Moderate pain was observed in both groups, and no patients experienced systemic toxicity.

Intralesional bleomycin in the treatment of cutaneous warts: a randomized clinical trial comparing it with cryotherapy. Dhar SB, Rashid MM, Islam A, et al. *Indian J Dermatol Venereol Leprol* 2009; 75: 262–7.

Eighty participants were randomized to cryotherapy (one to four sessions) versus 0.1% intralesional bleomycin injection. Treatments were 3-weekly, using one body side for each treatment and a maximum of four treatments. The clearance rates in context of number of patients and number of warts were 94.9% and 97% for bleomycin and 76.5% and 82% for cryotherapy, respectively ($p < 0.05$ by χ^2 analysis and $RR = 7.67$).

Recalcitrant warts and topical cidofovir: predictive factors of good response. Padilla España L, Del Boz J, Fernández-Morano T, et al. *J Eur Acad Dermatol Venereol* 2016; 30: 1218–20.

A retrospective study of 126 immunocompetent patients treated with 3% or 1% cidofovir cream, with or without occlusion and once or twice a day, showed complete response in 67 (53.2%) and partial response in 35 (27.8%). Median duration of treatment was 12 weeks and median follow-up 7 months. Based on their results, the authors recommended using cidofovir 3% cream initially twice daily with occlusion for a period of 12 weeks.

Intralesional cidofovir for the treatment of multiple and recalcitrant cutaneous viral warts. Broganelli P, Chiaretta A, Fragnelli B, et al. *Dermatol Ther* 2012; 25: 468–71.

In an open study, 288 patients were treated with monthly intralesional injections of cidofovir (15 mg/mL). Resolution of warts occurred in 98% of patients, with an average of 3.2 injections required.

Effectiveness of intralesional vitamin D₃ injection in the treatment of common warts: single-blinded placebo-controlled study. Kareem IMA, Ibrahim IM, Mohammed SFF, et al. *Dermatol Ther* 2019; 32(3): e12882.

Fifty patients were divided into two groups: 30 patients received two intralesional injections of 0.2 mL of vitamin D₃ (300,000 IU) into the base of the most troublesome viral wart, 1 month apart, and another 20 patients were injected with normal saline solution in a similar fashion as controls. Complete clearance of the target warts occurred in 40% of patients in the treatment group, but only in 5% of patients in the control group ($p \leq 0.001$).

The efficacy of duct tape vs. cryotherapy in the treatment of verruca vulgaris (the common wart). Focht DR, Spicer C, Fairchok MP. *Arch Pediatr Adolesc Med* 2002; 156: 971–4.

In this randomized study, 61 children and young adults received treatment with either cryotherapy with a 10-second freeze for a maximum of six treatments every 2–3 weeks or duct tape occlusion applied for 6.5 days every 7 days followed by debridement of the wart upon removal of tape for a maximum of 2 months. Complete resolution was achieved in 22/30 patients (71%) in the duct tape arm versus 15/31 (46%) in the cryotherapy group.

Efficacy of duct tape vs. placebo in the treatment of verruca vulgaris (warts) in primary school children. de Haen M, Spigt MG, van Uden CJT, et al. *Arch Paediatr Adolesc Med* 2006; 160: 1121–5.

No significant effect of duct tape occlusion.

Duct tape for the treatment of common warts in adults: a double blind randomized controlled trial. Wenner R, Askari SK, Cham PMH, et al. *Arch Dermatol* 2007; 143: 309–13.

No difference between duct tape and moleskin occlusion.

A randomized controlled proof-of-concept trial of digoxin and furosemide in adults with cutaneous warts. Rijsbergen M, Niemeyer-van der Kolk T, Hogendoorn G, et al. *Br J Dermatol* 2019; 180(5): 1058–68.

Topical ionic contraviral therapy with digoxin and furosemide inhibits the potassium influx on which DNA viruses rely for replication. Eighty adult patients with at least two cutaneous warts (plantar or common) were randomized to one of four treatments: digoxin + furosemide (0.125%); digoxin (0.125%); furosemide (0.125%); or placebo. The gel was administered once daily for 42 consecutive days. Wart size and HPV load reduction was achieved in all active treatment groups. A statistically significant reduction in wart diameter and HPV load of all treated warts was shown in the digoxin + furosemide treatment group versus placebo.

Plantar warts treated with topical adapalene. Gupta R. *Indian J Dermatol* 2011; 56: 513–4.

All 118 warts cleared within 8 weeks in 10 patients treated with topical 0.1% adapalene gel after paring of warts. This was followed by occlusive dressing with a polythene sheet for 1 week and continued until all the warts cleared.

Treatment of extensive and recalcitrant viral warts with acitretin. Choi YL, Lee KJ, Kim WS, et al. *Int J Dermatol* 2006; 45: 480–2.

In one case report, oral acitretin 1 mg/kg/day achieved almost complete clearance of recalcitrant warts on the hands after 2 months, but relapse occurred after cessation of therapy at 1 month, which promptly improved with resumption of acitretin.

A double-blind, randomized, placebo-controlled trial of oral isotretinoin in the treatment of recalcitrant facial flat warts. Olguin-Garcia MG, Jurado-Santa Cruz F, Peralta-Pedrero ML, et al. *J Dermatol Treat* 2015; 26: 78–82.

Isotretinoin 30 mg/day or placebo was administered to 16 and 15 patients, respectively, for 12 weeks. All patients in the active treatment group showed complete resolution of warts versus no improvement in the placebo group ($p = 0.0001$). The most frequent adverse event was cheilitis. The patients did not undergo follow-up to assess for recurrence after the study ended.

Complementary and Alternative Therapies

Effects of hypnotic, placebo, and salicylic acid treatments on wart regression. Spanos NP, Williams V, Gwynn MI. *Psychosom Med* 1990; 52: 109–14.

A randomized study comparing hypnosis with salicylic acid, control (no treatment), and placebo (base carrier from SA) showed a greater effect with hypnosis at 6-week follow-up, but the numbers were small (only 10 patients per group).

The successful treatment of flat warts with auricular acupuncture. Ning S, Li F, Qian L, et al. *Int J Dermatol* 2012; 51: 211–5.

This single-blind, randomized study compared weekly auricular acupuncture with tretinoin 0.1% ointment nightly for 10 weeks. Overall, 53% (16/30) of patients treated with acupuncture cleared, compared with 3% (1 of 30) in the tretinoin group.

Oral supplementation with a nutraceutical containing echinacea, methionine and antioxidant/immunostimulating compounds in patients with cutaneous viral warts. Cassano N, Ferrari A, Fai D, et al. *G Ital Dermatol Venereol* 2011; 146: 191–5.

The aim of this open-label study was to determine the effects of nutraceutical oral supplementation containing methionine, echinacea, zinc, and probiotics on the response of cutaneous warts to conventional standard therapy with salicylic and lactic acids or cryotherapy with liquid nitrogen. All 172 eligible patients were

allocated to conventional standard therapy alone or combined conventional standard therapy with nutraceutical oral supplementation for 4 months. Complete remission was achieved in 55% of patients in the conventional standard therapy group versus 86% in the conventional standard therapy and oral supplementation group at 6 months' follow-up.

Topical sandalwood oil for common warts. Haque M, Coury DL. *Clin Pediatr (Phila)* 2018; m57(1): 93–5.

Sandalwood oil was applied topically twice daily for 12 weeks. At the end of the study, eight of 10 (80%) had complete resolution of all treated warts. The remaining two subjects had improvement rated as moderate (25% to >90%). There were no adverse events reported.

Viral wart treatment with green tea sin catechins. Aranda Cazón C, Campos Muñoz L, Conde Taboada A, et al. *An Pediatr (Barc)* 2016; 84(4): 236–7.

Two male children with extragenital viral warts were treated successfully with topical green tea sin catechins 10%, three times a day for 1 and 2 months, respectively, achieving full resolution of the lesions with no associated side effects.

Wells syndrome

Felicity Ferguson, Emma Benton, Ian H. Coulson



Wells syndrome (eosinophilic cellulitis) is a rare inflammatory disorder resembling a bacterial cellulitis. Patients are often treated with antibiotics and fail to respond before the diagnosis of Wells syndrome is considered and then confirmed on skin biopsy. The pathogenesis remains obscure, but it is postulated that Wells syndrome represents a hypersensitivity reaction to a variety of stimuli, both endogenous and exogenous. Excessive production of interleukin-5 resulting in eosinophil accumulation and a local Th2 immune response have been documented. There are several recognized disease associations, including drug-induced disease. The condition can be recurrent, and although thought to be sporadic, familial patterns have been reported. The most common clinical manifestations are erythematous patches and plaques, but papulonodular and bullous types of Wells syndrome have been described. Characteristic histologic features include dermal edema with a marked eosinophilic infiltrate and flame figures (representing deposition of eosinophilic proteins and degradation products onto collagen fibers), although this is not specific to the condition. The usual course is of a pruritic sensation, followed rapidly by indurated, erythematous plaques of edema with violaceous edges that can form blisters. The lesions progress over a few days, resolving without scarring within 8 weeks. There is no anatomic predilection for plaques, and they may be solitary or multiple.

MANAGEMENT STRATEGY

Although there is no known cause, several precipitating factors have been suggested (Table 255.1). Some of the associations are well reported, others anecdotal. Injection site skin lesions have been associated with the tumor necrosis factor antagonists etanercept and adalimumab, the anti-IL-12/23 monoclonal antibody ustekinumab, with interferon- β . Interestingly, adalimumab has also been successfully used to treat refractory Wells syndrome in two cases. Minocycline can also induce a Wells syndrome-like disorder.

Suspect culprit drugs should be withdrawn. If an underlying systemic disease is identified, this will require treatment. Many cases of Wells syndrome associated with internal malignancy resolved with treatment of the initial tumor.

All treatment recommendations are limited to case reports and small case series. The most frequently reported therapy is with *systemic (oral) corticosteroids*, used at moderate doses to gain control of symptoms, followed by tapering. Cases may resolve spontaneously. Localized disease may respond to *superpotent topical steroids*. Topical *tacrolimus* has been used successfully. The H₁ antihistamine *cetirizine*, with antieosinophil action, has been effective; levocetirizine and hydroxyzine in combination have also proven successful. *Minocycline*, *dapsone*, *antimalarials*, *griseofulvin*, *adalimumab*, and *ciclosporin* are anecdotally beneficial. *Omalizumab* has proven effective in treatment resistant disease, and *mepolizumab* treatment in an asthmatic patient cleared concomitant Wells syndrome.

Specific Investigations

- Peripheral blood eosinophil count
- Skin biopsy
- Look for known associations of the disease

Wells syndrome: a clinical and histopathologic review of seven cases. Moossavi M, Mehregan DR. *Int J Dermatol* 2003; 42: 62–7.

Eosinophilic cellulitis-like reaction to subcutaneous etanercept injection. Winfield H, Lain E, Horn T, et al. *Arch Dermatol* 2006; 142: 218–20.

Eosinophilic cellulitis (Wells syndrome) as a cutaneous reaction to the administration of adalimumab. Boura P, Sarantopoulos A, Lefaki I, et al. *Ann Rheum Dis* 2006; 65: 839–40.

Systemic lupus erythematosus associated with Wells syndrome. Yin G, Xie Q. *Rheumatol Int* 2012; 32: 1087–9.

Wells syndrome associated with Churg–Strauss syndrome. Fujimoto N, Wakabayashi M, Kato T, et al. *Clin Exp Dermatol* 2011; 36: 46–8.

Wells syndrome associated with chronic myeloid leukemia. Nakazato S, Fujita Y, Hamade Y, et al. *Acta Derm Venereol* 2013; 93: 375–6.

Bullous eosinophilic cellulitis associated with giardiasis. Aslam A, Salman W, Chaudhry IH, et al. *Clin Exp Dermatol* 2014; 39: 264–5.

Eosinophilic cellulitis (Wells syndrome) caused by a temporary henna tattoo. Nacaroglu HT, Celegen M, Karkiner CS, et al. *Postepy Dermatol Alergol* 2014; 31: 322–4.

Pediatric Wells syndrome (eosinophilic cellulitis) after vaccination: a case report and review of the literature. Yu AM, Ito S, Leibson T, et al. *Pediatr Dermatol* 2018; 35: e262–4.

Other conditions anecdotally associated with Wells syndrome include chronic lymphocytic leukemia, angioimmunoblastic lymphadenopathy, mantle cell lymphoma, adenocarcinoma of the lung, gastric cancer, renal (clear cell) cancer, colon cancer, postradiotherapy in stage IIIA breast cancer, chronic spontaneous urticaria, botryomycosis, molluscum contagiosum, celiac disease, and ulcerative colitis. Some of the associations are based on single case reports and may be coincidental.

Table 255.1 Reported associations with eosinophilic cellulitis

Allergic asthma exacerbation
Allergic contact dermatitis (paraphenylenediamine [PPD] and black rubber in temporary henna tattoo)
Angioimmunoblastic lymphadenopathy
Chronic spontaneous urticaria
Churg–Strauss syndrome
Coeliac disease
Drugs (including vaccines, both those containing thimerosal and aluminum salts)
Hypereosinophilic syndrome
IgG4-related disease
Infections: bacterial, viral (HIV, herpes simplex, parvovirus, varicella, molluscum contagiosum, coxsackie), parasitic (<i>Ascaris</i> , toxocariasis, giardiasis), fungal (<i>Trichophyton</i>)
Insect bite reactions
Leukemia
Lymphoma
Metallic alloy implants
Radiotherapy
Solid cancers (lung, colon, gastric, renal)
Systemic lupus erythematosus
Ulcerative colitis

First-Line Therapy

- Oral corticosteroids

C

Recurrent granulomatous dermatitis with eosinophilia. Wells GC. *Trans St Johns Hosp Dermatol Soc* 1971; 57: 46–56.

Eosinophilic cellulitis. Wells GC, Smith NP. *Br J Dermatol* 1979; 100: 101–9.

The first publications by Wells on the disease. Oral prednisolone, ranging in doses of 20–40 mg/day, is a reasonable starting point, tapering the dose until control and hopefully resolution. One month of tapering prednisolone has been used successfully in patients.

Second-Line Therapies

- Cetirizine
- Levocetirizine/hydroxyzine
- Ciclosporin
- Dapsone
- Interferon- α
- Minocycline
- Sulfasalazine
- Griseofulvin
- Tacrolimus
- Adalimumab
- Omalizumab
- Mepolizumab

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Eosinophilic cellulitis in a child successfully treated with cetirizine. Aroni K, Aivaliotis M, Liossi A, et al. *Acta Derm Venereol* 1999; 79: 332.

Treatment of Wells syndrome in children with corticosteroids risks concerns regarding growth retardation, and the authors described a child successfully treated with cetirizine 10 mg daily.

Cetirizine 10–30 mg daily is a reasonable consideration in adults.

Eosinophilic cellulitis (Wells syndrome) successfully treated with low-dose ciclosporin. Herr H, Koh JK. *J Korean Med Sci* 2001; 16: 664–8.

A report of ciclosporin use in an adult with Wells syndrome; 2.5–5 mg/kg/day was used.

Successful treatment of eosinophilic cellulitis with dapsone. Coelho de Sousa V, Laureano Oliveira A, Cardoso J. *Dermatol Online J* 2016; 15: 22.

After multiple relapses following oral corticosteroids, treatment with single therapy with dapsone 50 mg resulted in disease clearance. Followed up to 1 year.

Doses of 50–150 mg/day would be an appropriate trial.

Interferon alfa treatment of a patient with eosinophilic cellulitis and HIV infection. Husak R, Goerdt S, Orfanos CE. *N Engl J Med* 1997; 337: 641–2.

Failure to control HIV-associated Wells syndrome with steroids prompted a successful trial of interferon- α treatment.

Eosinophilic cellulitis (Wells syndrome): treatment with minocycline. Stam-Westerveld EB, Daenen S, Van der Meer JB, et al. *Acta Derm Venereol* 1998; 78: 157.

Minocycline 200 mg daily was used to control disease, and 100 mg daily was used as maintenance.

Oral tacrolimus treatment for refractory eosinophilic cellulitis. Ohtsuka T. *Clin Exp Dermatol* 2009; 34: 597–8.

The author reports a case of eosinophilic cellulitis that had previously been responsive to oral corticosteroids (prednisolone 15 mg/day). The patient failed to respond to this treatment on recurrence and was successfully treated with oral tacrolimus (1 mg/day).

Wells syndrome mimicking facial cellulitis: a report of two cases. Cormerais M, Poizeau F, Darrieux L, et al. *Case Rep Dermatol* 2015; 9: 117–22.

The authors highlighted two patients who experienced no relapse during follow-up of between 3 and 12 months using levocetirizine 10 mg daily and hydroxyzine 50 mg daily.

Treatment of recalcitrant eosinophilic cellulitis with adalimumab. Sarin KY, Fiorentino D. *Arch Dermatol* 2012; 148: 990–2.

A 45-year-old woman with a 10-year history of Wells syndrome was unable to tolerate full-dose oral prednisolone and did not respond to systemic agents, including antihistamines, azathioprine, dapsone, and colchicine. The patient responded to fortnightly adalimumab.

Off-label use of TNF-alpha inhibitors in a dermatologic university department: retrospective evaluation of 118 patients. Sand FL, Thomsen SF. *Dermatol Ther* 2015; 28: 158–65.

The authors reported an elderly female patient with total clearance of disease on 6 months of adalimumab.

Wells syndrome and chronic spontaneous urticaria: report of four cases successfully treated with omalizumab. Ogueta I,

Spertino J, Deza G, et al. *J Eur Acad Dermatol Venereol* 2019; 33(10): e388–91.

The authors report on three female patients and one male patient with concomitant chronic spontaneous urticaria and Wells syndrome that achieved complete clearance of both diseases with omalizumab.

Eosinophilic cellulitis (Wells syndrome) successfully treated with mepolizumab. Herout S, Bauer WM, Schuster C, et al. *JAAD Case Rep* 2018; 4: 548–50.

A 33-year-old male patient with disease associated with bronchial asthma was successfully treated with mepolizumab after repeated flares on tapering of prednisolone.

Xanthomas

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Xanthomas are flat, yellow plaques or nodules consisting of abnormal lipid deposits. Clinically, xanthomas are classified as eruptive, tuberoeruptive, tuberous, tendinous, verruciform, or plane. Plane xanthomas are the most common and include xanthelasma palpebrarum, xanthoma striatum palmare, and intertriginous xanthomas. Verruciform xanthomas typically affect genital skin and may be a consequence of lymphedema. Necrobiotic xanthogranulomas are scarring, commonly ulcerated nodules with a predilection for the periorbital areas and are associated with paraproteinemia.

MANAGEMENT STRATEGY

Xanthomas may be idiopathic or a sign of underlying hyperlipidemia. Diagnosing and treating the underlying disease are necessary not only to decrease the size of the xanthomas but also to reduce the risk of atherosclerosis associated with lipoprotein disorders. Treatment of the hyperlipidemia initially consists of diet and lipid-lowering agents such as statins, fibrates, bile acid-binding resins, probucol, or nicotinic acid. The lipid-lowering effects of these agents have been well documented, but few studies document the efficacy of these drugs at resolving xanthomas. Anecdotally, eruptive xanthomas typically appear to resolve within weeks of initiating systemic treatment, and tuberous xanthomas after some months, but tendinous xanthomas may take years to resolve or even persist indefinitely. Surgery or locally destructive modalities are appropriate for idiopathic or unresponsive xanthomas.

Specific Investigations

- Serum lipid panel of cholesterol, triglycerides, VLDL, LDL, and HDL
- Gas-liquid and high-performance liquid chromatography to diagnose sitosterolemia
- Capillary gas chromatography of urine to diagnose cerebrotendinous xanthomatosis
- Serum protein electrophoresis, immunoelectrophoresis, or immunofixation to detect M proteins

Excluding an underlying condition is essential in the management of most clinical forms of xanthomas. Eruptive xanthomas typically occur in the setting of hypertriglyceridemia. Hypertriglyceridemia can be the result of lipoprotein lipase deficiency, familial hyperlipoproteinemia, or secondary causes such as diabetes mellitus, alcohol ingestion, or exogenous estrogens. Tuberoeruptive and tuberous xanthomas represent parts of a spectrum and are seen most commonly in the setting of familial dysbetalipoproteinemia. Tuberous xanthomas may also be a presentation of homozygous familial hypercholesterolemia, cerebrotendinous xanthomatosis (associated with neuropsychiatric symptoms), or sitosterolemia. Patients with sitosterolemia and cerebrotendinous xanthomatosis may have normal serum lipid panels; therefore, diagnosis may require liquid chromatography for plant sterols or urinary gas chromatography. Tendinous xanthomas may also occur with cerebrotendinous xanthomatosis, sitosterolemia, or, more commonly, heterozygous familial hypercholesterolemia. Certain xanthomas are diagnostic for an inherited hyperlipidemia: xanthoma striatum palmare for familial dysbetalipoproteinemia and intertriginous xanthoma for homozygous familial hypercholesterolemia. Even in the presence of these classic presentations, a serum lipid panel is still indicated to confirm the diagnosis.

Regarding xanthelasma palpebrarum, a type of plane xanthoma, levels of total cholesterol are elevated in only about half of patients; however, patients with xanthelasma may have elevated apolipoprotein B and decreased apolipoprotein A1 levels, as well as subclinical increases in carotid intima-media thickness. Moreover, xanthelasma is a risk factor for myocardial infarction, ischemic heart disease, severe atherosclerosis, and death, independently of plasma cholesterol and triglyceride concentrations. Less commonly, plane xanthomas can signal a monoclonal gammopathy. In this situation, the differential diagnosis of necrobiotic xanthogranuloma with paraproteinemia, a condition usually associated with lymphoproliferative disorders, should be considered.

First-Line Therapy

- Low-fat diet and systemic lipid-lowering therapy

B

Opposite effects on serum cholesteryl ester transfer protein levels between long-term treatments with pravastatin and probucol in patients with primary hypercholesterolemia. Inazu A, Koizumi J, Kajinami K, et al. *Atherosclerosis* 1999; 145: 405–13.

This prospective study examined whether pravastatin or probucol was better at regressing tendon xanthomas and xanthelasma in patients with primary hypercholesterolemia. In both groups,

xanthelasma regressed in two of four patients. Achilles tendon xanthoma regressed in four of five patients treated with pravastatin and two of five patients on probucol.

A comparative study of the therapeutic effect of probucol and pravastatin on xanthelasma. Fujita M, Shirai K. *J Dermatol* 1996; 23: 598–602.

Fifty-four patients were treated with probucol or pravastatin. Xanthelasmas regressed in 13 of 36 patients treated with probucol and in one of 18 patients treated with pravastatin.

Effects of probucol on xanthomata regression in familial hypercholesterolemia. Yamamoto A, Matsuzawa Y, Yokoyama S, et al. *Am J Cardiol* 1986; 57: H29–35.

Fifty-one patients, including eight homozygotes, received combinations of probucol, cholestyramine, clofibrate, and compactin. Achilles tendon xanthomas shrank in all patients who received probucol. Probucol possibly reduces the size of HDL particles, increasing reverse cholesterol transport.

Successful treatment of xanthoma disseminatum with combined lipid lowering agents. Kim WJ, Ko HC, Kim BS, et al. *Ann Dermatol* 2012; 24: 380–2.

Combination therapy with rosiglitazone 4 mg daily, simvastatin 10 mg daily, and fenofibrate 200 mg daily resulted in notable reduction of the skin lesions, maintained 2 years later.

Second-Line Therapies

• Surgery	B
• CO ₂ laser	B
• Pulsed dye laser	B
• Argon laser	B
• Erbium:YAG laser	C
• 1450-nm diode laser	C
• Low-voltage radiofrequency	C
• Q-switched Nd:YAG laser	D
• KTP laser	D

Treatment of xanthelasma by excision with secondary intention healing. Eedy DJ. *Clin Exp Dermatol* 1996; 21: 273–5.

Xanthelasmas were removed in 28 patients by scissor excision. After 18 months, two patients (one with hypercholesterolemia and one with primary biliary cirrhosis) had recurrence. One patient developed scarring. No ectropion developed.

Upper and lower eyelid reconstruction for severe disfiguring necrobiotic xanthogranuloma. Schaudig U, Al-Samir K. *Orbit* 2004; 23: 65–76.

Severe cicatricial eyelid deformation caused by necrobiotic xanthogranuloma can be treated successfully by excision and free skin grafting.

Successful treatment of scrotal verruciform xanthoma with shave debulking and fractionated carbon dioxide laser therapy. Joo J, Fung MA, Jagdeo J. *Dermatol Surg* 2014; 40: 214–7.

A patient received combined shave debulking and fractionated CO₂ laser ablation. No recurrence was noted at 18 months.

CO₂ laser treatment of xanthelasma palpebrarum in skin types III–IV: efficacy and complications after 9-month follow-up. Li D, Lin SB, Cheng B. *Photobiomodul Photomed Laser Surg* 2019; 37: 244–7.

Most studies of CO₂ laser therapy for xanthelasma have reported on White patients with skin types I–II. In this study of 38 treated Chinese patients (skin types III–IV), recurrence after CO₂ laser therapy occurred in half, especially in those with multiple lesions. At 3 months after treatment, complications occurred in 63%, mainly hypopigmentation that resolved at 9 months' follow-up; scarring occurred rarely.

Xanthelasma palpebrarum: treatment with the erbium:YAG laser. Borelli C, Kaudewitz P. *Lasers Surg Med* 2001; 29: 260–4.

Fifteen patients with 33 xanthelasmas were treated with an Er:YAG laser at settings of 300 mJ, 2 Hz for a 2-mm spot size and 1200 mJ, 6 Hz for a 10-mm spot size. All xanthelasmas were removed completely. Postoperative erythema resolved within 2 weeks. No scarring or ectropion developed. No lesions recurred over a 7- to 12-month follow-up period.

New operative technique for treatment of xanthelasma palpebrarum: laser-inverted resurfacing. Preliminary report. Levy JL, Trelles MA. *Ann Plast Surg* 2003; 50: 339–43.

The authors propose use of pulsed Er:YAG vaporization of the lipomatous tissue off the inner surface of the eyelid after incision and eversion of the incised tissue to expose the xanthelasma. In two patients treated by this technique, there was no recurrence in up to 1 year of follow-up.

Treatment of xanthelasma palpebrarum with a 1064-nm, Q-switched Nd:YAG laser. Heng JK, Chua SH, Goh CL, et al. *J Am Acad Dermatol* 2017; 77: 728–34.

In this retrospective review of 46 patients with 103 lesions of xanthelasma palpebrarum consecutively treated with Q-switched Nd:YAG laser, all lesions had excellent-to-complete clearance after at least four treatment sessions.

Is Q-switched neodymium-doped yttrium aluminium garnet laser an effective approach to treat xanthelasma palpebrarum? Results from a clinical study of 76 cases. Karsai S, Schmitt L, Raulin C. *Dermatol Surg* 2009; 35: 1962–9.

Most lesions failed to respond.

Treatment of xanthelasma palpebrarum with argon laser photocoagulation. Basar E, Oguz H, Oxdemir H, et al. *Int Ophthalmol* 2004; 25: 9–11.

In this study, 24 patients with 40 xanthelasmas were treated with an argon laser at settings of 500 nm, 0.1–0.2 seconds, and 900 mW. Complete removal of all lesions occurred with one to four sessions at intervals of 2–3 weeks. Six lesions recurred over 8–12 months and required retreatment. Erythema persisted for 1 month in eight lesions. Hyperpigmentation occurred in one patient and persisted for 3 months, whereas hypopigmentation occurred in two lesions.

Histopathological study of xanthelasma palpebrarum after pulsed dye laser. Soliman M. *J Eur Acad Dermatol Venereol* 2004; 18 (Suppl): 19–33.

Twenty-six patients were treated with fluences ranging from 6.5 to 8 J/cm², a spot size of 5 mm, and a pulse width of 450 ms. All experienced very good to excellent clinical improvement with one to three treatments at 3- or 4-week intervals.

KTP laser coagulation for xanthelasma palpebrarum. Berger C, Kopera D. *J Dtsch Dermatol Ges* 2005; 3: 775–9.

The authors employed the KTP laser (532 nm) to treat 14 patients. Over 70% tolerated laser irradiation without analgesia;

85.7% showed reduction of lesions after one to three treatment sessions, without reported side effects.

Xanthelasma palpebrarum treatment with a 1450-nm-diode laser. Park EJ, Youn SH, Cho EB, et al. *Dermatol Surg* 2011; 37: 791–6.

A group of 16 patients received one to four treatments using a 1450-nm diode laser at 12 J/cm², 6-mm spot size, and 20–30 ms; 12 patients experienced moderate to marked improvement. The patients tolerated the treatment well.

Effectiveness of low-voltage radiofrequency in the treatment of xanthelasma palpebrarum: a pilot study of 15 cases. Dincer D, Koc E, Erbil AH, et al. *Dermatol Surg* 2010; 36: 1973–8.

Fifteen patients received the superficial application of electrodes from a dual-frequency 4.0-MHz radiofrequency machine. Results were excellent in nine patients, and good in five.

Systematic review of laser therapy in xanthelasma palpebrarum. Nguyen AH, Vaudreuil AM, Huerter CJ. *Int J Dermatol* 2017; 56: e47–55.

This paper systematically reviews 21 studies of laser treatment for xanthelasma palpebrarum, including CO₂, yttrium aluminum garnet, pulsed dye, argon, and 1450-nm diode types. All these modalities provided moderate-to-excellent clearance rates and minimal side effects.

Third-Line Therapies

• Di- or trichloroacetic acid	C
• Cryotherapy	E
• Bleomycin	B
• Intralesional triamcinolone acetonide	D
• Chlorambucil	E
• Prednisolone	E
• Intravenous immunoglobulin	E
• Anakinra	E
• 2-Chlorodeoxyadenosine (cladribine)	E
• Topical imiquimod	E
• Bexarotene	E

Evaluation of three different strengths of trichloroacetic acid in xanthelasma palpebrarum. Haque MU, Ramesh V. *J Dermatolog Treat* 2006; 17: 48–50.

Three strengths of trichloroacetic acid (TCA) were tested on 51 patients. For papulonodular lesions, on average approximately two applications were required with 100% or 70% TCA versus approximately four applications with 50% TCA. For flat plaques an average of approximately 1.5 applications of 100% or 70% TCA sufficed vs. approximately three applications with 50% TCA. Macular lesions responded to a single application of all strengths of TCA studied.

Tolerability and effectiveness of liquid nitrogen spray cryotherapy with very short freeze times in the treatment of xanthelasma palpebrarum. Labandeira J, Vázquez-Osorio I, Figueroa-Silva O, et al. *Dermatol Ther* 2015; 28: 346–50.

Cryotherapy using liquid nitrogen is potentially effective but carries a risk of eyelid edema. The authors report on four patients who were effectively and safely treated with gentle liquid nitrogen spray cryotherapy for xanthelasma.

Treatment of xanthelasma palpebrarum with intralesional pingyangmycin. Wang H, Shi Y, Guan H, et al. *Dermatol Surg* 2016; 42: 368–76.

Twelve patients with xanthelasma palpebrarum had a total of 21 lesions injected with intralesional pingyangmycin (bleomycin A5). All patients except one received satisfactory results, and only one patient experienced a local recurrence, 1 year after treatment. There were no severe complications identified.

Intralesional injection of bleomycin in the treatment of xanthelasma palpebrarum: a clinical study. Lin X, Hu H, Qian Y, et al. *J Cosmet Dermatol* 2020 Jan 13. doi: 10.1111/jocd.13258.

Bleomycin was injected intralesionally into 44 xanthelasma lesions of 24 patients. All lesions resolved with good cosmetic outcome by 1 month after treatment; there were no adverse effects reported.

Local corticosteroid treatment of eyelid and orbital xanthogranuloma. Elner VM, Mintz R, Demirci H, et al. *Trans Am Ophthalmol Soc* 2005; 103: 69–73.

Six patients received two intralesional injections of triamcinolone acetonide (40 mg/mL) for eyelid and orbital necrobiotic xanthogranuloma (four patients) or adult-onset xanthogranuloma (two patients). Local control was obtained in all six cases with no complications noted.

Necrobiotic xanthogranuloma treated with chlorambucil. Torabian SZ, Fazel N, Knuttel R. *Dermatol Online J* 2006; 12: 11.

A 56-year-old man with a 5-year history of multiple necrobiotic xanthogranulomas involving the periorbital area, extremities, and trunk was treated with chlorambucil at 2 mg/day, later increased to 4 mg/day, which resulted in complete resolution of the lesions.

Necrobiotic xanthogranuloma of extremities in an elderly patient successfully treated with low-dose prednisolone. Kawakami Y, Yamamoto T. *Dermatol Online J* 2011; 17: 13.

A 93-year-old woman with an IgG-λ paraproteinemia and ulcerated, tender necrobiotic xanthogranulomas involving the left lower leg experienced resolution 4 weeks after starting treatment with oral prednisolone, 20 mg daily (0.5 mg/kg).

Successful treatment of necrobiotic xanthogranuloma with intravenous immunoglobulin. Hallermann C, Tittelbach J, Norgauer J, et al. *Arch Dermatol* 2010; 146: 957–60.

Two patients with necrobiotic xanthogranuloma and monoclonal gammopathy responded well to intravenous immunoglobulin, 0.5 g/kg/day, administered for 4 consecutive days at 4-week intervals.

Cerebral and cutaneous involvements of xanthoma disseminatum successfully treated with an interleukin-1 receptor antagonist: a case report and minireview. Campiero M, Campiero S, Guerrero J, et al. *Dermatology* 2016; 232: 171–6.

One patient with xanthoma disseminatum, including skin and brain lesions, received anakinra 100 mg subcutaneously daily, continued on a weekly dose for 2 years, and then as a monthly dose for 1 year. All skin lesions disappeared within 15 months, and there was a notable reduction in lesions of the brainstem, temporal lobes, and caudate nucleus; the patient remained asymptomatic at 5-year follow-up.

Xanthoma disseminatum: effective therapy with 2-chlorodeoxyadenosine in a case series. Khezri F, Gibson LE, Tefferi A. Arch Dermatol 2011; 147: 459–64.

Five patients received 2-chlorodeoxyadenosine at 0.14 mg/kg/day for 5 days, repeated monthly for 5–8 treatment cycles. After 3–5 cycles, new mucocutaneous lesions stopped developing in all patients, and all patients had substantial improvement in established lesions. There were no serious adverse effects reported. At follow-up ranging from 3 months to 8 years, all patients had achieved remission.

Successful treatment of verruciform xanthoma with imiquimod. Guo Y, Dang Y, Toyohara JP, et al. J Am Acad Dermatol 2013; 69: e184–6.

A 2-year-old girl with verruciform xanthoma on the vulva and around the anus received topical imiquimod cream 5% twice a week; the lesions almost entirely cleared 4 months later and remained in remission 9 months later.

Treatment of mycosis fungoides with bexarotene results in remission of diffuse plane xanthomas. Gregoriou S, Rigopoulos D, Stamou C, et al. J Cutan Med Surg 2013; 17: 52–4.

A patient with mycosis fungoides (MF) and plane xanthomas received bexarotene for MF. There was complete clinical remission of both the MF and the xanthomas after 6 months, and the patient remained free of xanthomas after 3 years.

Xeroderma pigmentosum

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Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder characterized by cellular hypersensitivity to the damaging effects of ultraviolet (UV) radiation, resulting in a 10,000-fold increased risk of sunlight-induced skin cancers that often develop in the first decade of life. About 50% of patients present with acute photosensitivity to minimal sun exposure, resulting in severe erythema and blistering. Burns can be so severe that child abuse is suspected. Most patients develop freckle-like pigmentation on sun-exposed skin before age 2 years, typically accompanied by dry skin (xeroderma), with 'aged' appearance, cheilitis, and photophobia. The eyes are particularly vulnerable, and damage may include dry eye, ectropion, pterygia, corneal clouding leading to blindness. Cancer occurs on sun-exposed sites including the lids, sclera, cornea, lips, and tip of the tongue. Approximately 25% of XP patients develop a progressive neurodegeneration with loss of deep tendon reflexes, progressive sensorineural hearing loss, dysphagia, and early death.

The progressive skin and eye damage is due to an inability to repair UV-induced DNA damage. Most XP patients have mutations in genes (*XPA*, *XPB*, *XPC*, *XPD*, *XPE*, *XPF*, or *XPG*) in the nucleotide excision repair (NER) pathway, which is critical for the removal, and repair of UV-induced DNA damage. XP 'variant' patients have mutations in DNA polymerase η , which bypasses unrepaired DNA damage.

MANAGEMENT STRATEGY

The diagnosis of XP is based on clinical features, and can be suspected in a child with a history of freckling on sun-exposed skin before age 2 years or severe sunburn after minimal sun exposure, photophobia, or cancer of the skin or eye. Once XP is suspected UV protection should be initiated immediately. Disorders that should be excluded include porphyria, lupus, LEOPARD syndrome, Carney complex, familial melanoma, and nevoid basal cell carcinoma syndrome.

DNA testing for mutations in several XP genes is available (www.genetests.org). Because mutation testing may not identify all XP gene mutations, failure to identify a mutation does not rule out the diagnosis of XP.

The most critical management goal for XP is ultraviolet (UV) protection. Utilizing multiple levels of protection provides security if one measure fails. Typical levels include management of environmental exposure, topical sun block agents, and physical barriers such as clothing, glasses, and face shields.

The major source of UV is the sun. Although window glass blocks most UVB wavelengths, UVA can pass through glass. Extremely sensitive XP patients have burned through window glass. The Americans with Disabilities Act mandates that children and adults with XP be provided safe educational and working environments. Windows in rooms where XP patients will be spending substantial amounts of time, such as at home, in a car, school, and work, should be shielded from UV radiation. This can be done with clear UV protective film or by creating a consistently safe distance from windows. Schools should make accommodations for XP students to stay indoors during fire drills and physical education activities. An Individualized Educational Plan should be developed to keep them protected from UV sources while encouraging interaction with other students.

Replacing unshielded fluorescent bulbs with light-emitting diode (LED) lights or placing plastic shielding over fluorescent bulbs can substantially reduce environmental UV exposure. Halogen lights emit substantial levels of UVB and should be avoided.

Although XP patients do not repair damage from UV exposure of tissues, they react normally to visible light. Because eradicating all exposure to UV radiation may not be attainable, efforts should be directed toward providing a safer environment. Environments with high UV levels, such as outdoors during daylight hours, require the most rigorous protection and sun avoidance. However, long periods of lower levels of exposure are also damaging. We can sense differences in the intensity of visible light, but not UV. Relatively inexpensive handheld UV meters can measure UVB and UVA and can be effective tools to guide activities. Medical care can be an unintended source of UV exposure such as from lights in waiting rooms, exam rooms, or surgical suites or during medical or dental procedures. Medical instruments such as dermatoscopes, ophthalmoscopes, and otoscopes should be assessed for UV levels. Replacing halogen bulbs with LED bulbs can substantially reduce UV levels.

Protective measures should be a daily routine. These include topically applied broad-spectrum sunblock preparations with an SPF (sun protection factor) of 30 or higher with protection against

both UVB (short-wavelength UV 290–320 nm) and UVA (long-wavelength UV 320–400 nm) and sun-protective lip balms and/or makeup. Daily sunblock applications should be applied to all exposed skin surface areas, and reapplied to uncovered skin (usually face, ears, neck, and hands) several times a day.

Clothing should cover as much skin surface as possible including long pants, long-sleeved shirts, socks with closed-toe shoes, hats that cover the ears, or UV-blocking face shields and hoods, and UV-blocking sunglasses with side shields. For daytime outdoor exposure gloves can be worn to protect hands. Clothing material should be tightly woven (e.g., denim) or double layered. A simple test of effective UV protection by clothing is to hold the material up to a bright light. Material that permits visible light to pass will not block UV. Commercially available clothing made from sun-blocking material is available. One alternative is a laundry additive called SunGuard, which is advertised to increase the ability of clothing to block UV.

XP patients should wear UV-blocking sunglasses. The glasses should 'wrap around' the eyes to protect the sides of the eyes and be large enough to fully protect both lids. Rigorous use of these measures should be initiated as soon as the diagnosis of XP is suspected to provide lifelong protection.

Medical alert bracelets (<http://www.medicalert.org/home/Homegradient.aspx>) and carrying an information card about XP can be helpful in emergencies when affected individuals may not be able to communicate their UV sensitivity.

Since vitamin D is produced in the skin by sun exposure, rigorous sun protection may lead to low levels of vitamin D in the blood and risk of bone fracture. Vitamin D-rich foods such as fish and vitamin D-supplemented milk can help maintain normal vitamin D levels along with oral supplementation and periodic monitoring of 25-hydroxyvitamin D levels in the blood.

XP patients should not use any type of tobacco product and should be protected from second-hand smoke. Carcinogens found in tobacco products induce DNA damage that is normally repaired by the NER pathway, putting the XP patient at high risk for oral and respiratory tract cancers.

The substantial *lifestyle adjustment* necessary to provide a safer UV environment can be a challenge for the family. Outdoor activities should be avoided during daylight hours, particularly between 10 a.m. and 2 p.m. Identifying appropriate indoor play and sports activities for the affected XP child, while continuing to meet the needs of the unaffected family members, can be difficult. *Emotional support* for the entire family is essential.

The need for frequent painful procedures and hospitalizations for more extensive surgeries can lead to posttraumatic stress disorder-type symptoms in some patients and families. It is important to consider pain management and stress reduction appropriate for the developmental level of the XP patient when planning care. The emotional and economic stability of the family is often affected and, as with any chronic illness, the family and patient will need to go through a period of adjustment to the lifestyle changes. Studies of XP patients in England found that families and patients who were able to incorporate the UV protective regimen into their normal routines were best able to effectively institute UV protection. In family situations with psychosocial pathologies (e.g., substance abuse or domestic violence), or if the family is having extreme difficulty coping with the diagnosis, referral to social services or a therapist may be advisable. The patients may be eligible for Social Security Disability Insurance or other medical assistance.

XP support groups help patients connect with other affected families and minimize social isolation; these groups also sponsor UV-safe family activities. These include the XP Family Support Group, <http://www.xpfamilysupport.org>; and the Xeroderma Pigmentosum Society, <http://www.xps.org> in the United

States; and the Xeroderma Pigmentosum Support Group UK, <http://xpsupportgroup.org.uk>. There are also support groups in Germany, Japan, and the Middle East.

Genetic considerations are important for XP management. XP is a recessive disorder, with probands having two mutated alleles, and clinically normal parents (heterozygotes) carrying one mutated allele. The risk of having another affected child is 1 in 4 for each subsequent pregnancy. *Prenatal diagnosis* may be possible, and consultation with a genetic counselor and Fetal Maternal Specialist can address genetic risks in future pregnancies.

Teaching patients and families to look for premalignant and malignant lesions can enable earlier identification and removal of small tumors. Depending on the rate of new tumor development, full skin examinations should be scheduled regularly (every 3–6 months). Baseline whole-body photographs and close-up photos of lesions with a ruler in the image for size comparison can help track changes. Digital images can be given to the family for use at home and also kept in the medical record.

Premalignant lesions including actinic keratoses can be treated with *cryotherapy*, *topical 5-fluorouracil (5-FU)*, or *topical imiquimod*. Care needs to be taken to ensure that existing skin cancers are adequately treated. When using topical 5-FU or imiquimod as field treatments there is a risk of treating the superficial areas of skin cancer but leaving deeper areas of tumor untreated. Well-controlled studies of topical field treatments in XP patients have not been published. Because of the known DNA damage produced by ultraviolet alone and with porphyrin, we would not recommend use of photodynamic treatment with daylight nor other light source.

Dermabrasion or *dermatome shaving* has been used to remove the superficial photodamaged epidermal layers. Theoretically, these procedures allow replacement of severely damaged epidermal cells with cells arising from the deeper, less UV-damaged adnexal structures. Newer techniques using *laser methodology for resurfacing* have also been used in a few XP patients. For patients developing many new lesions, chemoprevention with *oral retinoids* (isotretinoin or acitretin) has been used. A longitudinal study of a small number of XP patients performed at the National Institutes of Health found oral isotretinoin was effective in decreasing the number of new non-melanoma skin cancers. However, there were many side effects in these patients, especially at the higher drug dosages. Vismodegib (Erivedge) has also been used in a few XP patients who were experiencing multiple basal cell carcinomas. There was a good response while on treatment; however, this therapy is associated with multiple side effects. Early and adequate *treatment of skin cancers* is extremely important. All suspected tumors should be biopsied and removed. Standard techniques, including electrocautery and desiccation, surgical excision, or cryosurgical ablation, can be used for small superficial lesions. Due to the extensive poikilodermatous changes and scarring in XP patients, it can be difficult to differentiate recurrent from new lesions. Mohs micrographic surgery is optimal for combining effective tumor removal with tissue sparing. Several factors complicate skin cancer treatment in XP patients. Cancers may develop in a 'field' of extreme actinic damage, often with little normal-appearing skin either visibly or histologically. This complicates the goal of clear margins. A more practical goal would be a tumor-free margin. In addition, the quality of actinically damaged skin in XP differs from the non-XP skin cancer patient. The non-XP cancer patient typically has damage to both the epidermis and dermal connective tissue (collagen, elastic tissue, etc.) from high doses of UV exposure that result in lax, wrinkled skin. In contrast, damage in XP patients is caused by unrepaired DNA in the epidermis and the total dose of UV they have received is generally insufficient to cause typical solar elastosis, lax skin, and wrinkling. As a result they develop skin atrophy, with

very tight skin, which limits tissue movement for surgical repair. Movement of tissue with flaps can be complicated because of the presence of precancers or small skin cancers in the severely damaged surrounding skin. Skin cancer removal with minimal margins is also necessary to preserve tissue for future surgeries. Despite their hypersensitivity to UV, many XP patients have demonstrated a normal response to X-ray therapy when it is used to treat recurrent skin and eye cancers or brain and spinal cord neoplasms.

Recently, several case reports have been published on the use of PD-1 antibody chemotherapy for XP patients with widely metastatic melanoma. The patients' melanomas regressed with treatment as did many of their squamous cell carcinomas. Although the patients in the case reports did well with initial treatment, the papers did not report on long-term follow-up. This class of drugs can have very profound side effects including immune-mediated pneumonitis, nephritis, hepatitis, and immune-mediated dermatologic conditions including Stevens–Johnson syndrome. Long-term evaluations on XP patients have yet to be reported.

Several studies have noted that a few naturally occurring substances such as polypodium leucotomos, afamelanotide, and carotenoids may be useful as adjuvant therapies for lessening the effects of UVB exposure. However, none of these agents have been systematically studied in XP patients and should not be relied upon for UV protection.

XP patients have a substantially increased risk for developing cancers of the lips and squamous cell carcinoma of the tip of the tongue, and these areas should be regularly evaluated. Telangiectasia on the tip of the tongue is an early UV-induced change.

Ophthalmologic care is extremely important. Most ophthalmologic problems in XP patients occur in the anterior, UV-exposed surface structures of the eye and may begin in childhood as photophobia and conjunctivitis. Precancerous and cancerous lesions can arise on the cornea, sclera, lids, conjunctiva, and supporting tissues. UV damage on the cornea can lead to 'dry eye,' keratitis, and conjunctival inflammation. Ectropion of the lids, resulting in defects of eye closure, can occur secondary to eyelid atrophy and surgical removal of malignancies from the periocular skin. Ectropion exacerbates eye dryness and, if left untreated, can lead to corneal ulceration, scarring and opacification of the cornea, and blindness. Corneal transplants have been performed but frequently have led to rejection from vascularization of the area. A thorough ophthalmologic examination at least yearly can include the Schirmer test for dry eye and assessment of lid closure. Eye lubricants are recommended along with lubricating ointments at night, especially if lid closure is poor.

In the United States and Europe approximately 25% of XP patients develop progressive neurologic disease. The rate of symptom progression varies greatly among patients, with the most severe patients developing symptoms in early childhood (De Sanctis–Cachione syndrome). Routinely testing reflexes during skin examinations and performing annual audiograms can help identify XP patients at risk for neurologic disease. Loss of deep tendon reflexes, most notably in the lower extremities, may be the first manifestation of neurodegeneration and may be the only symptom for years. Some patients may have microcephaly. Progression includes hearing loss, cognitive decline, dysarthria, dysphagia, mobility difficulties with ataxia, and falls; eventually a wheelchair may be needed. Magnetic resonance imaging shows progressive dilation of the ventricles and loss of gray matter of the brain. Death may occur from aspiration pneumonia or other complications of severe debilitation. In a National Institutes of Health (NIH) study of 106 XP patients, the median age at death in XP patients with neurodegeneration (29 years) was significantly younger than those XP patients without neurodegeneration (37 years).

Progressive sensorineural hearing loss in XP patients may be diagnosed early, in the first decade of life, and may first be suspected secondary to inattentiveness in school. Audiology examinations provide a sensitive method for early detection. The hearing loss can be helped with hearing aids, and assisted hearing systems may be used in the classroom.

Some XP patients appear to have an increased risk for developing internal malignancies, including an approximately 50-fold increased risk of developing primary central nervous system tumors. These may respond to standard X-ray therapy with normal skin reaction. However, because some XP cell lines have increased sensitivity to X-radiation, a small test dose might be advised before full-dose exposure. In addition, XP patients have been reported with myelodysplasia, acute lymphoblastic leukemia, lymphoma, and thyroid cancer.

With improved healthcare and better protective measures, XP patients are living longer and more active lives, marrying, and having children. However, some adult women with XP, particularly those with mutations in the *XPC* gene, have developed premature menopause in their twenties and thirties. When a patient discusses contemplating a pregnancy, referral for preconceptual genetic counseling is recommended.

Optimal management of XP patients is a multidisciplinary process involving several medical specialties and active cooperation and input from the patient and family.

Specific Investigations

- Regular, frequent skin examination, which may include dermoscopy, to monitor for skin cancers
- Clinical photography
- High index of suspicion and low threshold for biopsy to identify possible skin cancers
- Regular examinations by ophthalmology, neurology, audiology, gynecology (for women)
- Regular overall history and physical examination for early detection of internal malignancy and thyroid abnormality (nodules, masses)
- Complete blood count
- DNA testing for XP gene mutations
- Exclusion of other photosensitive, pigmentary, or cancer-prone disorders (lupus, porphyria, LEOPARD syndrome, Carney complex, familial melanoma, nevroid basal cell carcinoma syndrome)

Total-body cutaneous examination, total-body photography, and dermoscopy in the care of a patient with xeroderma pigmentosum and multiple melanomas. Green WH, Wang SQ, Cognetta AB Jr. Arch Dermatol 2009; 145: 910–5.

Use of regular skin examination, photography, and dermoscopy in the management of one patient.

Unexpected extradermatological findings in 31 patients with xeroderma pigmentosum type C. Hadj-Rabia S, Oriot D, Soufir N, et al. Br J Dermatol 2013; 168: 1109–13.

Phenotypes of a group of *XP-C* patients in France with skin cancer and neoplasms of internal organs, short stature, and thyroid nodules.

Deep phenotyping of 89 xeroderma pigmentosum patients reveals unexpected heterogeneity dependent on the precise molecular defect. Fassihi H, Sethi M, Fawcett H, et al. Proc Natl Acad Sci USA 2016; 113: E1236–45.

Cancer and neurologic degeneration in xeroderma pigmentosum: long term follow-up characterises the role of DNA repair. Bradford PT, Goldstein AM, Tamura D, et al. *J Med Genet* 2011; 48: 168–76.

Shining a light on xeroderma pigmentosum. DiGiovanna JJ, Kraemer KH. *J Invest Dermatol* 2012; 132: 785–96.

A review of XP and the DNA repair disorders. Kraemer KH, DiGiovanna JJ, 2003 Jun 20 [Updated 2012 Mar 15]. In: Pagon RA, Bird TD, Dolan CR, et al., eds. *GeneReviews* [Internet]. Seattle, University of Washington, 1993; <http://www.genetests.org>.

Hereditary diseases of genome instability and DNA repair. Ruenger T, DiGiovanna JJ, Kraemer KH. In: Wolff K, Katz SI, Goldsmith L, et al., eds. *Fitzpatrick's Dermatology in General Medicine*, 8th ed. New York, McGraw-Hill, Ch. 139, 2012; 1654–71.

Ocular manifestations of xeroderma pigmentosum: long-term follow-up highlights the role of DNA repair in protection from sun damage. Brooks BP, Thompson AH, Bishop RJ, et al. *Ophthalmology* 2013; <https://doi.org/10.1016/j.ophtha.2012.12.044> [Epub ahead of print].

Auditory analysis of xeroderma pigmentosum 1971 to 2012: hearing function, sun sensitivity and DNA repair predict neurologic degeneration. Totonchy MB, Tamura D, Pantell MS, et al. *Brain* 2013; 136: 194–208.

Familial predisposition to TP53/complex karyotype MDS and leukemia in DNA repair-deficient xeroderma pigmentosum. Sarasin A, Quentin S, Droin N, et al. *Blood*. 2019; 133(25): 2718–24.

Predisposition to hematologic malignancies in patients with xeroderma pigmentosum. Oetjen KA, Levoska MA, Tamura D, et al. *Haematologica* 2019 Aug 22. pii: haematol.2019.223370. <https://doi.org/10.3324/haematol.2019.223370> [Epub ahead of print].

Hematologic neoplasms, including myelodysplastic syndrome, acute leukemias, and high grade lymphoma, have been found in XP patients with germline mutations in XPC.

Reproductive health in xeroderma pigmentosum: features of premature aging. Merideth M, Tamura D, Angra D, et al. *Obstet Gynecol* 2019; 134(4): 814–9.

Women with XP were found to have an increased incidence of premature menopause.

First-Line Therapies

- UV protection **C**
- Removal of skin cancers **C**
- Create active partnerships with patient/parents/family to facilitate frequent exams and procedures, and to minimize the stress and trauma related to anxiety and painful/disfiguring procedures. Have a multidisciplinary approach including access to therapists and social workers. Recognize early psychiatric symptoms such as depression **E**

Living with xeroderma pigmentosum: comprehensive photoprotection for highly photosensitive patients. Tamura D, DiGiovanna JJ, Khan SG, et al. *Photodermatol Photoimmunol Photomed* 2014; 30: 146–52.

Practical photoprotection for XP patients.

A patient's journey: xeroderma pigmentosum. Webb S. *BMJ* 2008; 336: 444–6.

Growing up in the hospital. Pao M, Ballard ED, Rosenstein DL. *JAMA* 2007; 297: 2752–5.

Cognitive, emotional, and social effects of childhood chronic conditions.

Psychological correlates of adherence to photoprotection in a rare disease: International survey of people with Xeroderma Pigmentosum. Walburn J, Canfield M, Norton S, Sainsbury K, et al. *Br J Health Psychol*. 2019; 24: 668–86.

Families and patients who were able to incorporate the UV protective regimen into their normal routines were best able to effectively institute UV protection.

Strict sun protection results in minimal skin changes in a patient with xeroderma pigmentosum and a novel c.2009delG mutation in XPD (ERCC2). Emmert S, Ueda T, Zumsteg U, et al. *Exp Dermatol* 2009; 18: 6468.

Strict UV protection in an XP child with neurologic degeneration. The UV protection did not affect the neurodegeneration; however, there were only very mild skin manifestations and no skin cancer.

Second-Line Therapies

- Topical imiquimod **B**
- Topical 5-fluorouracil **B**
- Oral retinoid therapy **C**

Therapeutic response of a brother and sister with xeroderma pigmentosum to imiquimod 5% cream. Weisberg NK, Varghese M. *Dermatol Surg* 2002; 28: 518–23.

Siblings with XP did not respond to oral retinoid chemoprophylaxis for multiple basal cell carcinomas. Topical imiquimod 5% cream resulted in reduction of rate of new tumor formation and resolution of basal cell carcinomas in both siblings. One sibling had a robust inflammatory response, and the other had little reaction.

5% 5-fluorouracil cream for the treatment of small superficial basal cell carcinoma: efficacy, tolerability, cosmetic outcome, and patient satisfaction. Gross K, Kircik L, Kricorian G. *Dermatol Surg* 2007; 33: 433–9.

Evaluated the efficacy, tolerability, cosmetic outcome, and patient satisfaction of topical 5% FU for superficial basal cell carcinomas in 29 non-XP patients. Histologic cure rate was 90%, and patients were satisfied with the treatment.

Prevention of skin cancer in xeroderma pigmentosum with the use of oral isotretinoin. Kraemer KH, DiGiovanna JJ, Moshell AN, et al. *N Engl J Med* 1988; 318: 1633–7.

Five XP patients were treated for 2 years with high-dose (2 mg/kg/day) isotretinoin. The patients had a total of 121 tumors before treatment, and only 25 tumors occurred during treatment.

The tumor frequency increased after the drug was discontinued. There were significant side effects including cutaneous, triglyceride, liver function, or skeletal problems.

Xeroderma pigmentosum: spinal cord astrocytoma with 9-year survival after radiation and isotretinoin therapy. DiGiovanna JJ, Patronas N, Katz D, et al. *J Cutan Med Surg* 1998; 2: 153–8.

XP patient received radiation therapy for a spinal cord astrocytoma with normal cutaneous response to standard dosages.

Topical imiquimod or fluorouracil therapy for basal and squamous cell carcinoma: a systematic review. Love WE, Bernhard JD, Bordeaux JS. *Arch Dermatol* 2009; 145: 1431–8.

Systematic review of topical imiquimod or FU therapy in the treatment of basal cell and squamous cell carcinomas in the general population. Includes a case report of an XP patient who had multiple skin grafts and experienced tumor recurrence, which originated under the skin graft.

Third-Line Therapy

- Resurfacing: dermabrasion and chemical peels

E

The role of dermabrasion and chemical peels in the treatment of patients with xeroderma pigmentosum. Nelson BR, Fader DJ, Gillard M, et al. *J Am Acad Dermatol* 1995; 32: 623–6.

Two XP patients treated periodically with trichloroacetic acid chemical peels; one also underwent dermabrasion. Both procedures provided some prophylactic effects.

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Xerosis

Ian H. Coulson



Xerosis is the term used to describe a condition where there is a rough, dry, textural feel to the skin, accompanied by fine scaling and sometimes fine fissuring. Increasing xerosis is usually accompanied by increasing itch. It may result from a combination of environmental conditions (low humidity, degreasing of the skin by excessive bathing, soap, or detergent use); genetic disorders of keratinization (ichthyoses); atopic eczema (where it may be a manifestation of a filaggrin mutation); endocrine disease states (hypothyroidism); diabetes mellitus (39% of patients); and a host of underlying disease states such as chronic renal failure, liver disease (including 69% of patients with primary biliary cirrhosis), malnutrition, anorexia nervosa (58% of patients), essential fatty acid and vitamin A deficiency, Sjögren syndrome (56% of patients), HIV infection, lymphoma (where it may result in an acquired ichthyosis), and carcinomatosis (especially hematologic). It is common in the elderly. Drugs (retinoids, statins, and targeted chemotherapeutic agents such as epidermal growth factor receptor [EGFR] and BRAF inhibitors) are increasingly implicated. It is reported to be more frequent in the winter. It may be generalized, or localized (particularly the feet).

MANAGEMENT STRATEGY

Initial evaluation should seek to distinguish simple xerosis from a genetic ichthyosis, although management is similar for both conditions. Family history, distribution, and morphology will help to differentiate the two. A history of weight loss, diarrhea, dietary history, and body mass index may give clues toward an underlying metabolic or malabsorptive disorder. Dry eyes and mouth may indicate underlying Sjögren syndrome. History and clinical examination should seek symptoms and signs of hypothyroidism, diabetes mellitus, and chronic renal disease. Drug use and sexual contact history may reveal HIV infection. Xerosis is an almost universal accompaniment of atopic eczema.

The mainstay of therapy for xerosis after any underlying disorders (if possible) are corrected is *improvement of the humidity* in the patient's environment, *avoidance of exacerbating factors* such as soap and detergents, and the use of *emollients or humectants*.

Low environmental humidity both at home and work will exacerbate xerosis of any cause. Arid air is a problem in air-conditioned homes, offices, and vehicles. Hot, dry air directed to the lower legs during the winter in the front of automobiles is a common cause of lower leg xerosis. In the home or workplace, humidifiers can be fitted over radiators; alternatively, placing wet towels or containers of water over them will increase air humidity.

Soaps and detergents degrease the skin, reduce epidermal thickness, and increase scale and itch, and so are best avoided, and light emollient cleansers (soap substitutes) are suggested in their place. Bathing in tepid water is often preferred by patients, and patting the skin dry will produce less scale and dryness than vigorous toweling.

Emollients (which simply produce an impervious film over the epidermis and prevent 'transpiration') and humectants (such as lactic acid, urea, or glycerin that hold water in the epidermis osmotically) are the mainstays of therapy. Few good comparative studies exist for the most common type of xerosis, which is surprising because they are the most frequently used dermatologic products; indeed, a large review failed to justify recommendation of one constituent over another for foot xerosis. They should be used liberally and as frequently as possible and applied in the direction of hair growth; emollients are particularly valuable after bathing or showering to hold water in the epidermis. Light emollients for use in the shower or bath may be preferred to *bath oils* by some. Choice of emollient is entirely personal to the patient. A pack with small amounts of a variety of products for home trial or a self-selection 'tub tray' for the clinic is likely to enhance compliance. The best emollient is the one the patient likes; the most expensive is the one where 99% remains in the tub!

Agents containing *α-hydroxy acids (AHAs)* and *ceramides* may offer some advantages over conventional paraffin-based emollients, but this may be at the expense of irritation in some people. Low-concentration *salicylic acid* may help reduce scale in more severe xerosis, but it is essential to remember that systemic absorption and salicylism can occur.

Topical retinoids have only been used in the more severe ichthyoses and are too irritating for use in xerosis. Systemic therapies have little part to play in most patients.

Specific Investigations

If indicated by history or symptoms:

- Thyroid function tests
- Renal function tests
- Random glucose
- Consider tests for Sjögren syndrome, HIV infection, malignancies, and malabsorption, if clinically indicated
- Drug history

Sjögren's syndrome: a retrospective review of the cutaneous features of 93 patients by the Italian Group of Immunodermatology. Bernacchi E, Amato L, Parodi A, et al. Clin Exp Rheumatol 2004; 22: 55–62.

Over half of 93 patients with Sjögren syndrome had xerosis, and its presence correlated with the presence of SSA and SSB antibodies.

HIV-associated pruritus: etiology and management. Singh F, Rudikoff D. *Am J Clin Dermatol* 2003; 4: 177–88.

Xerosis is one of the more common causes of itch in HIV infection and AIDS.

Noninfectious skin conditions associated with diabetes mellitus: a prospective study of 308 cases. Diris N, Colomb M, Leymarie F, et al. *Ann Dermatol Venereol* 2003; 130: 1009–14.

Xerosis was noted in 39% of 309 patients.

Eating disorders and the skin. Strumia R. *Clin Dermatol* 2013; 31: 80–5.

Xerosis is a common feature of anorexia.

Xerosis from lithium carbonate. Hoxtell E, Dahl MV. *Arch Dermatol* 1975; 111: 1073–4.

Incidence and risk of xerosis with targeted anticancer therapies. Valentine J, Belum VR, Duran J, et al. *J Am Acad Dermatol* 2015; 72: 656–72.

About 20% of patients receiving targeted therapies develop significant xerosis.

Litt's Drug Eruption Reference and Database lists in excess of 150 drugs (from acebutolol to zonisamide) that have been implicated in causing xerosis. Retinoids, cimetidine, protease inhibitors, statins, and nicotinamide are perhaps the best known. Epidermal growth factors and targeted chemotherapy agents are new agents that have xerosis among their protean dermatologic side effects.

First-Line Therapies

• Soap avoidance	A
• Humidification	C
• Emollients	B
• Bath oils	B

Moisturizers are effective in the treatment of xerosis irrespective of their particular formulation: results from a prospective, randomized, double-blind controlled trial. Shim JH, Park JH, Lee J, et al. *J Eur Acad Dermatol Venereol* 2016; 30: 276–81.

A double-blind trial evaluating the effect of four conventional popular emollients, as well as a new cream containing recombinant epidermal growth factor and its control vehicle. All the evaluated agents improved the clinical symptoms of xerosis. Consistent and regular moisturization was more important than the emollients' particular formulation. This reinforces the dogma that the best emollient is the one the patient likes and uses.

Emollients improve treatment results with topical corticosteroids in childhood atopic dermatitis: a randomized comparative study. Szczepanowska J, Reich A, Szepietowski JC. *Pediatr Allergy Immunol* 2008; 19: 614–8.

In a study of 52 children with atopic dermatitis, those applying emollients concurrently with topical corticosteroids had significantly improved xerosis.

How useful are soap substitutes? Berth-Jones J, Graham-Brown RAC. *J Dermatol Treat* 1992; 3: 9–11.

Thirty-eight subjects with atopic dermatitis, psoriasis, or senile xerosis were treated with emulsifying ointment BP or Wash E45 as soap substitutes. Dryness and itching improved in both groups. Wash E45 was considered more effective as a cleanser.

Numerous soap substitutes, available around the world, can benefit patients with xerosis.

The value of oil baths for adjuvant basic therapy of inflammatory dermatoses with dry, barrier-disrupted skin. Melnik B, Braun-Falco O. *Hautarzt* 1996; 47: 665–72. [German.]

The use of oil baths with emollients is an integral and indispensable constituent of maintenance therapy in dry skin conditions, atopic eczema, and inflammatory dermatoses.

Moisturisers for the treatment of foot xerosis: a systematic review. Parker J, Scharfbillig R, Jones S. *J Foot Ankle Res*. 2017; 7:10:9.

Poor quality studies preclude recommendation of any one active ingredient over another!

Second-Line Therapies

• Urea-containing creams	A
• Lactic acid-containing creams	A
• Ammonium lactate creams	A
• Colloidal oatmeal	A
• AHA creams	B
• Thyroxine cream	D
• Glycerol containing creams	B
• Ceramide containing creams	C
• Dilinoleic acid-containing creams	C

A double-blind comparison of two creams containing urea as the active ingredient. Assessment of efficacy and side effects by noninvasive techniques and a clinical scoring scheme. Serup J. *Acta Derm Venereol* 1992; 177: 34–43.

A comparison of 3% and 10% urea cream showed that both were effective at reducing scale, dryness, and laboratory parameters (transepidermal water loss and colorimetric changes). The 10% cream was better at restoring the skin's water barrier function.

Clinical evaluation of 40% urea and 12% ammonium lactate in the treatment of xerosis. Ademola J, Frazier C, Kim SJ, et al. *Am J Clin Dermatol* 2002; 3: 217–22.

A double-blind study comparing 40% urea cream with 12% ammonium lactate cream showing superiority of the urea cream. Flexural irritation was a problem.

Many urea-containing products contain lower concentrations than those used in this study.

Use of a urea, arginine and carnosine cream versus a standard emollient glycerol cream for treatment of severe xerosis of the feet in patients with type 2 diabetes: a randomized, 8 month, assessor-blinded, controlled trial. Federici A, Federici G, Milani M. *Curr Med Res Opin* 2015; 31: 1063–9.

Fifty diabetics with severe foot xerosis fared better with the combination cream in comparison to a simple glycerine-containing emollient.

A controlled two-center study of lactate 12 percent lotion and a petrolatum-based creme in patients with xerosis. Wehr R, Krochmal L, Bagatell F, et al. *Cutis* 1986; 37: 205–7.

Lactate lotion 12% was significantly more effective than a petrolatum-based cream in reducing the severity of xerosis during treatment and posttreatment phases.

A double-blind clinical trial comparing the efficacy and safety of pure lanolin versus ammonium lactate 12% cream for the treatment of moderate to severe foot xerosis. Jennings MB, Alfieri DM, Parker ER, et al. *Cutis* 2003; 71: 78–82.

A study showing equivalence of a petrolatum compound and 12% ammonium lactate cream for foot xerosis.

A randomized controlled clinical study to evaluate the effectiveness of an active moisturizing lotion with colloidal oatmeal skin protectant versus its vehicle for the relief of xerosis. Kalaaji AN, Wallo W. *J Drugs Dermatol* 2014; 13: 1265–8.

A randomized, double-blind, controlled clinical study to objectively compare a commercially available moisturizing product against its own vehicle. The active colloidal oatmeal moisturizer used in this study showed significant benefits versus its vehicle control in several dermatologic parameters used to measure skin dryness.

An evaluation of the effect of an alpha hydroxy acid-blend skin cream in the cosmetic improvement of symptoms of moderate to severe xerosis, epidermolytic hyperkeratosis, and ichthyosis. Kempers S, Katz HI, Wildnauer R, et al. *Cutis* 1998; 61: 347–50.

Twenty subjects completed a course of treatment with either regular or extra-strength AHA-blend cream on a test site compared with a currently marketed, non-AHA moisturizing lotion on a control site. Improvements were significant compared with baseline and compared with sites treated with the control lotion, but the AHA cream did cause some local mild-to-moderate adverse effects; all subjects were able to continue using the test product for the duration of the study.

Randomized, double-blind study with glycerol and paraffin in uremic xerosis. Balaskas E, Szepietowski JC, Bessis D, et al. *Clin J Am Soc Nephrol* 2011; 6: 748–52.

An emollient containing glycerol and paraffin compared side to side with an emulsion devoid of these agents. The active treatment helped reduce the physical signs of xerosis as well as the pruritus.

The benefit of a ceramide-linoleic acid-containing moisturizer as an adjunctive therapy for a set of xerotic dermatoses. Yang Q, Liu M, Li X, et al. *Dermatol Ther.* 2019; 32: e13047.

Use of this emollient with a potent steroid improved winter itch and atopic eczema, but not chronic eczema.

Efficacy of an emollient containing diethylene glycol/dilinoleic acid copolymer for the treatment of dry skin and pruritus in patients with senile xerosis. Izumi R, Negi O, Suzuki T, et al. *J Cosmet Dermatol* 2017; 16: e37–41.

A comparison of 10% and 20% DG/DLA against white petrolatum: 20% active therapy produced a rapid reduction of dry skin, excoriations, and itch in senile xerosis.

Effectiveness of topical chia seed oil on pruritus of end-stage renal disease (ESRD) patients and healthy volunteers. Jeong SK, Park HJ, Park BD, et al. *Ann Dermatol* 2010; 22: 143–8.

A small study demonstrating effectiveness using this *n*-3 fatty acid-containing oil in normal people and renal failure sufferers with xerosis.

Yellow nail syndrome

Robert Baran, Stéphane Vignes



Yellow nails are the main clinical manifestation (88% of cases) leading to yellow nail syndrome (YNS) diagnosis. Xanthonychia is unsightly and varies from pale yellow to a more or less dark and greenish color. The nail plate becomes thickened with enhanced transverse over-curvature, sometimes with a notable hump cross-riding and a hard and difficult-to-trim nail plate. The cuticle may disappear, leading to erythema of the proximal nailfold causing a chronic paronychia. The nail grows half as fast and twice as thick. The color of the nail is due to lipofuscin, a pigment arisen from colorless lipid precursors and transformed by oxidation in tissue to produce varying degrees of yellow.

Contrasting with the xanthonychia belonging to YNS, which may improve without specific therapies in about one-half of patients (but may relapse), the other varieties of yellow nails are transient.

Lymphedema is observed in approximately 40% of cases and involves mainly the lower limbs. The most distal body parts are always more severely affected than proximal parts. Stemmer sign, which shows the inability to pinch the skin on the dorsal side or the base of the second toe, is pathognomonic. The face is rarely, and the eyelids are exceptionally, affected.

Respiratory disorders are observed in roughly 50% of patients; the most common respiratory manifestations of YNS are, in descending order, chronic cough, bronchiectasis, recurrent pneumonia, and restrictive lung disease (mainly due to the presence of a pleural effusion).

Specific Investigations

- Rule out nail fungal or *Pseudomonas* infection
- Complete blood count
- Urinalysis and evaluation of proteinuria
- Immunoelectrophoresis
- Thyroid stimulating hormone
- Waaler–Rose test for serum rheumatoid factors
- Chemistry profile with blood creatinine
- Sinus and chest radiography
- Cone beam computed tomography
- Ear, nose, and throat, and pulmonary investigations
- Liver enzymes, alkaline phosphatases
- Exposure to titanium dioxide:
 - Foods such as candy, chewing-gum, and chocolate
 - Personal care items, such as shampoo, sunscreen, and toothpaste
 - Drugs such as multivitamins
- Search for titanium dioxide in the nail

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Role of titanium in the development of YNS. Decker A, Doly D, Scher RK. *Skin Appendage Disord* 2015; 1: 28–30.

Titanium, sinusitis and the YNS. Berglund F, Cazlmark B. *Biol Trace Elem Res* 2011; 143: 1–7.

MANAGEMENT STRATEGY

Systemic drugs such as bucillamine, gold, methotrexate, penicillamine, and tiopronin possibly are associated with YNS and consequently prohibited, as well as exposure to titanium dioxide (found in foods, personal care items, medications, dental and surgical devices), which is detectable in the nails.

Association with a paraneoplastic disease is still controversial and some consider it to be a coincidental event. The YNS-to-cancer diagnosis interval ranges from days to years, with gradual development of the complete YNS triad. Various types of cancers have been associated with YNS (Box 259.1).

First-Line Therapies

- Fluconazole 300 mg once weekly + α -tocopherol 1000
- Long-term clarithromycin 300–400 mg daily

Combination of fluconazole and α -tocopherol in the treatment of yellow-nail syndrome. Baran R, Thomas L. *J Drugs Dermatol* 2009; 8: 276–8.

Daily treatment with 500 mg oral vitamin E morning and evening associated with weekly 300 mg fluconazole as long as needed.

Box 259.1 Malignancies associated with YNS

- Breast
- Bronchial
- Endometrium
- Gallbladder
- Larynx
- Melanoma
- Multiple myeloma after hematopoietic stem-cell transplantation
- Non-Hodgkin lymphoma
- Renal

Effectiveness of clarithromycin in patients with yellow nail syndrome. Matsubayashi S, Suzuki M, Suzuki T, et al. *BMC Pulm Med* 2018; 18(1): 138.

Five patients with YNS responded to oral clarithromycin 400–600 mg daily. Long-term treatment with 400 mg daily was recommended and time to nail improvement ranged from one month to 2.5 years.

Second-Line Therapies

- Fluconazole 300 mg once weekly + triamcinolone acetonide intralesional monthly injections in the fingernail units
- Long-term clarithromycin 300–400 mg daily + IL triamcinolone acetonide
- Vaccination against flu and pneumococci
- Physiotherapy

Dramatic improvement of yellow nail syndrome with a combination of intralesional triamcinolone, fluconazole and sinusitis management. Imadojemu S, Rubin A. *Int J Dermatol* 2015; 54: e497–9.

A 64-year-old man with YNS was treated with intralesional triamcinolone acetonide 5 mg/cc 0.1–0.2 cc monthly for 18 months. After 10 months, fluconazole 300 mg weekly was added, and nails improved dramatically.

Syndrôme des ongles jaunes d'évolution favorable: rôle de la kinesithérapie respiratoire. Fournier C, Just N, Leroy S, et al. *Rev Mal Resp* 2003; 20: 969–72.

In addition to the nail manifestations, the patient presented with bilateral bronchiectasis. Daily physiotherapy with bronchial

drainage led to a progressive improvement in the respiratory signs. The nail abnormalities disappeared after 2 years of treatment.

Improvement in lymphatic function and partial resolution of nails, after complex decongestive physiotherapy in yellow nail syndrome. Szolnok G, Lakatos B, Husz S, et al. *Int J Dermatol* 2005; 44: 501–3.

Manual lymphatic drainage was performed on each leg for 45 minutes, and multi-layered compression bandaging was subsequently applied. This was repeated daily for 2 weeks, except at weekends, when the compression was not accompanied by massage. The edema reduction and the increase of lymph flow were associated with an improvement in the appearance of the toenail plates. Fingernails failed to show any change.

Third-Line Therapies

- Oral zinc supplementation
- Octreotide 30 mg once per month or lanreotide
- Low-fat diet supplemented with medium-chain triglycerides

Improvement of yellow nail syndrome with oral zinc supplementation. Arroyo JF, Cohen ML. *Clin Exp Dermatol* 1993; 18: 62–4.

Total resolution of yellow nails and lymphedema was observed after oral zinc supplementation for 2 years.

Doses of zinc 300 mg daily have been used.

Yellow nail syndrome in a 10-year-old girl. Göçmen A, Küçükosmanoğlu O, Kiper N, et al. *J Pediatr* 1997; 39: 105–9.

Low-fat diet supplemented with medium-chain triglycerides brought moderate improvement in the lymphedema of the lower extremities.

Yellow nail syndrome: report of a case successfully treated with octreotide. Lotfollahi I, Abedini A, Alavi Darazam I, et al. *Tanaffos* 2015; 14: 67–71.

In this case, dyspnea was associated with pleural effusion and yellow nails. Pulmonary symptoms and X-ray changes resolved 3 months after IV octreotide 100 mcg TD for 3 days, 50 mcg TD for 1 week, and 50 mcg daily for 3 weeks. The report does not mention resolution of nail changes.