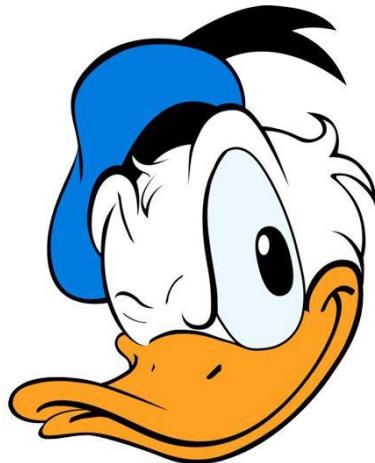


DERMATOLOGY

CME

2020





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Sexually acquired syphilis

Historical aspects, microbiology, epidemiology, and clinical manifestations

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Learning objectives

After completing this learning activity, participants should be able to review pertinent history, pathophysiology and clinical manifestations of infection with *T pallidum* and describe emerging epidemiologic trends.

Disclosures

Editors

The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

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Syphilis is caused by infection with the spirochetal bacterium *Treponema pallidum* subsp. *pallidum*. It was first recognized in the late 15th century. Since 2000, the incidence of sexually acquired syphilis has increased substantially in the developed world, with men who have sex with men and persons living with HIV infection disproportionately affected. Clinical manifestations of syphilis are protean and often include mucocutaneous manifestations. The first article in this continuing medical education series reviews historical aspects, microbiology, epidemiology, and clinical manifestations of sexually acquired syphilis. (J Am Acad Dermatol 2020;82:1-14.)

Key words: dermatology; sexually transmitted disease; syphilis.

INTRODUCTION

Key points

- Syphilis is caused by the spirochete *Treponema pallidum* subsp. *pallidum*
- The incidence of syphilis is increasing worldwide

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Abbreviations used:

CDC: Centers for Disease Control and Prevention
MSM: men who have sex with men



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- **Stages of syphilis infection include primary, secondary, early nonprimary nonsecondary, and unknown duration or late syphilis**

Syphilis is an infection caused by the spirochete *Treponema pallidum* subsp. *pallidum*. First described in the late 15th century, syphilis has been a frequent—and often controversial—topic in medicine, public health, and social commentary. Because its protean clinical manifestations can mimic other diseases, syphilis has been called “the great imitator.” “He who knows syphilis,” Sir William Osler famously said, “knows medicine.”

Since 2000, the incidence of syphilis has increased in the United States.¹ Because syphilis has prominent mucocutaneous manifestations, dermatologists can play important roles in both diagnosis and management. The first article in this continuing medical education series covers historical aspects, microbiology, epidemiology, and clinical manifestations of acquired syphilis in adults. The second article in this series addresses testing and management of syphilis. Multiple organizations have released guidelines for syphilis management. In this continuing medical education series we cite guidelines from the U.S. Centers for Disease Control and Prevention (CDC). Although congenital syphilis is an increasingly important issue, it is not covered here.

History

The origins of syphilis remain controversial. It was first reported in the Old World in the 1490s, when Italian physicians described a new disease affecting invading French soldiers. The “Columbian hypothesis” holds that syphilis was a New World disease brought to the Old World in 1493 by Columbus’s returning seamen. Competing hypotheses include the “pre-Columbian hypothesis,” which postulates that syphilis existed in both the Old and New Worlds before Columbus’s voyage, and the “evolutionary/Unitarian hypothesis,” which theorizes that treponemal diseases were distributed worldwide, with different treponemes affecting different populations.^{2,3}

Syphilis spread quickly across Europe. It was initially a virulent disease, called “the Great Pox,” characterized by large, painful, foul-smelling sores and significant mortality.³ Within about 50 years, however, it began presenting more mildly. That evolution may have been the result of natural selection for less virulent strains because more virulent strains caused disease that was debilitating to the infected and obvious to potential sexual partners.⁴

The name syphilis comes from a poem written by Girolamo Fracastoro in 1530 in which a shepherd

named Syphilus angers the god Apollo, who curses the population with a disease bearing the shepherd’s name.^{5,6} Syphilis is also called *lues*, from the Latin word for plague.⁷

Pre-penicillin era treatments included purgative agents, heat, and pyrogens. Mercury was used widely in topical salves, oral compounds, injections, and fumigation. Treatment could last for years, giving rise to the saying, “A night with Venus, and a lifetime with mercury.”⁸

Nobel Prizes in Physiology or Medicine were twice awarded for syphilis treatments. Dr Paul Ehrlich received one in 1908 for discovering arsphenamine, an arsenical compound called “the magic bullet.”⁵ The second went to Dr Julius Wagner-Jauregg in 1927 for developing malariotherapy to treat neurosyphilis. Malariotherapy rested on the belief that fevers induced by inoculating patients with *Plasmodium vivax* killed heat-sensitive *T. pallidum* bacteria. Notably, about 15% of patients undergoing malariotherapy died.⁹

Penicillin was reported as an effective treatment for syphilis in 1943 and remains the recommended therapy, with no known resistant cases.¹⁰

Microbiology and transmission

T. pallidum subsp. *pallidum* is a slow-growing, motile spirochete bacterium with a long spiral shape. Humans are its only natural host and it cannot be cultured in vitro. It is closely related (>99% DNA homology) to other pathogenic treponemes, including *Treponema pallidum* subsp. *pertenue*, which causes yaws; *Treponema carateum*, which causes pinta; and *Treponema pallidum* subsp. *endemicum*, which causes endemic syphilis or bejel.¹¹

Sexual acquisition of syphilis occurs when an infectious lesion (chancre, mucous patch, or condyloma lata) contacts the skin or mucous membrane of an uninfected person, often (but not exclusively) during oral, vaginal, or anal sex. The risk of transmission after sexual exposure is estimated at approximately 33%.¹² Bloodborne and in utero transmission can also occur.

Epidemiology

Public health practitioners typically focus on the epidemiology of primary and secondary syphilis because those stages of syphilis are infectious and represent a barometer of infectivity in a population. Here we present case counts (with incidence in parentheses, expressed as cases per 100,000 population per year) for primary and secondary syphilis in the United States.

Table I. Case definitions for syphilis stages from the U.S. Centers for Disease Control and Prevention

Stage	Clinical description	Laboratory criteria for diagnosis	Case classification
Primary	≥ 1 chancre(s)	Confirmatory: demonstration of <i>Treponema pallidum</i> by darkfield microscopy* OR by PCR [†] Supportive: a reactive nontreponemal test [‡] OR reactive treponemal test [§]	Probable: meets clinical description and supportive laboratory criteria Confirmed: meets clinical description and confirmatory laboratory criteria
Secondary	Localized or diffuse mucocutaneous lesions, often with generalized lymphadenopathy; chancre(s) may still be present	Confirmatory: demonstration of <i>T pallidum</i> by darkfield microscopy* OR by PCR [†] Supportive: a reactive nontreponemal test [‡] AND reactive treponemal test [§]	Probable: meets clinical description and supportive laboratory criteria Confirmed: meets clinical description and confirmatory laboratory criteria
Early nonprimary nonsecondary	Infection within previous 12 months, but no signs or symptoms of primary or secondary syphilis	Supportive: current nontreponemal test [‡] titer with fourfold or greater increase from last titer	Probable: no signs or symptoms of primary or secondary syphilis with 1 of the following: <ul style="list-style-type: none">• No history of syphilis AND a current reactive nontreponemal test[‡] AND a current reactive treponemal test[§] OR• History of syphilis and meets supportive laboratory criteria AND evidence of having acquired syphilis within previous 12 months[¶]
Unknown duration or late	Infection occurred >12 months previously, or insufficient evidence to conclude that infection was acquired during previous 12 months	None	Probable: no clinical signs or symptoms of primary or secondary syphilis with 1 of the following: <ul style="list-style-type: none">• No history of syphilis and a current reactive nontreponemal test and a current reactive treponemal test OR• History of syphilis and a current nontreponemal test titer demonstrating fourfold or greater increase from last titer OR• Signs or symptoms and laboratory results that meet criteria for neurologic, ocular, otic, or late clinical manifestations of syphilis[#] AND no evidence of having acquired syphilis within preceding 12 months[¶]

*On a clinical specimen not obtained from the oropharynx and not potentially contaminated by stool.

[†]Or equivalent direct molecular method, in any specimen.

[‡]Nontreponemal test: rapid plasma reagin, Venereal Disease Research Laboratory, or equivalent serologic test.

[§]Treponemal test: *Treponema pallidum* particle agglutination, enzyme immunoassay, chemiluminescence immunoassay, or equivalent serologic test.

^{||}Unless increase not sustained for >2 weeks

[¶]Based on ≥ 1 of the following criteria:

- Documented seroconversion or fourfold or greater increase in titer of a nontreponemal test during the previous 12 months, unless not sustained for >2 weeks
- Documented seroconversion of a treponemal test during the previous 12 months
- History of symptoms consistent with primary or secondary syphilis during the previous 12 months
- Meets epidemiologic criteria, as follows:
 - Sexual exposure to a partner within 12 months who had primary, secondary, or early nonprimary nonsecondary syphilis
 - Only sexual contact (sexual debut) was within previous 12 months

[#]For explanations of neurologic, ocular, and otic syphilis, see case definitions by the U.S. Centers for Disease Control and Prevention.³⁴



Fig 1. **A** and **B**, Single and (**C**) multiple chancres on the penis. **D**, Perianal chancre.

In 1941, when syphilis surveillance began, there were 68,231 cases (51.7).¹³ The highest case count and incidence occurred in 1946, which saw 94,957 cases (70.9).¹³ The widespread use of penicillin and improved prevention and control efforts led to a decline; in 1956, 6392 cases (3.9) occurred.¹³ Cases and incidence waxed and waned during the 1960s and 1970s. During an epidemic in the 1980s and 1990s, cases and incidence rose to a high of 50,578 (20.3) in 1990.¹³ Starting in 1995, cases and incidence rates fell yearly, leading CDC to launch a national plan to eliminate syphilis.¹⁴

However, after reaching a nadir in 2000, with 5979 cases (2.1), syphilis has increased every year since.^{15,16} The 30,644 cases (9.5) in 2017, the last year for which national data were available, represented more than a quadrupling since 2000 and an 10% increase from 2016.¹

In 2017, 88% of cases overall occurred in men, and 58% of cases overall occurred in men who have sex with men (MSM), including 52% who had sex with men only, and 6% who had sex with men and women.¹ Risk factors for syphilis infection among MSM include methamphetamine use, acquiring sexual partners from the Internet, and previous syphilis infection.¹⁷⁻¹⁹ The ongoing syphilis epidemic among MSM underscores the importance of eliciting a sexual history, including gender(s) of sex partner(s), from patients in whom syphilis is suspected.²⁰ Eliciting gender identity should also be

considered because some studies show that transgender women are at higher risk.^{21,22}

Among women, syphilis cases and incidence during 2000 to 2012 fluctuated, with a high of 2445 (1.7) in 2000 and a low of 1217 (0.8) in 2003. Syphilis among women has increased yearly since 2003, more than doubling from 1458 cases (0.9) in 2012 to 3722 cases (2.3) in 2017. That rise has been accompanied by a near-tripling in congenital syphilis cases, from 334 in 2012 to 918 in 2017.^{1,23}

Syphilis has increased in all age groups. In 2017, syphilis cases and incidence were highest in the 25- to 29-year-old age group, with 6838 cases (29.9). In adolescents 10 to 14 years of age and 15 to 19 years of age there were 20 cases (0.1) and 1421 cases (6.7), respectively, in 2017, compared with 15 cases (0.1) and 1298 cases (6.1), respectively, in 2016. In persons >65 years of age, cases increased to 349 (0.7) in 2017 from 279 (0.6) in 2016.¹

Disproportionately higher rates of primary and secondary syphilis have occurred among African American men and women and among Hispanic men.²⁰

Rates of HIV infection are higher among persons with syphilis than the general population. In 2017, HIV coinfection was present in 46% of MSM, 8.8% of men who have sex with women, and 4.5% of women diagnosed with primary or secondary syphilis.¹ By comparison, the estimated overall HIV prevalence in

the United States among persons ≥ 13 years of age was 0.4% in 2015.²⁴ All persons diagnosed with syphilis who are not known to be coinfected with HIV should be tested for HIV.²²

Outbreaks of ocular syphilis in the United States have increasingly occurred since 2014, prompting the CDC to issue a clinical advisory in 2015 that was still in effect as of August 2018.^{25,26} The epidemiology of persons affected with ocular syphilis has mirrored that of syphilis overall.²⁵

As in the United States, syphilis incidence among MSM has increased throughout the developed world.^{27,28} As for the global burden of disease, among persons 15 to 49 years of age in 2012, an estimated 18 million were infected with syphilis, with the highest prevalence in Africa; in addition, 5.6 million new infections occurred, translating to an incidence of 150 in 100,000 persons.²⁹

CLINICAL MANIFESTATIONS

Key points

- The clinical manifestations of syphilis are highly variable
- Syphilis staging nomenclature continues to evolve
- Neurosyphilis, otic syphilis, and ocular syphilis can occur during any stage

Most information on the natural history of syphilis comes from either the preantibiotic era^{30,31} or the infamous Tuskegee study, in which penicillin was intentionally withheld from poor African American participants from 1932 until 1972.³²

The infection proceeds through stages that have distinct clinical manifestations and management recommendations (Table I).²² The CDC's staging nomenclature (which differs from World Health Organization staging³³) continues to evolve, with the most recent update in 2018.³⁴ Current CDC classifications might differ substantially from what many recall from their medical training. For example, CDC staging nomenclature no longer uses the term "latent syphilis," which implied complete absence of signs or symptoms. The new nomenclature helps clarify that neurosyphilis, otic syphilis, and ocular syphilis can occur during any stage after infection.

Notably, "tertiary syphilis" is not a stage. CDC uses the term tertiary syphilis synonymously with "late clinical manifestations of syphilis," which include gummatous lesions of the cardiovascular system, skin, bone, or other tissue, and the neurologic manifestations of general paresis and tabes dorsalis. In the updated classification, the stage that contains

Table II. Differential diagnosis of primary syphilis (chancres) and exanthem of secondary syphilis

Mucocutaneous manifestation	Differential diagnosis
Primary syphilis—chancres(s)	<ul style="list-style-type: none"> • Infectious diseases <ul style="list-style-type: none"> ○ Herpes simplex virus infection ○ Staphylococcus aureus infection ○ Chancroid* ○ Granuloma inguinale/ donovanosis† ○ Lymphogranuloma venereum‡ ○ Vaccinia • Noninfectious diseases <ul style="list-style-type: none"> ○ Trauma ○ Neoplasm, including squamous cell carcinoma ○ Aphthous ulcer ○ Behçet disease ○ Fixed drug eruption ○ Zoon balanitis
Secondary syphilis—exanthem	<ul style="list-style-type: none"> • Truncal rash <ul style="list-style-type: none"> ○ Acute HIV infection ○ Other viral exanthems ○ Pityriasis rosea ○ Drug eruption ○ Psoriasis • Palmoplantar rash <ul style="list-style-type: none"> ○ Erythema multiforme ○ Hand, foot, and mouth disease ○ Rocky Mountain spotted fever

*Rare in the United States; in 2016, 7 cases of chancroid were reported.

†The Centers for Disease Control and Prevention did not report the number of cases of granuloma inguinale in 2016. The infection is rare in the United States but has been reported.¹⁰⁴

‡The incidence of lymphogranuloma venereum is unknown because methods to differentiate lymphogranuloma venereum from non–lymphogranuloma venereum *Chlamydia trachomatis* are not widely available. Outbreaks of lymphogranuloma venereum proctocolitis among men who have sex with other men have been reported. Classic lymphogranuloma venereum genital ulcer disease is rare but has been reported.¹⁰⁵

these late manifestations is called "late or unknown duration syphilis."³⁴

Primary syphilis

In primary syphilis, lesion(s) called chancres form at the site(s) of inoculation approximately 21 days (range 3–90 days) after exposure.³⁵ Chancres are typically 0.5- to 3-cm indurated, painless ulcers with raised borders that are pink, red, or grayish (Fig 1). The presence of induration and the dory flop sign—when the prepuce flips



Fig 2. Typical exanthem of secondary syphilis.



Fig 3. Palmoplantar involvement in secondary syphilis.

over all at once when retracted—can help distinguish chancres from other causes of genital ulcers.^{36,37} However, chancres can vary significantly in presentation, and additional testing should be performed to rule out other causes of genital ulcers (Table II).

Chancres may be single or multiple and can occur at any exposed site, including the fingers, nipples, and the mucosal or keratinized surfaces of the anogenital area or mouth.³⁸⁻⁴⁷ Regional

lymphadenopathy may be present.^{36,38,48} Without treatment, chancres heal without scarring, usually within 3 to 6 weeks.⁴⁹

Secondary syphilis

Hematogenous dissemination of spirochetes causes the manifestations of secondary syphilis, which typically occurs 3 to 12 weeks after the resolution of a chancre but can be concurrent. Secondary syphilis most commonly consists of

Table III. Cutaneous morphologies of secondary syphilis

Clinical pattern	Features
Exanthem	Diffuse, symmetric scaly red-brown macular or papular eruption on trunk and extremities. Palmoplantar involvement is common
Follicular papules	Mimics folliculitis or follicular mycosis fungoides ¹⁰⁶
Lichenoid	Resembles lichen planus
Psoriasiform	Mimics psoriasis or sebopsoriasis ¹⁰⁷
Corymbiform	Derived from the Greek “korymbos,” or cluster of fruit or flowers. Central plaque surrounded by a ring of discrete papules ¹⁰⁸
Nodular	Erythematous to violaceous plaques or nodules ^{64,109-121} Spares palms and soles. Solitary lesions described. Significant spirochete infiltration in the face can cause leonine facies ¹²²
Annular	Variations: annular, arcuate, verrucous, tinea imbricata-like. ¹²³⁻¹²⁷ Location: oral commissures, cheeks with “nickels and dimes” appearance > scalp, palms, soles, intertriginous areas
Frambesiform	“Raspberry-like.” Variations: ulcerative, keratotic, verrucous. Location: periorificial, scalp, trunk, extremities, genitals, and palms ¹²⁸⁻¹³¹
Leukoderma	Location: neck (venereal necklace), trunk, genitals, palms ^{132,133}
Lues maligna	Ulcerative lesions that can be destructive to surrounding tissue. Can form “rupioid” plaques with dark heaped-up mounds of crust. Patients systemically ill. Associated with high nontreponemal titers and HIV infection ^{80,134}
Clavi syphilitici	Palmoplantar hyperkeratotic lesions similar to warts or calluses ¹³⁵⁻¹³⁷
Acral pebbles	Palmar gray-white firm, round papules ¹³⁸
Pustular	Miliary—minute perifollicular pustules. ^{139,140} Acneiform—localized to face, acne mimicker. ¹⁴¹ Varioliform—pustules with crusts that then form punched out ulcers. ¹⁴² Ecthymiform—ulcers with overlying crust ≤5 cm. ¹⁴³ Impetiginoid—pustules and yellow crusts on the face, scalp, and intertriginous areas



Fig 4. Morphologies of secondary syphilis: (A) annular, (B) psoriasiform, and (C) nodular.

mucocutaneous lesions (90-97%), with or without systemic signs and symptoms, such as generalized lymphadenopathy (50-85%), malaise (13-20%), sore throat (15-30%), body aches (6-8%), and low-grade fevers (5-8%).^{38,40,50} Nearly any organ system can be affected, which can produce a diverse array of clinical presentations.

The term “syphilid” refers to any mucocutaneous manifestation of syphilis other than the chancre of primary syphilis. Syphilids can be localized or generalized and asymptomatic or pruritic.⁵⁰ The most common syphilid of secondary syphilis is a diffuse exanthem on the trunk and extremities with scaly macules or papules that are red-brown or



Fig 5. Perianal condyloma lata.

“ham colored” (Fig 2). The palms and soles are involved in 40% to 80% of cases.^{38,50} Palmoplantar lesions are often pink, red, or brown macules or papules with or without collarette scale (Fig 3). However, nearly any morphology and configuration is possible, including psoriasiform, annular, lichenoid, and nodular (Table III; Fig 4). Vesicles and bullae are rare in secondary syphilis.⁵¹⁻⁵³ Lesions typically do not scar, and heal with postinflammatory hyperpigmentation. Findings can be subtle; 27% of secondary syphilis patients in one study did not notice the rash.¹⁵ A brief differential diagnosis of the syphilis exanthem is shown in Table II.

Condyloma lata are highly infectious moist papules or nodules in areas of skin apposition (Fig 5). The anogenital area, medial thighs, and inframammary creases are the most common sites.⁵⁴ The surface can be smooth, verrucous, hypertrophic, or covered with exudate. Condyloma lata can mimic condyloma acuminata or squamous cell carcinoma.⁵⁴⁻⁵⁷

Mucosal syphilitic occur in 30% to 40% of patients.⁵⁸ Mucous patches are highly infectious, well-demarcated oval exudative erosions with erythematous borders, most commonly presenting on the tongue and lips (Fig 6). They can coalesce and form serpiginous “snail track ulcers,” or white plaques on the tongue mimicking leukoplakia.⁵⁹⁻⁶¹ On the dorsal surface of the tongue, depapillation results in smooth round patches.⁶² At the oral commissures, mucous patches can appear as papules with transverse erosions, called “split papules.”^{62,63}

Other mucosal syphilitic include specific angina (an enanthem of sharply demarcated erythematous macules on the palate, uvula, and tonsils), painless tongue nodules,⁶⁴ bullous-eruptive lesions mimicking pemphigus vulgaris,⁶⁵ and nonspecific shallow ulcers.^{66,67}

Alopecia occurs in 4% to 12% of patients,⁶⁸ usually accompanied by other syphilitic, and typically has a

“moth-eaten” pattern that reverses after treatment.⁶⁹ Other presentations include alopecia areata-like and diffuse alopecia.⁶⁹⁻⁷¹

Nail changes, including brittleness, splitting, pitting, onycholysis, onychomadesis, transverse grooves, and Beau lines, can occur because of involvement of the nail matrix or bed. Syphilitic paronychia can result from a peri- or subungual inflammatory process.⁷²⁻⁷⁴

Lues maligna, or nodoulcerative syphilis, typically presents with asymmetric ulcers or round necrotic plaques with heaped up lamellar or rupioid crusts on the scalp, face, trunk, and extremities (Fig 7). Oral ulcers can occur. Systemic signs and symptoms, including fever, headache, and lymphadenopathy, are often present. Nontreponemal titers are usually high. Risk factors include HIV infection with low CD4 count, malnutrition, MSM, previous syphilis, diabetes mellitus, and alcohol abuse.⁷⁵⁻⁸⁷ Some patients with lues maligna experience severe Jarisch–Herxheimer reactions (discussed in the second article in this continuing medical education series).^{87,88}

Untreated, secondary syphilis typically self-resolves after 4 to 12 weeks.

Early nonprimary nonsecondary syphilis

This stage refers to infections that are diagnosed only based on serology, that lack signs or symptoms of primary or secondary syphilis, and that can be shown to have been acquired within the previous 12 months (Table I). Because most dermatologists typically care for patients presenting with mucocutaneous complaints, they are less likely to diagnose this stage of syphilis.

Unknown duration or late syphilis

This stage refers to infections that lack signs or symptoms of primary or secondary syphilis and do not have evidence of acquisition within the past 12 months. Only serologic evidence of infection (or reinfection) may be present or late clinical or neurologic manifestations may be present.

About one-third of patients with untreated syphilis develop late clinical manifestations of syphilis years to decades after infection.⁸⁹ These include inflammatory lesions of the cardiovascular system (aortitis or coronary vessel disease), skin (gummatous or nodoulcerative lesions), bone (osteitis), or other tissue.

Cutaneous lesions occur in 16% of patients with late clinical manifestations,⁸⁹ and only a handful of cases have been reported in the last few decades.⁸⁹⁻⁹⁶ Lesions are classified as nodoulcerative or gummatous.⁹³ Both types are usually single to few



Fig 6. **A**, Mucous patch on the tongue. **B**, Split papule on the oral commissure.



Fig 7. Secondary syphilis. Lues maligna in a single patient on the **(A)** arm and **(B)** leg.

in number, unilateral, and can be asymptomatic or pruritic.⁹⁴

Nodoulcerative lesions are superficial brown-to-red nodules that enlarge to form arciform or serpiginous plaques with ulceration and central clearing. Cutaneous gummas are painless rubbery nodules that evolve into punched out ulcers that can grow to many centimeters and that drain necrotic material.^{96,97} Gummas are destructive, can invade deeply into tissue and bone, and heal with deeply retracted scars.⁹⁷

Neurosyphilis, otic syphilis, and ocular syphilis

Neurosyphilis, otic syphilis, and ocular syphilis result from treponemal invasion into the central nervous system or eye. They can occur during any stage of infection and are not themselves stages of

syphilis.^{22,34} Risk factors include male gender, younger age, MSM, and HIV infection.^{49,98}

Neurosyphilis can be symptomatic or asymptomatic. In asymptomatic neurosyphilis, there is evidence of central nervous system infection on cerebrospinal fluid analysis (reactive Venereal Disease Research Laboratory test and elevated protein or leukocyte count) but the patient does not have clinical manifestations.³⁴ It can occur early in infection, particularly in HIV-coinfected persons. However, because treatment of asymptomatic neurosyphilis during early syphilis infection has not been shown to improve outcomes in persons who are otherwise treated appropriately for syphilis, the CDC only recommends cerebrospinal fluid analysis for patients with primary, secondary, or early non-primary nonsecondary syphilis who have neurologic, ocular, or otic signs or symptoms.²² As

Table IV. Review of systems and focused neurologic examination for early neurosyphilis for all syphilis patients from the California Department of Public Health¹⁴⁴

Review of systems

- General: fever, fatigue, headache, weakness, dizziness
- Head, eyes, ears, nose and throat:
 - Eyes—pain, redness, loss of vision, double or blurred vision, photophobia, and flashing lights or spots
 - Ears—ringing in the ears, loss of hearing
- Gastrointestinal: nausea, vomiting
- Musculoskeletal: neck pain/stiffness and muscle weakness
- Neurologic: headache, dizziness, muscle weakness, difficulty speaking, confusion, loss of consciousness, and seizures
- Psychiatric: confusion

Focused neurologic examination

- Cranial nerve examination*
 - I: visual acuity* and visual fields*
 - II: pupillary reactions to light* and accommodation*
 - II, IV, VI: extraocular movements* and ptosis*
 - V: corneal reflexes and jaw strength and facial sensation
 - VII: facial movements* (raise eyebrows, frown, tightly close eyes, show teeth smile, and puff out both cheeks)
 - VIII: hearing* (rub fingers together)
 - IX: swallowing, gag reflex, and rise of palate
 - V, VII, X, XII: voice and speech
 - XI: shoulder shrug and trapezius muscle inspection
 - XII: inspection of tongue and lateral movement of tongue while protruded
- Motor: muscle strength testing upper and lower extremities
- Nuchal rigidity testing:
 - Chin to chest—stiffness/pain with flexion of neck, flexion of hips and knees in response to neck flexion (Brudzinski sign)
 - Jolt accentuation maneuver—worsening of headache when patient rotates head rapidly from side to side
- Deep tendon reflexes: assess for hyperreflexia of the bicep, supinator, knee, ankle

*Key maneuvers.

recommended by the CDC, physicians should perform a review of systems and focused neurologic examination in all patients with syphilis (Table IV) and should refer patients with positive signs or symptoms for further evaluation, including cerebrospinal fluid analysis and ophthalmologic examination.

The most common early symptoms of neurosyphilis are mild meningeal signs, headache, and nausea. Cranial nerve palsies can occur, most frequently affecting cranial nerves III (oculomotor), VI (abducens), VII (facial), and VIII (vestibulocochlear), with unilateral or bilateral hearing loss with or without tinnitus. Meningitis can cause fever, meningismus, and photophobia. In meningovascular syphilis, arteritis causes infarcts in the brain or spinal cord. Symptomatic late neurosyphilis, which is rare in the antibiotic era, most commonly causes general paresis (also called general paresis of the insane or dementia paralytica), which can manifest as dementia, seizures, and other psychiatric manifestations; and tabes dorsalis, which can manifest as lightning pains, ataxia, the Argyll–Robinson pupil, a loss of reflexes, and impaired vibratory sense.^{49,98}

Early ocular syphilis, which can occur with or without neurosyphilis or otic syphilis, most commonly presents as uveitis, although other presentations can occur.⁹⁹ Among patients reported as part of ocular syphilis outbreaks in the United States in 2014 and 2015, symptoms included blurry vision (64%), vision loss (33%), and eye pain or red eye (14%). Diagnoses included uveitis (46%), retinitis (13%), optic neuritis (11%), and retinal detachment (4%).²⁵ In otic syphilis, *T pallidum* infects the cochleovestibular system; manifestations can include sensorineural hearing loss, tinnitus, and vertigo.³⁴

Syphilis and HIV

It is controversial whether syphilis manifests in HIV-positive patients differently than HIV-negative patients. Reports include increased rates of central nervous system infection (particularly during early infection), higher risk for neurologic complications, and higher rates of treatment failure.^{100–102} Though not fully known, the magnitude of these risks is felt to be small,²² and no enhanced treatment regimen for HIV-infected patients has been shown to change clinical outcomes.¹⁰³ Under

the current CDC guidelines, HIV status does not affect diagnostic or antibiotic treatment recommendations but may warrant closer clinical and serologic follow-up.

From a cutaneous perspective, multiple chancres and more severe and atypical manifestations including lues maligna are reported.^{52,75} When differences in clinical manifestations have been studied in larger populations, they generally have not been statistically significant. This may either represent limitations in the study of rare events or may reflect the great variation in presentation with provider confirmation bias.^{49,103}

REFERENCES

1. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance 2017. Available at: https://www.cdc.gov/std/stats17/2017-STD-Surveillance-Report_CDC-clearance-9.10.18.pdf; 2018. Accessed October 1, 2018.
2. de Melo FL, de Mello JC, Fraga AM, Nunes K, Eggers S. Syphilis at the crossroad of phylogenetics and paleopathology. *PLoS Negl Trop Dis.* 2010;4:e575.
3. Sefton AM. The Great Pox that was...syphilis. *J Appl Microbiol.* 2001;91:592-596.
4. Knell RJ. Syphilis in renaissance Europe: rapid evolution of an introduced sexually transmitted disease? *Proc Biol Sci.* 2004; 271(suppl 4):S174-S176.
5. Tampa M, Sarbu I, Matei C, Benea V, Georgescu SR. Brief history of syphilis. *J Med Life.* 2014;7:4-10.
6. Fracastoro G. *Hieronymi Fracastorii Syphilis sive morbus gallicus.* Basilae; 1536.
7. "Lues." Merriam-Webster.com. Available at: <https://merriam-webster.com>. Accessed June 3, 2019.
8. O'Shea JG. Two minutes with venus, two years with mercury—mercury as an antisyphilitic chemotherapeutic agent. *J R Soc Med.* 1990;83:392-395.
9. Austin SC, Stolley PD, Lasky T. The history of malariotherapy for neurosyphilis. Modern parallels. *JAMA.* 1992;268:516-519.
10. Mahoney JF, Arnold RC, Harris A. Penicillin treatment of early syphilis—a preliminary report. *Amer J Public Health Nations Health.* 1943;33:1387-1391.
11. Giacani L, Lukehart SA. The endemic treponematoses. *Clin Microbiol Rev.* 2014;27:89-115.
12. Hook EW 3rd, Marra CM. Acquired syphilis in adults. *N Engl J Med.* 1992;326:1060-1069.
13. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance 2015. 2016. Available at: <https://www.cdc.gov/std/stats>. Accessed November 5, 2017.
14. Centers for Disease Control and Prevention. The national plan to eliminate syphilis from the United States. Available at: <https://www.cdc.gov/stopsyphilis/Plan.pdf>. Accessed June 16, 2018.
15. Centers for Disease Control and Prevention. Primary and secondary syphilis—United States, 1998. *MMWR Morb Mortal Wkly Rep.* 1999;48:873-878.
16. Mitka M. US effort to eliminate syphilis moving forward. *JAMA.* 2000;283:1555-1556.
17. Wong W, Chaw JK, Kent CK, Klausner JD. Risk factors for early syphilis among gay and bisexual men seen in an STD clinic: San Francisco, 2002-2003. *Sex Transm Dis.* 2005;32:458-463.
18. Landovitz RJ, Tseng CH, Weissman M, et al. Epidemiology, sexual risk behavior, and HIV prevention practices of men who have sex with men using GRINDR in Los Angeles, California. *J Urban Health.* 2013;90:729-739.
19. Cohen SE, Chew Ng RA, Katz KA, et al. Repeat syphilis among men who have sex with men in California, 2002-2006: implications for syphilis elimination efforts. *Am J Public Health.* 2012;102:e1-e8.
20. Patton ME, Su JR, Nelson R, Weinstock H. Primary and secondary syphilis—United States, 2005-2013. *MMWR Morb Mortal Wkly Rep.* 2014;63:402-406.
21. Lucar J, Hart R, Rayeed N, et al. Sexually transmitted infections among HIV-infected individuals in the District of Columbia and estimated HIV transmission risk: data from the DC Cohort. *Open Forum Infect Dis.* 2018;5:ofy017.
22. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64:1-137.
23. Bowen V, Su J, Torrone E, Kidd S, Weinstock H. Increase in incidence of congenital syphilis - United States, 2012-2014. *MMWR Morb Mortal Wkly Rep.* 2015;64:1241-1245.
24. Centers for Disease Control and Prevention. Estimated HIV incidence and prevalence in the United States, 2010-2015. *HIV Surveillance Suppl Rep.* 2018;3.
25. Oliver SE, Aubin M, Atwell L, et al. Ocular syphilis - eight jurisdictions, United States, 2014-2015. *MMWR Morb Mortal Wkly Rep.* 2016;65:1185-1188.
26. Centers for Disease Control and Prevention. Clinical advisory: ocular syphilis in the United States. 2016. Available at: <https://www.cdc.gov/std/syphilis/clinicaladvisoryos2015.htm>. Accessed June 16, 2018.
27. Abara WE, Hess KL, Neblett Fanfair R, et al. Syphilis trends among men who have sex with men in the United States and Western Europe: a systematic review of trend studies published between 2004 and 2015. *PLoS One.* 2016;11:e0159309.
28. Fenton KA, Breban R, Vardavas R, et al. Infectious syphilis in high-income settings in the 21st century. *Lancet Infect Dis.* 2008;8:244-253.
29. Newman L, Rowley J, Vander Hoorn S, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. *PLoS One.* 2015;10:e0143304.
30. Gjestland T. The Oslo study of untreated syphilis; an epidemiologic investigation of the natural course of the syphilitic infection based upon a re-study of the Boeck-Bruusgaard material. *Acta Derm Venerol Suppl.* 1955; 35(suppl 34):3-368.
31. Rosahn PD, Black-Schaffer B. Studies in syphilis: III. Mortality and morbidity findings in the Yale Autopsy Series. *Yale J Biol Med.* 1943;15:587-602.
32. Rockwell DH, Yobs AR, Moore MB Jr. The Tuskegee Study of untreated syphilis; the 30th year of observation. *Arch Intern Med.* 1964;114:792-798.
33. World Health Organization. *Guidelines for the treatment of Treponema pallidum (syphilis).* Geneva, Switzerland: World Health Organization; 2016.
34. Centers for Disease Control and Prevention. Syphilis (*Treponema pallidum*) 2018 case definition. Available at: <https://www.cdc.gov/nndss/conditions/syphilis/case-definition/2018/>. Accessed April 5, 2018.
35. Sparling PF. Natural history of syphilis. In: Holmes KK, Mardh PA, Sparling PF, et al., eds. *Sexually Transmitted Diseases.* New York: McGraw-Hill; 1990:213.
36. DiCarlo RP, Martin DH. The clinical diagnosis of genital ulcer disease in men. *Clin Infect Dis.* 1997;25:292-298.
37. Katz KA. Dory flop sign of syphilis. *Arch Dermatol.* 2010;146: 572.

38. Mindel A, Tovey SJ, Timmins DJ, Williams P. Primary and secondary syphilis, 20 years' experience. 2. Clinical features. *Genitourin Med.* 1989;65:1-3.
39. Tucker HA, Mulherin JL. Extranodal chancres; a survey of 219 cases. *Am J Syph Gonorrhea Vener Dis.* 1948;32:345-364.
40. Singh AE, Romanowski B. Syphilis: review with emphasis on clinical, epidemiologic, and some biologic features. *Clin Microbiol Rev.* 1999;12:187-209.
41. Lee JY, Lin MH, Jung YC. Extranodal syphilitic chancre manifesting as a solitary nodule of the nipple. *J Eur Acad Dermatol Venereol.* 2006;20:886-887.
42. Oh Y, Ahn SY, Hong SP, Bak H, Ahn SK. A case of extranodal chancre on a nipple from a human bite during sexual intercourse. *Int J Dermatol.* 2008;47:978-980.
43. Sim JH, Lee MG, In SI, et al. Erythematous erosive patch on the left nipple—quiz case. Diagnosis: extranodal syphilitic chancres. *Arch Derm.* 2010;146:81-86.
44. Chiu HY, Tsai TF. A crusted plaque on the right nipple. *JAMA.* 2012;308:403-404.
45. Zheng S, Liu J, Xu XG, et al. Primary syphilis presenting as bilateral nipple-areola eczematoid lesions. *Acta Derm Venereol.* 2014;94:617-618.
46. Podlipnik S, Giavedoni P, Alsina M, et al. An erythematous nodule on the nipple: an unusual presentation of primary syphilis. *J Cutan Pathol.* 2015;42:239-243.
47. Yebenes M, Toll A, Gimenez-Arnau A, et al. Pseudotumoral primary syphilis on the tongue in an HIV positive patient. *Clin Exp Dermatol.* 2008;33:509-511.
48. Chapel TA. The variability of syphilitic chancres. *Sex Transm Dis.* 1978;5:68-70.
49. Hook EWR. Syphilis. *Lancet.* 2017;389:1550-1557.
50. Chapel TA. The signs and symptoms of secondary syphilis. *Sex Transm Dis.* 1980;7:161-164.
51. Lawrence P, Saxe N. Bullous secondary syphilis. *Clin Exp Dermatol.* 1992;17:44-46.
52. Nnoruka EN, Ezeoke AC. Evaluation of syphilis in patients with HIV infection in Nigeria. *Trop Med Int Health.* 2005;10:58-64.
53. Arora S, Dhali TK, Haroon MA. Vesicular syphilid in a seropositive patient. *Int J STD AIDS.* 2013;24:905-907.
54. Kim JS, Kang MS, Sagong C, Ko JY, Yu HJ. An unusual extensive secondary syphilis: condyloma lata on the umbilicus and perineum and mucous patches on the lips. *Clin Exp Dermatol.* 2009;34:e299-e301.
55. Mosojane KI, Lee LW, Kovarik CL. Eroded and pedunculated buttock nodule. *JAMA Dermatol.* 2015;151:335-336.
56. Tham SN, Lee CT. Condyloma latum mimicking keratoacanthoma in patient with secondary syphilis. *Genitourin Med.* 1987;63:339-340.
57. Deshpande DJ, Nayak CS, Mishra SN, Dhurat RS. Verrucous condyloma lata mimicking condyloma acuminata: an unusual presentation. *Indian J Sex Transm Dis AIDS.* 2009;30:100-102.
58. Leo JC, Gueiros LA, Porter SR. Oral manifestations of syphilis. *Clinics.* 2006;61:161-166.
59. Junkins-Hopkins JM. Multiple painful oral ulcerations. Secondary syphilis. *Arch Fam Med.* 1996;5:379-380.
60. Singh PV, Patil R. Atypical oral manifestations in secondary syphilis. *Indian J Dent Res.* 2013;24:142-144.
61. Aquilina C, Viraben R, Denis P. Secondary syphilis simulating oral hairy leukoplakia. *J Am Acad Dermatol.* 2003;49:749-751.
62. Eyer-Silva WA, Freire MAL, Horta-Araujo CA, et al. Secondary syphilis presenting as glossodynia, plaques en prairie fauchee, and a split papule at the oral commissure: case report and review. *Case Rep Med.* 2017;1980798.
63. Ficarra G, Zaragoza AM, Stendardi L, et al. Early oral presentation of lues maligna in a patient with HIV infection. A case report. *Oral Surg Oral Med Oral Pathol.* 1993;75:728-732.
64. Dalmau J, Alegre M, Sambeat MA, et al. Syphilitic nodules on the tongue. *J Am Acad Dermatol.* 2006;54(2 suppl):S59-S60.
65. Mignogna MD, Fortuna G, Leuci S, et al. Secondary syphilis mimicking pemphigus vulgaris. *J Eur Acad Dermatol Venereol.* 2009;23:479-480.
66. Ramirez-Amador V, Anaya-Saavedra G, Crabtree-Ramirez B, et al. Clinical spectrum of oral secondary syphilis in HIV-infected patients. *J Sex Transm Dis.* 2013;2013:892427.
67. Leuci S, Martina S, Adamo D, et al. Oral syphilis: a retrospective analysis of 12 cases and a review of the literature. *Oral Dis.* 2013;19:738-746.
68. Bi MY, Cohen PR, Robinson FW, Gray JM. Alopecia syphilitica - report of a patient with secondary syphilis presenting as moth-eaten alopecia and a review of its common mimickers. *Dermatol Online J.* 2009;15:6.
69. Lee JW, Jang WS, Yoo KH, et al. Diffuse pattern essential syphilitic alopecia: an unusual form of secondary syphilis. *Int J Dermatol.* 2012;51:1006-1007.
70. Lee JY, Hsu ML. Alopecia syphilitica, a simulator of alopecia areata: histopathology and differential diagnosis. *J Cutan Pathol.* 1991;18:87-92.
71. Hernandez-Bel P, Unamuno B, Sanchez-Carazo JL, et al. Syphilitic alopecia: a report of 5 cases and a review of the literature. *Actas Dermosifiliogr.* 2013;104:512-517.
72. Noriega L, Gioia Di Chiaccio N, Cury Rezende F, et al. Periungual lesion due to secondary syphilis. *Skin Appendage Disord.* 2017;2:116-119.
73. Danielian EE, Mokrousov MS. Lesion of the nail plates in a patient with secondary fresh syphilis. *Vestn Dermatol Venerol.* 1979;12:59-61.
74. Dourmishev LA, Dourmishev AL. Syphilis: uncommon presentations in adults. *Clin Dermatol.* 2005;23:555-564.
75. Sands M, Markus A. Lues maligna, or ulceronodular syphilis, in a man infected with human immunodeficiency virus: case report and review. *Clin Infect Dis.* 1995;20:387-390.
76. Weis L, Bonamigo RR, Weber MB, Petry V, Luzzatto L. Malignant syphilis and neurolues in an HIV infected patient. *Int J Dermatol.* 2010;49:590-592.
77. Kelly JD, LeLeux TM, Citron DR, Musher DM, Giordano TP. Ulceronodular syphilis (lues maligna praecox) in a person newly diagnosed with HIV infection. *BMJ Case Rep.* 2011;2011.
78. De Socio GV, Simonetti S, Tomasini C, et al. Malignant syphilis with ocular involvement in an HIV-infected patient. *Int J STD AIDS.* 2011;22:298-300.
79. Ali L, Helm T, Brouha B, Gladys J, Cockerell C. Rapidly enlarging nodoulcerative lesions. Lues maligna. *Cutis.* 2014;94:E20-E22.
80. Wang H, Wang X, Li S. A case of lues maligna in an AIDS patient. *Int J STD AIDS.* 2012;23:599-600.
81. Requena CB, Orasmo CR, Ocaña JP, et al. Malignant syphilis in an immunocompetent female patient. *An Bras Dermatol.* 2014;89:970-972.
82. Alves J, Antonio AM, Matos D, Coelho R, Cachao P. Malignant lues in an immunocompetent patient. *Int J STD AIDS.* 2015;26:518-520.
83. Shulkin D, Tripoli L, Abell E. Lues maligna in a patient with human immunodeficiency virus infection. *Am J Med.* 1988;85:425-427.
84. Hofmann UB, Hund M, Brocker EB, Hamm H. "Lues maligna" in a female patient with diabetes. *J Dtsch Dermatol Ges.* 2005;3:780-782.

85. Li JH, Guo H, Zheng S, Li B, Gao XH, Chen HD. widespread crusted skin ulcerations in a man with type II diabetes: a quiz. Diagnosis: malignant syphilis. *Acta Dermatol Venereol.* 2015; 95:632-633.
86. Haslund A. Syphilis maligna. *Arch Dermatol Syph.* 1897;38: 345-392.
87. Witkowski JA, Parish LC. The great imitator: malignant syphilis with hepatitis. *Clin Dermatol.* 2002;20:156-163.
88. Fisher DA, Chang LW, Tuffanelli DL. Lues maligna. Presentation of a case and a review of the literature. *Arch Derm.* 1969;99:70-73.
89. Clark EG, Danbolt N. The Oslo study of the natural history of untreated syphilis; an epidemiologic investigation based on a restudy of the Boeck-Bruusgaard material; a review and appraisal. *J Chron Dis.* 1955;2:311-344.
90. Revathi TN, Bhat S, Asha GS. Benign nodular tertiary syphilis: a rare presenting manifestation of HIV infection. *Dermatol Online J.* 2011;17:5.
91. Chung G, Kantor GR, Whipple S. Tertiary syphilis of the face. *J Am Acad Dermatol.* 1991;24(5 pt 2):832-835.
92. Matsuda-John SS, McElgunn PS, Ellis CN. Nodular late syphilis. *J Am Acad Dermatol.* 1983;9:269-272.
93. Benzaquen M, Horreau C, Koeppl MC, Berbis P. A pseudotumoral facial mass revealing tertiary syphilis. *Clin Exp Dermatol.* 2017;42:714-716.
94. Wu SJ, Nguyen EQ, Nielsen TA, Pellegrini AE. Nodular tertiary syphilis mimicking granuloma annulare. *J Am Acad Dermatol.* 2000;42(2 pt 2):378-380.
95. Tanabe JL, Huntley AC. Granulomatous tertiary syphilis. *J Am Acad Dermatol.* 1986;15(2 pt 2):341-344.
96. Boyd AS. Syphilitic gumma arising in association with foreign material. *J Cutan Pathol.* 2016;43:1028-1030.
97. Goette DK, Prescott CE. Late benign syphilis of the skin. *South Med J.* 1978;71:505-508.
98. Marra CM. Neurosyphilis. *Continuum (Minneapolis Minn).* 2015; 21(6 neuroinfectious disease):1714-1728.
99. Aldave AJ, King JA, Cunningham ET Jr. Ocular syphilis. *Curr Opin Ophthalmol.* 2001;12:433-441.
100. Johns DR, Tierney M, Felsenstein D. Alteration in the natural history of neurosyphilis by concurrent infection with the human immunodeficiency virus. *N Engl J Med.* 1987;316: 1569-1572.
101. Musher DM, Hamill RJ, Baughn RE. Effect of human immunodeficiency virus (HIV) infection on the course of syphilis and on the response to treatment. *Ann Intern Med.* 1990;113:872-881.
102. Centers for Disease Control and Prevention. Symptomatic early neurosyphilis among HIV-positive men who have sex with men—four cities, United States, January 2002–June 2004. *MMWR Morb Mortal Wkly Rep.* 2007;56:625-628.
103. Rolfs RT, Joesoef MR, Hendershot EF, et al. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. The Syphilis and HIV Study Group. *N Engl J Med.* 1997;337: 307-314.
104. Ornelas J, Kiuru M, Konia T, Larsen L. Granuloma inguinale in a 51-year-old man. *Dermatol Online J.* 2016;22.
105. Marcotte T, Lee Y, Pandori M, Jain V, Cohen SE. Lymphogranuloma venereum causing a persistent genital ulcer. *Sex Transm Dis.* 2014;41:280-282.
106. Villasenor-Park J, Clark E, Ho J, English JC 3rd. Folliculotropic non-alopecic secondary syphilis. *J Am Acad Dermatol.* 2011; 65:686-687.
107. Wanat KA, Rutnin S, Kovarik CL. Scaly pruritic plaques in an HIV-positive patient. *Arch Derm.* 2012;148:1317-1318.
108. Kennedy CT, Sanderson KV. Corymbose secondary syphilis: occurrence as a solitary group of lesions. *Arch Derm.* 1980; 116:111-112.
109. Jang YH, Sim JH, Kim YC, Lee ES. Single nodular lesion on the scalp: a quiz. Diagnosis: nodular secondary syphilis. *Acta Dermatol Venereol.* 2011;91:491-494.
110. Vibhagool C, Raimer SS, Sanchez RL. A nodule on the lip. Nodular secondary syphilis. *Arch Derm.* 1996;132, 822-3, 5-6.
111. Moon HS, Park K, Lee JH, Son SJ. A nodular syphilitid presenting as a pseudolymphoma: mimicking a cutaneous marginal zone B-cell lymphoma. *Am J Dermatopathol.* 2009; 31:846-848.
112. Papini M, Bettacchi A, Guiducci A. Nodular secondary syphilis. *Br J Dermatol.* 1998;138:704-705.
113. Glatz M, Achermann Y, Kerl K, Bosshard PP, Cozzio A. Nodular secondary syphilis in a woman. *BMJ Case Rep.* 2013;2013.
114. Rysgaard C, Alexander E, Swick BL. Nodular secondary syphilis with associated granulomatous inflammation: case report and literature review. *J Cutan Pathol.* 2014;41:370-379.
115. Liu J, Ma D. Disseminated nodular and granulomatous secondary syphilis. *J Dermatol.* 2014;41:650-651.
116. Alarcon-Cabrera R, Partarrieu-Mejias F, Perez-Velasquez F. Disseminated red violaceous papulonodular lesions. *JAMA Dermatol.* 2016;152:83-84.
117. Breznik V, Potocnik M, Miljkovic J. Papulonodular secondary syphilis in a 52-year-old non-HIV heterosexual patient. *Acta Dermatovenerol Alp Pannonica Adriat.* 2010;19:27-30.
118. Sapra S, Weatherhead L. Extensive nodular secondary syphilis. *Arch Derm.* 1989;125:1666-1669.
119. Graham WR Jr, Duvic M. Nodular secondary syphilis. *Arch Derm.* 1982;118:205-206.
120. Dave S, Gopinath DV, Thappa DM. Nodular secondary syphilis. *Dermatol Online J.* 2003;9:9.
121. So SG, Kovarik CL, Hoang MP. Skin clues to a systemic illness. Secondary syphilis. *Arch Pathol Lab Med.* 2006;130: 737-738.
122. Pandhi D, Reddy BS, Khurana N, Agarwal S. Nodular syphilis mimicking histoid leprosy. *J Euro Acad Dermatol Venereol.* 2005;19:256-257.
123. Pournaras CC, Masouye I, Piletta P, Piguet V, Saurat JH, French LE. Extensive annular verrucous late secondary syphilis. *Br J Dermatol.* 2005;152:1343-1345.
124. Cotterman C, Eckert L, Ackerman L. Syphilis mimicking tinea imbricata and erythema annulare centrifugum in an immunocompromised patient. *J Amer Acad Dermatol.* 2009; 61:165-167.
125. Sarojini PA, Dharmaratnam AD, Pavithran K, Gangadharan C. Concentric rings simulating tinea imbricata in secondary syphilis. A case report. *Br J Vener Dis.* 1980;56:302-303.
126. Husein-Elahmed H, Ruiz-Carrascosa JC. Secondary syphilis presenting as rash and annular hyperkeratotic lesions. *Int J Infect Dis.* 2011;15:e220.
127. Ma DL, Vano-Galvan S. Images in clinical medicine. Annular secondary syphilis. *N Engl J Med.* 2014;371:2017.
128. Tham SN, Ng SK. Secondary syphilis with framboesiform lesions. *Genitourin Med.* 1990;66:99-100.
129. Lee EH, Lee JH, Kim DH, Yoon MS, Lee SE. Solitary framboesiform syphilitid on the scalp. *J Dermatol.* 2012;39:568-569.
130. Beck MH, Hubbard HC, Dave VK, Haye KR. Secondary syphilis with framboesiform facial lesions: a case report. *Br J Vener Dis.* 1981;57:103-105.
131. McDonagh JE. Framboesiform syphilide of palms. *Proc R Soc Med.* 1913;6(Dermatol Sect):107-109.
132. Miranda MF, Bittencourt Mde J, Lopes Ida C, Cumino Sdo S. Leucoderma syphiliticum: a rare expression of the secondary

- stage diagnosed by histopathology. *An Bras Dermatol.* 2010; 85:512-515.
133. Pandhi RK, Bedi TR, Bhutani LK. Leucomelanoderma in early syphilis. *Br J Vener Dis.* 1975;51:348.
 134. Tucker JD, Shah S, Jarell AD, et al. Lues maligna in early HIV infection case report and review of the literature. *Sex Transm Dis.* 2009;36:512-514.
 135. Kishimoto M, Lee MJ, Mor A, et al. Syphilis mimicking Reiter's syndrome in an HIV-positive patient. *Am J Med Sci.* 2006;332: 90-92.
 136. Moreira C, Pedrosa AF, Lisboa C, Azevedo F. Clavi syphilitici—an unusual presentation of syphilis. *J Am Acad Dermatol.* 2014;70:e131-e132.
 137. Shinkuma S, Abe R, Nishimura M, et al. Secondary syphilis mimicking warts in an HIV-positive patient. *Sex Transm Infect.* 2009;85:484.
 138. Zawar V, Goyal T. Acral pebbles: a novel manifestation of partially treated syphilis. *Indian J Sex Transm Dis.* 2017;38:92-94.
 139. Mikhail GR, Chapel TA. Follicular papulopustular syphilid. *Arch Dermatol.* 1969;100:471-473.
 140. Noppakun N, Dinehart SM, Solomon AR. Pustular secondary syphilis. *Int J Dermatol.* 1987;26:112-114.
 141. Lambert WC, Bagley MP, Khan Y, Schwartz RA. Pustular acneiform secondary syphilis. *Cutis.* 1986;37:69-70.
 142. Lejman K, Starzycki Z. Early varioliform syphilis. A case report. *Br J Vener Dis.* 1981;57:25-29.
 143. Zui GI, Mikhailov VN. Case of ecthymiform and rupioid syphilid. *Vest Dermatol Venereol.* 1981;10:67-68.
 144. California Department of Public Health. Neurosyphilis. Available at: <https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/NeurosyphilisGuide.pdf>. Accessed July 25, 2018.



Sexually acquired syphilis

Laboratory diagnosis, management, and prevention

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Learning objectives

After completing this learning activity, participants should be able to list diagnostic tests, including rapid diagnostic tests, and discuss sensitivity, specificity, false positives, false negatives, and availability; explain the current recommended diagnostic algorithm and recent changes; review treatment recommendations and describe requirements for disease reporting and management of persons exposed to syphilis.

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The methods used for the laboratory diagnosis of syphilis include direct detection of *Treponema pallidum* subspecies *pallidum* and serologic testing. Serologic testing relies on both nontreponemal and treponemal tests. In newly developed reverse-sequence screening algorithms, treponemal tests are performed before nontreponemal tests. The management of syphilis requires appropriate staging, treatment, and follow-up of patients along with the prompt reporting of infections to public health authorities to assist with prevention and control efforts. Benzathine penicillin G remains the treatment of choice for all stages of syphilis. Screening of populations at higher risk for syphilis is recommended by the US Centers for Disease Control and Prevention, the US Preventive Services Task Force, and the World Health Organization. The second article in this continuing medical education series reviews the testing for and the management of sexually acquired syphilis. (J Am Acad Dermatol 2020;82:17-28.)

Key words: dermatology; sexually transmitted disease; syphilis.

LABORATORY DIAGNOSIS

Key points

- **Laboratory diagnosis relies on direct detection of *Treponema pallidum* subspecies *pallidum* and serologic testing**

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- **Serologic testing involves treponemal and nontreponemal tests**

Treponema pallidum subspecies *pallidum* cannot be cultured, and therefore direct detection and



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Abbreviations used:

CDC:	Centers for Disease Control and Prevention
CLIA:	chemiluminescence immunoassay
EIA:	enzyme immunoassay
PCR:	polymerase chain reaction
RPR:	rapid plasma reagent
STD:	sexually transmitted disease
VDRL:	Venereal Disease Research Laboratory

serologic testing are used for laboratory diagnosis.¹ Diagnosing syphilis does not necessarily require a histopathologic examination of skin biopsy specimens. If the pretest probability is high for secondary syphilis, when serologies are typically reactive, physicians could consider ordering serologic tests, foregoing obtaining skin biopsy specimens and, in the meantime, treating empirically. Test performance characteristics are summarized in Table I.

Direct detection

Direct detection means identifying *T pallidum* subspecies *pallidum* in tissue specimens. It can be particularly useful for chancres because serologies can be nonreactive during primary syphilis. Of the methods listed below, only darkfield microscopy and polymerase chain reaction (PCR) meet US Centers for Disease Control and Prevention (CDC) criteria for laboratory confirmation of syphilis.

Histopathologic staining. Histopathologic staining enables the identification of spirochetes or treponemes in formalin-fixed tissue samples using silver or immunohistochemical stains. When used in lesions of primary and secondary syphilis, silver stains, including Warthin–Starry stain, are difficult to interpret because of low specificity (because of high background staining) and low sensitivity (33–86%).^{2–6} Immunohistochemical stains using antibodies to treponemal antigens are more sensitive (71–100%)^{4–6} and are highly specific.⁶

Darkfield microscopy. Darkfield microscopy involves expressing lesional exudate onto a wet mount and examining it within minutes under a darkfield microscope to identify organisms with characteristic spirochetal morphology and motility.^{7,8} Darkfield microscopy is most useful for suspected chancres and condyloma lata, which are teeming with spirochetes. For those lesions, when viewed by expert microscopists, sensitivity ranges from 71% to 100%.⁹ Darkfield microscopy is less sensitive, and less commonly performed, on other lesions, including those on keratinized skin, which have a lower treponemal burden. It cannot be used on oral lesions, or on lesions potentially contaminated with stool, because nonpathogenic treponemes can cause false

positive results.⁹ Use of darkfield microscopy is limited because it requires a microscope and trained personnel, both in close proximity to patients.⁸ In the United States, darkfield microscopy is typically conducted only at sexually transmitted disease (STD) clinics.

Direct fluorescent antibody. In direct fluorescent antibody testing, specimens are collected as for darkfield microscopy. The test uses antibodies specific for pathogenic *T pallidum* strains, allowing for testing of lesions from any area. Sensitivity for experts approaches 100%.⁹ Specialized supplies, equipment, and training are required.¹⁰

PCR. PCR assays detect DNA sequences specific to *T pallidum*, some of which have been designed to distinguish *T pallidum* subspecies.¹¹ None are commercially available, limiting their use to laboratories that have validated assays in-house. The sensitivities and specificities of lesional smears in primary and secondary lesions range from 80% to 96% and 96% to 100%, respectively.^{6,12–14}

Neither PCR assays nor direct fluorescent antibody testing is widely used in the United States.

Histopathologic examination of routinely prepared tissue specimens

T pallidum subspecies *pallidum* cannot be visualized in tissue specimens stained with hematoxylin–eosin, but histopathologic findings can suggest syphilis. As with clinical manifestations, histopathologic patterns vary widely. Findings can be nonspecific and subtle and can mimic many other conditions.³ Two fundamental histopathologic features are endothelial cell swelling and proliferation, as well as dermal infiltration by lymphocytes and plasma cells. In secondary and gummas of late syphilis, granulomatous infiltrates with epithelioid histiocytes and giant cells can be present.¹⁵ Histologic features of mucocutaneous syphilis are listed in Table II.

Serologic testing

Two types of serologic tests for syphilis exist: nontreponemal and treponemal. Both are important in diagnosing syphilis. Diagnosis and management cannot be based on current serologic testing alone, however, because clinical information and serologic history (or lack thereof) are needed to determine whether the case is new (and if so, which stage) or previously treated. Tests that detect antibodies are called reactive, and those that do not nonreactive. Because of *T pallidum* subspecies *pallidum*'s high degree of genetic homology with other pathogenic treponemes, neither type of serologic test can

Table I. Sensitivity and specificity of commonly used serologic tests and direct detection methods for syphilis

Test	Sensitivity, % (range)				Specificity, % (range)
	Primary	Secondary	Asymptomatic	Late disease	
Serology, nontreponemal					
VDRL ⁹	78 (74-87)	100	96 (88-100)	71 (34-94)	98 (96-99)
RPR ⁹	86 (77-99)	100	98 (95-100)	73	98
USR ⁹	80 (72-88)	100	95 (88-100)	NA	99
TRUST ⁹	85 (77-86)	100	98 (95-100)	NA	99 (98-99)
Serology, treponemal					
FTA-ABS ⁹	84 (70-100)	100	100	96	96 (95-100)
TP-PA ¹⁰	88 (86-100)	100	100	94	96 (95-100)
TPHA ⁶⁶	86	100	100	99	96
MHA-TP ⁹	76 (69-90)	100	97 (97-100)	94	99 (98-100)
EIA					
IgG-ELISA ⁶⁷	100	100	100	NA	98
IgM-EIA ⁶⁸	93	85	64	NA	95
CLIA ⁶⁹	98	100	100	100	99
Direct detection (skin, mucosa, and exudates)					
Darkfield microscopy ^{6,12,70}	84 (71-100)	60 (25-100)	—	—	92 (88-100)
Silver stain histochemistry ⁶	86 (50-100)	40 (0-92)	—	4 (0-11)	—
Immunohistochemistry ⁶	100	87 (58-100)	—	36 (11-60)	100
PCR (tissue) ⁶	100	67 (42-100)	—	7 (0-14)	—
PCR (lesional smear) ^{6,12}	90 (80-96)	83 (80-86)	—	—	98 (96-100)

CLIA, Chemiluminescence immunoassay; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; FTA-ABS, fluorescent treponemal antibody absorption assay; IgG, immunoglobulin G; IgM, immunoglobulin M; MHA-TP, microhemagglutination assay for *Treponema pallidum* antibodies; NA, not available; RPR, rapid plasma reagent; TPHA, *Treponema pallidum* hemagglutination assay; TP-PA, *Treponema pallidum* passive particle agglutination assay; TRUST, toluidine red unheated serum test; USR, unheated serum reagent; VDRL, Venereal Disease Research Laboratory.

distinguish syphilis from other treponemal infections.

Nontreponemal tests. Nontreponemal tests include rapid plasma reagent (RPR) and Venereal Disease Research Laboratory (VDRL) tests. Both measure tissue damage caused by syphilis by detecting antibodies to cardiolipin, cholesterol, and lecithin, which are normal components of human cells. Antibodies are thought to result from damaged host cells releasing antigens or from *T pallidum* subspecies *pallidum* binding and converting inert lipids to antigens.^{9,16,17}

When a nontreponemal test is reactive, the laboratory quantifies the amount of antibody present, expressing it as a titer. A titer represents the most dilute serum (after serial 1:1 dilutions with nonreactive serum) that still yields a reactive test. For example, a 1:16 titer means that the test is reactive after 4, but not 5, dilutions of a patient's serum.

Monitoring titers over time enables the assessment of response to treatment. RPR titers are typically higher than VDRL titers and cannot be compared directly. In addition, RPR or VDRL titers can differ between laboratories, making subsequent testing at the same laboratory optimal. In many patients who are successfully treated for syphilis, a

nontreponemal test ultimately becomes nonreactive (seroreversion). Persistently reactive nontreponemal tests after successful treatment—typically with low titers (1:1 to 1:4) and more commonly in HIV-infected patients—are called serofast reactions.

False positive nontreponemal test results can occur in numerous conditions (Table III).¹⁸

False negative nontreponemal tests occur most commonly in early or late infections and with the prozone phenomenon.¹⁹ Although nontreponemal tests are reactive in 70% to 80% of patients with primary syphilis,¹⁰ seroconversion can take up to 3 months.²⁰⁻²² In the prozone phenomenon, high antibody concentrations prevent formation of the antigen–antibody complexes required to produce a reactive result. After serial dilutions to decrease antibody concentrations, the test becomes reactive. The prozone phenomenon is rare (<2%) and is associated with pregnancy, HIV coinfection, neurosyphilis, and a high clinical burden of disease (for example, lues maligna).^{10,23}

Treponemal tests. Treponemal tests measure immunoglobulin M (IgM) and IgG antibodies that are specific to *T pallidum* proteins. They include older assays (*T pallidum* particle agglutination, fluorescent treponemal antibody absorption, and *T pallidum* hemagglutination tests) and newer assays (enzyme

Table II. Histopathologic features of mucocutaneous syphilis

Variant	Histopathology
Primary syphilis	
Chancre	<ul style="list-style-type: none"> Epidermal acanthosis, spongiosis. Papillary dermal edema⁷¹ Dense inflammation of full dermis: lymphocytes, histiocytes, and plasma cells Staining: numerous spirochetes
Secondary syphilis	
Typical exanthem	<ul style="list-style-type: none"> Epidermis most commonly shows psoriasiform hyperplasia, spongiosis, basovacuolar change, elongation of rete ridges. Can see parakeratosis, lymphocyte exocytosis, and necrotic keratinocytes Dermal inflammation can be subtle or brisk, superficial and deep perivascular, interstitial, lichenoid, or granulomatous. Variable mix of lymphocytes, histiocytes, neutrophils, and plasma cells. 25% of cases lack plasma cells⁷² Atypical lymphocytic nuclei can mimic mycosis fungoides or lymphoma⁷¹ Epidermis ulcerated, florid hyperplasia, neutrophilic microabscesses³ Staining: numerous spirochetes⁷¹
Condyloma lata	
Alopecia	<ul style="list-style-type: none"> Superficial and deep perivascular and perifollicular infiltrate of lymphocytes and plasma cells that permeate the outer root sheath Increase in telogen hairs Staining: may see spirochetes in peribulbar region with matrix penetration^{3,73}
Pustular	
Nodular	<ul style="list-style-type: none"> Subcorneal and intrafollicular neutrophils, often with noncaseating granulomas^{74,75} Lichenoid or dense nodular granulomatous infiltrate of lymphocytes, histiocytes, and plasma cells.⁷⁶⁻⁷⁸ Can mimic cutaneous lymphoma^{79,80}
Lues maligna	<ul style="list-style-type: none"> Endarteritis obliterans of dermal vessels with ischemic necrosis Dense dermal infiltrate of lymphocytes, plasmas > neutrophils, giant cells Staining: spirochetes absent or sparse⁸¹⁻⁸⁴
Late syphilis	
Nodoulcerative	<ul style="list-style-type: none"> Granulomatous inflammation of lymphocytes, multinucleated giant cells, and plasma cells. No significant necrosis⁸⁵
Gummatous	<ul style="list-style-type: none"> Extensive caseating necrosis⁸⁶

Table III. Causes of false positive treponemal and nontreponemal tests

Nontreponemal	Treponemal
Advanced age	Advanced age
Autoimmune/chronic inflammatory disease—rheumatoid arthritis, systemic lupus erythematosus, thyroiditis, or ulcerative colitis	Autoimmune disease—systemic lupus or scleroderma
Intravenous drug use	Intravenous drug use
Pregnancy	Pregnancy
Idiopathic (1% general population)	Immunizations
Immunizations	
Immunoglobulin abnormalities	
Infection—HCV, HIV, EBV, endocarditis, TB, leprosy, varicella, measles, mumps, malaria pinta, yaws, rickettsia, brucellosis, chancroid, or lymphogranuloma venereum	Infection: brucellosis, HSV, EBV, leptospirosis, leprosy, Lyme disease, malaria, pinta, or yaws
Malignancy	
Vasculitis	

EBV, Epstein-Barr virus; HCV, hepatitis C virus; HSV, herpes simplex virus; TB, tuberculosis.

immunoassay [EIA] and chemiluminescence immunoassay [CLIA]). Results are typically reported qualitatively only (reactive or nonreactive), without titers.

Treponemal tests are typically more sensitive than nontreponemal tests during early infection. IgM and

IgG are often detectable 2 and 4 weeks after exposure, respectively, and in some cases within 3 days of a chancre's appearance.^{24,25} Higher sensitivity during early infection is important when caring for patients without a history of syphilis who are

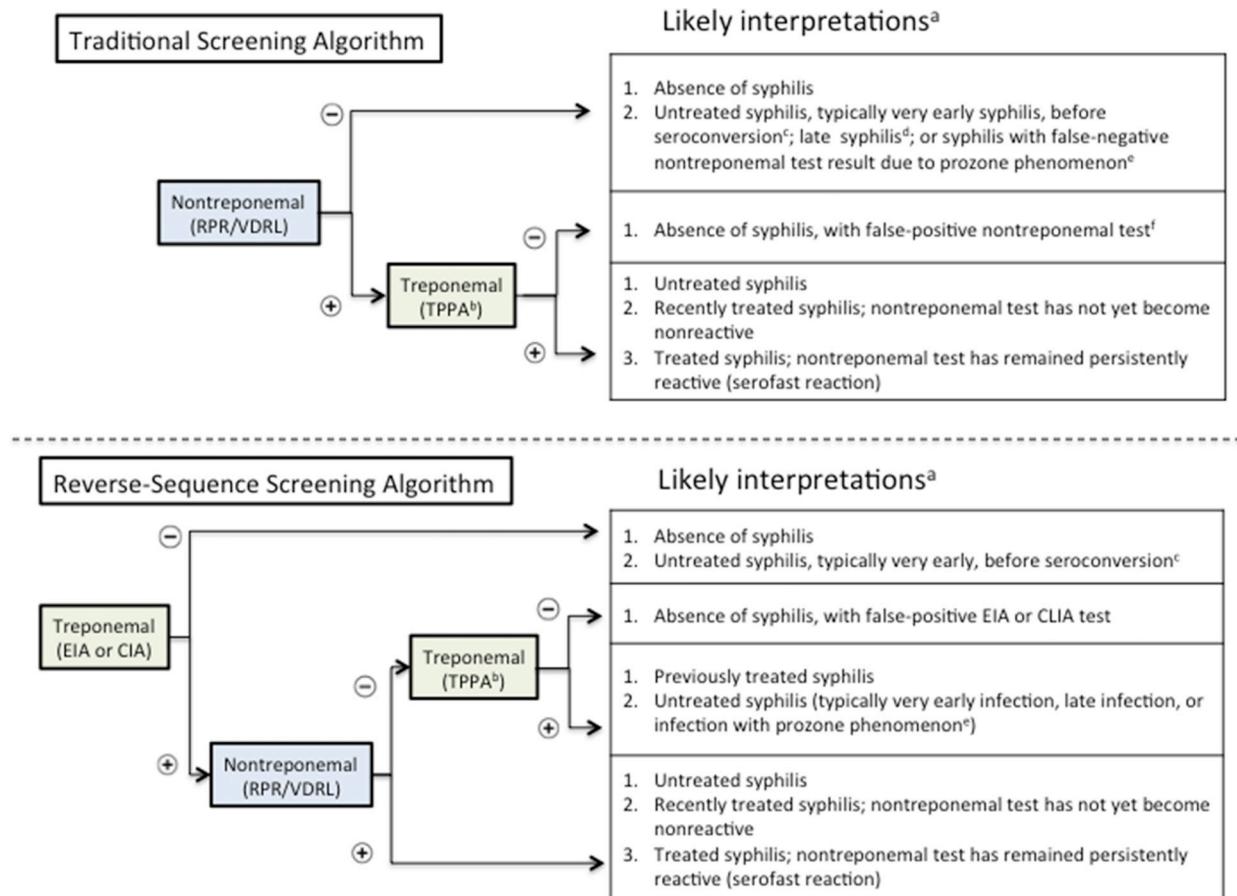


Fig 1. Screening algorithms for the laboratory diagnosis of syphilis. ^aSerologic results should always be interpreted in connection with clinical findings and epidemiologic suspicion for infection. In complicated cases, seek consultation from a specialist for assistance with interpretation of serologic test results. ^bOr other non-EIA, non-CLIA treponemal test. ^cIf suspected, request that the laboratory perform a treponemal test, which typically becomes reactive before the nontreponemal test. If the treponemal test is also nonreactive, consider empiric treatment, repeat testing, or use of direct detection methods. ^dIf suspected, request that the laboratory perform a treponemal test, which typically remains reactive for life. ^eIf suspected, request that the laboratory dilute the serum to overcome the prozone phenomenon. ^fSee Table III for etiologies of false positive test results. If syphilis is strongly suspected clinically, consider repeating TPPA later, performing a different treponemal test, using direct detection methods (if possible), or treating empirically for syphilis. +, Reactive; -, nonreactive; CLIA, chemiluminescence assay; EIA, enzyme immunoassay; RPR, rapid plasma reagent test; TPPA, *Treponema pallidum* particle agglutination test; VDRL, Venereal Disease Research Laboratory test. Adapted from Centers for Disease Control and Prevention (<https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6005a1.htm> and <https://www.cdc.gov/std/tg2015/default.htm>).

suspected of having primary syphilis. If there is suspicion of primary syphilis (in a patient without a previous syphilis infection) and the nontreponemal test is nonreactive, physicians should request a treponemal test—something that laboratories typically would not reflexively do. Sensitivities of treponemal tests approach 100% and exceed 95% for secondary and tertiary syphilis, respectively. Causes of false positive results are shown in Table III. The

prozone phenomenon does not occur in treponemal serologic tests.

Syphilis patients whose treponemal tests are reactive will likely have reactive tests for life, and subsequent treponemal testing cannot distinguish between previous and current infections. The exception occurs among some patients successfully treated during early infections whose treponemal tests sometimes revert to nonreactive.

Sequence of serologic tests in laboratory screening algorithm

Historically, nontreponemal tests were less costly and complicated to perform than treponemal tests. Therefore, nontreponemal tests are done first in the traditional screening algorithm (Fig 1). Only if the nontreponemal test is reactive is a treponemal test conducted (unless specifically requested by a provider).

Newer treponemal tests (EIA and CLIA) are automated high-throughput assays, making them less costly and complicated to perform than nontreponemal tests. For that financial reason, many laboratories now perform EIA or CLIA tests first, in the so-called reverse sequence screening algorithm. EIA and CLIA tests are more sensitive in early or late infections. False positive rates might be higher in the reverse sequence algorithm compared with the traditional screening algorithm, depending on the background prevalence of syphilis in the population.²⁶

The CDC sanctions both screening algorithms. Interpretation of either can be complicated, particularly when treponemal and nontreponemal tests are discordant.^{26,27} A guide to interpretation is outlined in Figure 1, but a full discussion is beyond the scope of this continuing medical education article. Physicians seeking guidance in these cases should consult a specialist or their state or local public health department. Physicians should be aware of the algorithm their laboratory uses so that they can appropriately interpret serologic test results.

Rapid point-of-care tests

Relatively inexpensive point-of-care treponemal serologic tests that provide results within 30 minutes are commercially available.²⁸ Most use immunochromatographic strips coated with *T pallidum* recombinant antigens to detect IgM, IgG, or IgA antibodies.^{20,29} Sensitivities (74-98%) and specificities (93-99%) are similar to conventional treponemal tests.²⁹⁻³⁴ Like other treponemal tests, they cannot distinguish between previous and current infections. Dual treponemal/nontreponemal point-of-care tests have been developed, but they have a lower sensitivity.^{28,31,35}

Rapid point-of-care tests have been used most commonly in resource-poor settings, particularly for antenatal screening and for persons at high risk who are unlikely to follow up.³⁴ In 2014, the US Food and Drug Administration granted a waiver permitting use of a rapid treponemal test in clinical or nonclinical sites, including by nonlicensed personnel.³⁶ However, in the field the test had lower sensitivity and specificity than claimed.³⁷

Neurosyphilis

Testing for the diagnosis of neurosyphilis is covered in detail in CDC STD Treatment Guidelines.²²

MANAGEMENT

Key points

- **Benzathine penicillin G is the recommended treatment for all syphilis stages**
- **Duration of treatment and route of administration depend on stage and pregnancy status, whether the patient is allergic to penicillin, and whether the patient has neurosyphilis, otic syphilis, or ocular syphilis**
- **Follow-up clinical and serologic evaluation should occur at 3- to 6-month intervals**

Both the CDC and the World Health Organization have issued syphilis treatment guidelines.^{22,38} The following recommendations follow CDC guidelines.

Order appropriate laboratory testing

Regardless of stage or nonserologic tests, all patients with syphilis should undergo serologic testing with both nontreponemal and treponemal (if not known to have reactive treponemal tests because of a history of syphilis) tests. In addition, even if a nontreponemal test has been performed recently, a repeat nontreponemal test on the day of treatment—a so-called day-of-treatment titer—should be performed to enable the evaluation of serologic response to treatment.

Determine stage of infection

Dermatologists most often diagnose primary or secondary syphilis, which have mucocutaneous manifestations. For patients with current reactive serologies without signs or symptoms of primary, secondary, or tertiary syphilis, physicians must ascertain whether the serologies represent previously treated infection (and if so, whether treatment was successful) or new infection (and if so, determine duration of infection to stage the patient). Doing so requires eliciting a sexual and medical history and reviewing the patient's serologic history, if available. Because all reactive serologic tests for syphilis in the United States must be reported to public health departments, physicians can contact their local jurisdiction for help in obtaining and, if needed, interpreting past reactive serologic test results.

Assess for presence of neurosyphilis, otic syphilis, or ocular syphilis, and make appropriate referrals

Refer to the first article in this continuing medical education series for a discussion of signs and

Table IV. U.S. Centers for Disease Control and Prevention treatment recommendations, by stage, for nonpregnant and pregnant adults* with syphilis who do not have neurosyphilis, otic syphilis, or ocular syphilis²²

Stage	Patient	Recommended regimen*	For penicillin-allergic patients [†]
Primary, secondary, or early nonprimary nonsecondary	Nonpregnant	Benzathine penicillin G 2.4 million units intramuscular × 1 dose	Doxycycline 100 mg twice per day × 14 days, [‡] or tetracycline 500 mg 4 times per day × 14 days, [‡] or ceftriaxone [§] or azithromycin
	Pregnant	Benzathine penicillin G 2.4 million units intramuscular × 1 dose [¶]	Desensitize and treat with penicillin
Unknown duration or late	Nonpregnant	Benzathine penicillin G 2.4 million units intramuscular × 3 weekly doses [#]	Doxycycline 100 mg twice per day × 28 days, or tetracycline 500 mg 4 times per day × 28 days, or ceftriaxone [§]
	Pregnant	Benzathine penicillin G 2.4 million units intramuscular × 3 weekly doses [#]	Desensitize and treat with penicillin
Neurosyphilis, ocular syphilis, or otic syphilis	Pregnant or nonpregnant	Aqueous penicillin G 18-24 million units per day IV divided into doses every 4 hours or continuous infusion × 10-14 days, or procaine penicillin G 2.4 million units IM daily plus probenecid 500 mg PO every 6 hours × 10-14 days	Desensitize and treat with penicillin

Note: treatment recommendations do not depend on HIV status or titer.

IM, Intramuscular; *IV*, intravenous; *PO*, per os.

*U.S. Centers for Disease Control and Prevention dosing recommendations for pediatric patients are available at <https://www.cdc.gov/std/tg2015/syphilis.htm>.

[†]Close follow-up is required for all non—benzathine penicillin G treatments. Penicillin-allergic patients whose compliance or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin G.

[‡]Compliance is likely better with doxycycline than tetracycline.^{63,88,90,91}

[§]Discuss with a specialist or contact the public health department.⁸⁷⁻⁸⁹

[#]Use with caution because of widespread resistance and do not use in men who have sex with men, persons with HIV, or pregnant women.^{92,93}

[¶]Some evidence suggests that additional therapy is beneficial for pregnant women. A second dose can be administered 1 week after the first dose.

^{||}Consult U.S. Centers for Disease Control and Prevention treatment guidelines, a specialist, or a public health department regarding management of missed doses.

symptoms of these manifestations and how to detect them. Referrals for cerebrospinal fluid examination via lumbar puncture, according to CDC guidelines, are recommended only for patients who meet 1 of the following conditions: (1) signs or symptoms of neurosyphilis, otic syphilis, or ocular syphilis; (2) suspected treatment failure; or (3) tertiary syphilis. Patients with syphilis who have ocular symptoms should be referred for an ophthalmologic evaluation in addition to cerebrospinal fluid examination.

Provide appropriate antibiotic treatment

Benzathine penicillin G, a penicillin formulation with a long half-life, is the recommended treatment for all syphilis stages. Duration and route of

administration depend on stage and pregnancy status (Table IV). Alternative treatments in Table IV may be considered for nonpregnant patients who are allergic to penicillin and for whom compliance can be assured. However, because benzathine penicillin G is the only therapy with documented efficacy for treating both the pregnant person and the fetus, pregnant patients must be desensitized and treated with penicillin.^{22,38,69}

Physicians should ensure treatment with penicillin formulations containing only benzathine penicillin G (Bicillin L-A), rather than with other formulations that contain both benzathine penicillin G and procaine penicillin (Bicillin C-R). When administered intramuscularly, procaine penicillin does not adequately penetrate sequestered sites,

such as the central nervous system, and should not be used to treat syphilis, although in numerous cases it mistakenly has been.^{22,39,40}

Neurosyphilis, otic syphilis, and ocular syphilis require treatment with intravenous aqueous crystalline penicillin G or an alternative (if compliance can be ensured) of intramuscular penicillin G plus probenecid for 10 to 14 days. Because durations of both regimens are shorter than the duration of the regimen used for unknown duration or late syphilis, benzathine penicillin G 2.4 million units intramuscularly once per week for ≤ 3 weeks can be considered for patients in that stage after completion of neurosyphilis treatment.

CDC treatment recommendations for all stages and for neurosyphilis, otic syphilis, and ocular syphilis do not depend on HIV status or nontreponemal test titer.

Physicians should consider empiric treatment if, based on clinical presentation and epidemiologic risk, the index of suspicion is high, particularly if follow-up cannot be assured.

Counsel patients about possible treatment reactions

Treatment might precipitate a Jarisch–Herxheimer reaction, which typically presents within 1 day as fever, headache, myalgia, and possibly worsening rash. The proposed mechanism is spirochete destruction causing the release of lipoproteins, immune complex formation, and cytokine cascades, including tumor necrosis factor–alpha, interleukin-6, and interleukin-8.⁴¹ The reaction occurs more commonly and severely in patients with a higher clinical burden of disease and higher nontreponemal test titers.⁴²⁻⁴⁴ Often mistaken for a drug allergy, the reaction resolves spontaneously, typically within 24 hours. Antipyretics and hydration can be used for symptomatic relief. Pretreatments, such as acetaminophen and antihistamines, do not prevent the reaction. It can induce early labor, and pregnant women should be treated and monitored in coordination with obstetricians.⁴⁵

Ensure that other sexual health needs are met

Patients who are diagnosed with syphilis often have other unmet sexual health needs, including screening for HIV and other STDs,⁴⁶ sexual health–related vaccinations,⁴⁷ and preexposure prophylaxis⁴⁸ or nonoccupational postexposure prophylaxis⁴⁹ for HIV. A full discussion of these needs is beyond the scope of this continuing medical education series. The CDC recommends HIV testing for all patients with syphilis who are not known to have HIV. In addition, a syphilis diagnosis

within the previous 6 months is 1 CDC criterion for initiating preexposure prophylaxis.⁵⁰ Among men (including men who have sex with men⁵¹), a syphilis diagnosis is associated with a higher risk for subsequent HIV seroconversion. Eliciting a sexual and gender identity history, including the gender(s) of sex partners, is essential to assess patients' sexual health needs. Physicians who are not able to identify or meet these needs should refer patients for additional care.

Encourage the patient to inform their sex partner(s) of possible exposure to syphilis

Physicians should encourage patients with syphilis to disclose their diagnosis to recent sex partner(s) to improve those persons' health and to stop onward transmission. Health departments can also assist with partner notification, if patients desire. Relevant time frames for exposure of sex partners are as follows: primary syphilis, 3 months plus duration of symptoms; secondary syphilis, 6 months plus duration of symptoms; and early nonprimary nonsecondary syphilis, 1 year. Patients should be counseled to abstain from sexual activity for ≥ 1 week and until symptoms completely resolve.

Report the case to the appropriate public health department and inform the patient of the requirement to do so

Syphilis is a legally reportable disease throughout the United States for both clinicians and laboratories. Mechanisms and details of reporting depend on state or local regulations. Physicians should consult their local health department for more information. Physician reporting, which includes stage, enables health departments to prioritize outreach efforts to primary and secondary syphilis patients who are likely to have been recently infectious to recent sex partners and helps with disease surveillance. Informing patients that the case will be reported, and that the public health department might follow up with them, can facilitate subsequent positive interactions.

Follow-up to ensure clinical and serologic response

Treatment response is assessed clinically and serologically. The CDC recommends clinical evaluation and nontreponemal tests at 6, 12, and 24 months for HIV-uninfected patients and at 3, 6, 9, 12, and 24 months for HIV-infected patients with HIV infection.²² Patients should be counseled to return for care if symptoms fail to resolve within 2 weeks.

Serologic response is defined as a fourfold or greater decline in nontreponemal test titers (for

Table V. Syphilis screening recommendations for syphilis from the U.S. Centers for Disease Control and Prevention and the U.S. Preventative Services Task Force

Organization or agency	Recommendations
U.S. CDC ^{22,94}	<p>Pregnant women</p> <ul style="list-style-type: none"> Screen all pregnant women at first prenatal visit Rescreen early in third trimester and at delivery if at high risk <p>MSM</p> <ul style="list-style-type: none"> At least annually for sexually active men Every 3-6 months if at increased risk <p>Persons with HIV</p> <ul style="list-style-type: none"> For sexually active individuals, screen at first HIV evaluation, and at least annually thereafter More frequent screening might be appropriate depending on individual risk behaviors and the local epidemiology
U.S. Preventive Services Task Force ^{*,95,96}	<p>Pregnant women</p> <ul style="list-style-type: none"> Screen all pregnant women as early as possible, whether at first prenatal visit or at delivery if patient has not received prenatal care Many organizations recommend rescreening women at high risk during the third trimester and at delivery, including (according to the CDC⁹⁷): <ul style="list-style-type: none"> History of syphilis infection, incarceration, or drug use Multiple or concurrent sex partners Women who live in high-prevalence areas <p>Nonpregnant adults and adolescents</p> <ul style="list-style-type: none"> MSM and persons living with HIV have the highest risk Other risk factors <ul style="list-style-type: none"> History of incarceration History of commercial sex work Geography (southern and western United States and metropolitan areas) Race/ethnicity (black, Hispanic, American Indian/Alaska Native, and Native Hawaiian/Pacific Islander) Males <29 years of age Optimal screening frequency not well established MSM or persons living with HIV may benefit from screening every 3 months

CDC, Centers for Disease Control and Prevention; MSM, men who have sex with men.

*Both recommendations (for pregnant women and for nonpregnant adults and adolescents) are "A" grade recommendations, meaning that the Task Force recommends the service, with high certainty that the net benefit is substantial, and that clinicians should offer or provide the service. Under the Affordable Care Act, insurance companies must cover "A" grade services without requiring copayment by patients.

example, from 1:64 to 1:16 or lower). Treatment failure should be considered if titer decline does not occur by the following time points: 1 year for HIV-uninfected patients with primary or secondary syphilis; 2 years for HIV-uninfected patients with early nonprimary nonsecondary syphilis; or 2 years for HIV-infected patients with primary, secondary, or early nonprimary nonsecondary syphilis. Suspected treatment failure warrants additional evaluation and management that is beyond the scope of this continuing medical education series. Lack of titer decline (called serologic nonresponse) affects 12% to 20% of patients with primary and secondary syphilis^{52,53} and is associated with lower baseline nontreponemal titer, older age, late stage infection, and possibly HIV infection.⁵⁴⁻⁶³ In addition, rising titers in a recently treated patient might indicate reinfection, which, as mentioned in the first

article in this continuing medical education series, is not uncommon among patients with a history of syphilis.⁶⁴

Syphilis in infants and children

Infants and children >1 month of age who are diagnosed with syphilis should have birth and maternal records reviewed to assess whether the infection was congenitally or sexually acquired. Management should be coordinated with a pediatric infectious disease specialist and should include evaluation for sexual abuse, typically by consulting child protection services.²²

PREVENTION AND CONTROL

Syphilis prevention and control efforts by national, state, and local public health agencies include disease surveillance, epidemiologic analyses, education of

providers and the public, support for clinical and prevention services, outreach to recently diagnosed patients and their sex partners, and screening of persons who are at high risk for syphilis. Screening means assessing for the presence of a disease in persons without signs or symptoms of that disease; by comparison, testing is conducted in persons with signs or symptoms of a disease. While a full discussion of syphilis prevention and control efforts is beyond the scope of this continuing medical education series, screening recommendations from the CDC and the U.S. Preventive Services Task Force are shown in Table V. The World Health Organization has also published screening guidelines for pregnant women.⁶⁵

In conclusion, syphilis is an increasingly important public health and clinical issue. Dermatologists can play key roles in the diagnosis and management of syphilis and can contribute to prevention and control efforts.

REFERENCES

1. Centers for Disease Control and Prevention. Syphilis (*Treponema pallidum*) 2018 case definition. Available at: <https://www.cdc.gov/nndss/conditions/syphilis/case-definition/2018/>. Accessed April 5, 2018.
2. Martin-Ezquerro G, Fernandez-Casado A, Barco D, et al. *Treponema pallidum* distribution patterns in mucocutaneous lesions of primary and secondary syphilis: an immunohistochemical and ultrastructural study. *Hum Pathol.* 2009;40:624-630.
3. Jeerapaet P, Ackerman AB. Histologic patterns of secondary syphilis. *Arch Dermatol.* 1973;107:373-377.
4. Phelps RG, Knispel J, Tu ES, Cernainu G, Saruk M. Immunoperoxidase technique for detecting spirochetes in tissue sections: comparison with other methods. *Int J Dermatol.* 2000;39:609-613.
5. Hoang MP, High WA, Molberg KH. Secondary syphilis: a histologic and immunohistochemical evaluation. *J Cutan Pathol.* 2004;31:595-599.
6. Carlson JA, Dabiri G, Cribier B, Sell S. The immunopathobiology of syphilis: the manifestations and course of syphilis are determined by the level of delayed-type hypersensitivity. *Am J Dermatopathol.* 2011;33:433-460.
7. Kennedy E, Creighton E. *Darkfield Microscopy for the Detection and Identification of Treponema pallidum. Manual of Tests for Syphilis.* 9th ed. Atlanta, GA: Centers for Disease Control and Prevention; 1998.
8. Pierce EF, Katz KA. Darkfield microscopy for point-of-care syphilis diagnosis. *MLO Med Lab Obs.* 2011;43:30-31.
9. Larsen SA, Steiner BM, Rudolph AH. Laboratory diagnosis and interpretation of tests for syphilis. *Clin Microbiol Rev.* 1995;8:1-21.
10. Ratnam S. The laboratory diagnosis of syphilis. *Can J Infect Dis Med Microbiol.* 2005;16:45-51.
11. Chi KH, Danavall D, Taleo F, et al. Molecular differentiation of *Treponema pallidum* subspecies in skin ulceration clinically suspected as yaws in Vanuatu using real-time multiplex PCR and serological methods. *Am J Trop Med Hyg.* 2015;92:134-138.
12. Grange PA, Gressier L, Dion PL, et al. Evaluation of a PCR test for detection of *Treponema pallidum* in swabs and blood. *J Clin Microbiol.* 2012;50:546-552.
13. Orle KA, Gates CA, Martin DH, Body BA, Weiss JB. Simultaneous PCR detection of *Haemophilus ducreyi*, *Treponema pallidum*, and herpes simplex virus types 1 and 2 from genital ulcers. *J Clin Microbiol.* 1996;34:49-54.
14. Liu H, Rodes B, Chen CY, Steiner B. New tests for syphilis: rational design of a PCR method for detection of *Treponema pallidum* in clinical specimens using unique regions of the DNA polymerase I gene. *J Clin Microbiol.* 2001;39:1941-1946.
15. Kahn LB, Gordon W. Sarcoid-like granulomas in secondary syphilis. A clinical and histopathologic study of five cases. *Arch Pathol.* 1971;92:334-337.
16. Belisle JT, Brandt ME, Radolf JD, Norgard MV. Fatty acids of *Treponema pallidum* and *Borrelia burgdorferi* lipoproteins. *J Bacteriol.* 1994;176:2151-2157.
17. Lafond RE, Lukehart SA. Biological basis for syphilis. *Clin Microbiol Rev.* 2006;19:29-49.
18. Hook EWR. Syphilis. *Lancet.* 2017;389:1550-1557.
19. Gao Y, Katz KA. Clinical and serologic evolution of multiple penile chancres in a man who has sex with men. *JAMA Dermatol.* 2018;154:108-109.
20. Sena AC, White BL, Sparling PF. Novel *Treponema pallidum* serologic tests: a paradigm shift in syphilis screening for the 21st century. *Clin Infect Dis.* 2010;51:700-708.
21. Hart G. Syphilis tests in diagnostic and therapeutic decision making. *Ann Intern Med.* 1986;104:368-376.
22. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Morb Mortal Wkly Rep.* 2015;64:1-137.
23. Liu LL, Lin LR, Tong ML, et al. Incidence and risk factors for the prozone phenomenon in serologic testing for syphilis in a large cohort. *Clin Infect Dis.* 2014;59:384-389.
24. Luger A. Serological diagnosis of syphilis; current methods. In: Young H, McMillan A, eds. *Immunological diagnosis of sexually transmitted diseases.* New York: Marcel Dekker; 1998:249-274.
25. Baker-Zander SA, Roddy RE, Handsfield HH, Lukehart SA. IgG and IgM antibody reactivity to antigens of *Treponema pallidum* after treatment of syphilis. *Sex Transm Dis.* 1986;13:214-220.
26. Centers for Disease Control and Prevention. Discordant results from reverse sequence syphilis screening—five laboratories, United States, 2006–2010. *MMWR Morb Mortal Wkly Rep.* 2011; 60:133-137.
27. Centers for Disease Control and Prevention. Syphilis testing algorithms using treponemal tests for initial screening—four laboratories, New York City, 2005–2006. *MMWR Morb Mortal Wkly Rep.* 2008;57:872-875.
28. World Health Organization. *Rapid diagnostic tests for sexually transmitted infections.* Geneva, Switzerland: World Health Organization; 2006.
29. Zarakolu P, Buchanan I, Tam M, Smith K, Hook EW 3rd. Preliminary evaluation of an immunochromatographic strip test for specific *Treponema pallidum* antibodies. *J Clin Microbiol.* 2002;40:3064-3065.
30. Yin YP, Chen XS, Wei WH, et al. A dual point-of-care test shows good performance in simultaneously detecting nontreponemal and treponemal antibodies in patients with syphilis: a multisite evaluation study in China. *Clin Infect Dis.* 2013;56:659-665.
31. Castro AR, Esfandiari J, Kumar S, et al. Novel point-of-care test for simultaneous detection of nontreponemal and treponemal antibodies in patients with syphilis. *J Clin Microbiol.* 2010;48:4615-4619.
32. Herring AJ, Ballard RC, Pope V, et al. A multi-centre evaluation of nine rapid, point-of-care syphilis tests using archived sera. *Sex Transm Dis.* 2006;82(suppl 5):v7-v12.

33. World Health Organization. *The sexually transmitted diagnostics initiative (SDI): special programme for research and training in tropical diseases (TDR)*. Geneva, Switzerland: World Health Organization; 2003.
34. Jafari Y, Peeling RW, Shivkumar S, et al. Are *Treponema pallidum* specific rapid and point-of-care tests for syphilis accurate enough for screening in resource limited settings? Evidence from a meta-analysis. *PLoS One*. 2013;8:e54695.
35. Causier LM, Kaldor JM, Conway DP, et al. An evaluation of a novel dual treponemal/nontreponemal point-of-care test for syphilis as a tool to distinguish active from past treated infection. *Clin Infect Dis*. 2015;61:184-191.
36. FDA grants CLIA waiver expanding availability of rapid screening test for syphilis. Available at: <https://www.mycme.com/mycme-quick-takes/fda-grants-clia-waiver-expanding-the-availability-of-rapid-screening-test-for-syphilis/article/388405/>. Accessed June 25, 2019.
37. Matthias J, Dwiggins P, Totten Y, et al. Notes from the field: evaluation of the sensitivity and specificity of a commercially available rapid syphilis test - Escambia County, Florida, 2016. *MMWR Morb Mortal Wkly Rep*. 2016;65:1174-1175.
38. World Health Organization. *Guidelines for the treatment of Treponema pallidum (syphilis)*. Geneva, Switzerland: World Health Organization; 2016.
39. Centers for Disease Control and Prevention. Inadvertent use of Bicillin C-R to treat syphilis infection—Los Angeles, California, 1999–2004. *MMWR Morb Mortal Wkly Rep*. 2005;54:217-219.
40. Centers for Disease Control and Prevention. Inadvertent use of Bicillin C-R for treatment of syphilis—Maryland, 1998. *MMWR Morb Mortal Wkly Rep*. 1999;48:777-779.
41. Pound MW, May DB. Proposed mechanisms and preventative options of Jarisch-Herxheimer reactions. *J Clin Pharm Ther*. 2005;30:291-295.
42. Yang CJ, Lee NY, Lin YH, et al. Jarisch-Herxheimer reaction after penicillin therapy among patients with syphilis in the era of the hiv infection epidemic: incidence and risk factors. *Clin Infect Dis*. 2010;51:976-979.
43. Brown ST. Adverse reactions in syphilis therapy. *J Am Vener Dis Assoc*. 1976;3(2 pt 2):172-176.
44. Aronson IK, Soltani K. The enigma of the pathogenesis of the Jarisch-Herxheimer reaction. *Br J Vener Dis*. 1976;52:313-315.
45. Rac MW, Revell PA, Eppes CS. Syphilis during pregnancy: a preventable threat to maternal-fetal health. *Am J Obstet Gynecol*. 2017;216:352-363.
46. Centers for Disease Control and Prevention. Screening recommendations and considerations referenced in treatment guidelines and original sources. Available at: <https://www.cdc.gov/std/tg2015/screening-recommendations.htm>. Accessed July 25, 2018.
47. Centers for Disease Control and Prevention. Recommended immunization schedule for adults aged 19 years or older by medical conditions and other indications. Available at: <https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html>. Accessed July 25, 2018.
48. Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States - 2017. Update: a clinical practice guideline. Available at: <https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf>. Accessed July 25, 2018.
49. Centers for Disease Control and Prevention. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV - United States, 2016. Available at: <https://www.cdc.gov/hiv/pdf/programresources/cdc-hiv-npep-guidelines.pdf>. Accessed July 25, 2018.
50. Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States - 2017 update. Available at: <https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf>. Accessed July 25, 2018.
51. Solomon MM, Mayer KH, Glidden DV, et al. Syphilis predicts HIV incidence among men and transgender women who have sex with men in a preexposure prophylaxis trial. *Clin Infect Dis*. 2014;59:1020-1026.
52. Rolfs RT, Joesoef MR, Hendershot EF, et al. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. The Syphilis and HIV Study Group. *N Engl J Med*. 1997;337:307-314.
53. Sena AC, Wolff M, Behets F, et al. Response to therapy following retreatment of serofast early syphilis patients with benzathine penicillin. *Clin Infect Dis*. 2013;56:420-422.
54. Ghanem KG, Erbelding EJ, Wiener ZS, Rompalo AM. Serological response to syphilis treatment in HIV-positive and HIV-negative patients attending sexually transmitted diseases clinics. *Sex Transm Infect*. 2007;83:97-101.
55. Jinno S, Anker B, Kaur P, Bristow CC, Klausner JD. Predictors of serological failure after treatment in HIV-infected patients with early syphilis in the emerging era of universal antiretroviral therapy use. *BMC Infect Dis*. 2013;13:605.
56. Tittes J, Aichelburg MC, Antoniewicz L, Geusau A. Enhanced therapy for primary and secondary syphilis: a longitudinal retrospective analysis of cure rates and associated factors. *Int J STD AIDS*. 2013;24:703-711.
57. Tong ML, Lin LR, Liu GL, et al. Factors associated with serological cure and the serofast state of HIV-negative patients with primary, secondary, latent, and tertiary syphilis. *PLoS One*. 2013;8:e70102.
58. Long CM, Klausner JD, Leon S, et al. Syphilis treatment and HIV infection in a population-based study of persons at high risk for sexually transmitted disease/HIV infection in Lima, Peru. *Sex Transm Dis*. 2006;33:151-155.
59. Manavi K, McMillan A. The outcome of treatment of early latent syphilis and syphilis with undetermined duration in HIV-infected and HIV-uninfected patients. *Int J STD AIDS*. 2007;18:814-818.
60. Sena AC, Wolff M, Martin DH, et al. Predictors of serological cure and Serofast State after treatment in HIV-negative persons with early syphilis. *Clin Infect Dis*. 2011;53:1092-1099.
61. Knaute DF, Graf N, Lautenschlager S, Weber R, Bosshard PP. Serological response to treatment of syphilis according to disease stage and HIV status. *Clin Infect Dis*. 2012;55:1615-1622.
62. Li J, Wang LN, Zheng HY. Predictors of serological cure and serofast state after treatment in HIV-negative patients with early syphilis in China. *Sex Transm Infect*. 2013;89:69.
63. Tsai JC, Lin YH, Lu PL, et al. Comparison of serological response to doxycycline versus benzathine penicillin G in the treatment of early syphilis in HIV-infected patients: a multi-center observational study. *PLoS One*. 2014;9:e109813.
64. Cohen SE, Chew Ng RA, Katz KA, et al. Repeat syphilis among men who have sex with men in California, 2002-2006: implications for syphilis elimination efforts. *Am J Public Health*. 2012;102:e1-e8.
65. World Health Organization. Syphilis screening and treatment for pregnant women. Available at: <http://apps.who.int/iris/bitstream/handle/10665/259003/9789241550093-eng.pdf?sequence=1>. Accessed July 25, 2018.
66. Lesinski J, Krach J, Kadziewicz E. Specificity, sensitivity, and diagnostic value of the TPHA test. *Br J Vener Dis*. 1974;50:334-340.

67. Castro R, Prieto ES, Santo I, Azevedo J, Exposito Fda L. Evaluation of an enzyme immunoassay technique for detection of antibodies against *Treponema pallidum*. *J Clin Microbiol*. 2003;41:250-253.
68. Lefevre JC, Bertrand MA, Bauriaud R. Evaluation of the Captia enzyme immunoassays for detection of immunoglobulins G and M to *Treponema pallidum* in syphilis. *J Clin Microbiol*. 1990; 28:1704-1707.
69. Young H, Pryde J, Duncan L, Dave J. The Architect Syphilis assay for antibodies to *Treponema pallidum*: an automated screening assay with high sensitivity in primary syphilis. *Sex Transm Infect*. 2009;85:19-23.
70. Hook EW 3rd, Roddy RE, Lukehart SA, Hom J, Holmes KK, Tam MR. Detection of *Treponema pallidum* in lesion exudate with a pathogen-specific monoclonal antibody. *J Clin Microbiol*. 1985;22:241-244.
71. Crowson N, Magro C, Mihm M. Treponemal diseases. In: Elder DE, ed. *Lever's Histopathology of the Skin*. 11th ed. Philadelphia: Wolters Kluwer; 2015.
72. Abell E, Marks R, Jones EW. Secondary syphilis: a clinicopathological review. *Br J Dermatol*. 1975;93:53-61.
73. Nam-Cha SH, Guhl G, Fernandez-Pena P, Fraga J. Alopecia syphilitica with detection of *Treponema pallidum* in the hair follicle. *J Cutan Pathol*. 2007;34(suppl 1):37-40.
74. Noppakun N, Dinehart SM, Solomon AR. Pustular secondary syphilis. *Int J Dermatol*. 1987;26:112-114.
75. Kazlouskaya V, Wittmann C, Tsikhanouskaya I. Pustular secondary syphilis: report of three cases and review of the literature. *Int J Dermatol*. 2014;53:e428-e431.
76. Tsai KY, Brenn T, Werchniak AE. Nodular presentation of secondary syphilis. *J Am Acad Dermatol*. 2007;57(2 suppl):S57-S58.
77. Rosmaninho A, Sanches M, Lobo I, Alves R, Selores M. Nodular secondary syphilis. *Eur Dermatol*. 2011;21:136-137.
78. Pavithran K. Nodular secondary syphilis. *Int J Dermatol*. 1991; 30:799-800.
79. Hodak E, David M, Rothen A, Bialowance M, Sandbank M. Nodular secondary syphilis mimicking cutaneous lymphoreticular process. *J Am Acad Dermatol*. 1987;17(5 pt 2):914-917.
80. Moon HS, Park K, Lee JH, Son SJ. A nodular syphilitid presenting as a pseudolymphoma: mimicking a cutaneous marginal zone B-cell lymphoma. *Am J Dermatopathol*. 2009;31:846-848.
81. Witkowski JA, Parish LC. The great imitator: malignant syphilis with hepatitis. *Clin Dermatol*. 2002;20:156-163.
82. Fisher DA, Chang LW, Tuffanelli DL. Lues maligna. Presentation of a case and a review of the literature. *Arch Dermatol*. 1969;99:70-73.
83. D'Amico R, Zalusky R. A case of lues maligna in a patient with acquired immunodeficiency syndrome (AIDS). *Scand J Infect Dis*. 2005;37:697-700.
84. Pleimes M, Hartschuh W, Kutzner H, Enk AH, Hartmann M. Malignant syphilis with ocular involvement and organism-depleted lesions. *Clin Infect Dis*. 2009;48:83-85.
85. Chung G, Kantor GR, Whipple S. Tertiary syphilis of the face. *J Am Acad Dermatol*. 1991;24(5 pt 2):832-835.
86. Boyd AS. Syphilitic gumma arising in association with foreign material. *J Cutan Pathol*. 2016;43:1028-1030.
87. Hook EW 3rd, Roddy RE, Handsfield HH. Ceftriaxone therapy for incubating and early syphilis. *J Infect Dis*. 1988; 158:881-884.
88. Psomas KC, Brun M, Causse A, Atoui N, Reynes J, Le Moing V. Efficacy of ceftriaxone and doxycycline in the treatment of early syphilis. *Med Mal Infect*. 2012;42:15-19.
89. Liang Z, Chen YP, Yang CS, et al. Meta-analysis of ceftriaxone compared with penicillin for the treatment of syphilis. *Int J Antimicrob Agents*. 2016;47:6-11.
90. Ghanem KG, Erbelding EJ, Cheng WW, Rompalo AM. Doxycycline compared with benzathine penicillin for the treatment of early syphilis. *Clin Infect Dis*. 2006;42:e45-e49.
91. Dai T, Qu R, Liu J, Zhou P, Wang Q. Efficacy of doxycycline in the treatment of syphilis. *Antimicrob Agents Chemother*. 2016; 61:e01092-16.
92. Mitchell SJ, Engelman J, Kent CK, Lukehart SA, Godornes C, Klausner JD. Azithromycin-resistant syphilis infection: San Francisco, California, 2000-2004. *Clin Infect Dis*. 2006;42: 337-345.
93. Lukehart SA, Godornes C, Molini BJ, et al. Macrolide resistance in *Treponema pallidum* in the United States and Ireland. *N Engl J Med*. 2004;351:154-158.
94. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2015. Screening recommendations and considerations referenced in treatment guidelines and original sources. Available at: <https://www.cdc.gov/std/tg2015/screening-recommendations.htm>. Accessed July 25, 2018.
95. Bibbins-Domingo K, Grossman DC, Curry SJ, et al, U.S. Preventative Services Task Force. Screening for syphilis infection in nonpregnant adults and adolescents: US Preventive Services Task Force recommendation statement. *JAMA*. 2016;315:2321-2327.
96. US Preventive Services Task Force, Curry SJ, Krist AH, Owens DK, et al. Screening for syphilis infection in pregnant women: US Preventive Services Task Force reaffirmation recommendation statement. *JAMA*. 2018;320: 911-917.
97. Centers for Disease Control and Prevention. Women and children deserve the best health possible. Available at: <https://www.cdc.gov/std/sam/2017women.htm>. Accessed September 10, 2018.

Dermatomyositis: Clinical features and pathogenesis



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Learning objectives

After completing this learning activity, participants should be able to define dermatomyositis and its variants in both adults and children; recognize the clinical features of DM (both cutaneous and systemic) and potential differences in presentation between adults and children; discuss DM pathogenesis, including genetic, environmental, and immune factors, with updated review on recently identified auto-antibodies; and recognize common features of DM on cutaneous and muscle biopsy as well as their significance in diagnosis of JDM.

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Dermatomyositis (DM) is an idiopathic inflammatory myopathy that is clinically heterogeneous and that can be difficult to diagnose. Cutaneous manifestations sometimes vary and may or may not parallel myositis and systemic involvement in time course or severity. Recent developments in our understanding of myositis-specific antibodies have the potential to change the diagnostic landscape of DM for dermatologists. Although phenotypic overlap exists, anti-Mi2, -MDA5, -NXP2, -TIF1, and -SAE antibodies may be correlated with distinct DM subtypes in terms of cutaneous manifestations, systemic involvement, and malignancy risk. This review highlights new findings on the DM-specific myositis-specific antibodies and their clinical associations in both adults and children. (J Am Acad Dermatol 2020;82:267-81.)

Key words: amyopathic dermatomyositis; dermatomyositis; juvenile dermatomyositis; idiopathic inflammatory myopathy; interstitial lung disease; malignancy-associated dermatomyositis; Mi2; MDA5; myositis-specific antibodies; NXP2; SAE; TIF1.

Dermatomyositis (DM) is an idiopathic inflammatory myopathy (IIM) that is characterized by distinct skin lesions and a clinically heterogeneous constellation of systemic manifestations. In the absence of characteristic dermatologic findings or myopathy, DM can be

difficult to diagnose. In addition, historical approaches to the diagnosis of DM have embraced the use of “overlap” syndromes to account for clinical heterogeneity, making diagnosis even more difficult. The first article in this continuing medical education series discusses the epidemiology, clinical

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Abbreviations used:

CADM:	clinically amyopathic dermatomyositis
CAJDM:	clinically amyopathic juvenile dermatomyositis
DM:	dermatomyositis
IFN:	interferon
IIM:	idiopathic inflammatory myopathy
ILD:	interstitial lung disease
JDM:	juvenile dermatomyositis
MDA5:	melanoma differentiation associated protein 5
MSA:	myositis-specific antibody
NXP2:	nuclear matrix protein 2
RP-ILD:	rapidly progressive interstitial lung disease

characteristics, histopathology, and pathogenesis of DM. Emphasis will be placed on the unique clinical manifestations associated with the presence of myositis-specific antibodies (MSAs).

EPIDEMIOLOGY

The epidemiology of DM is difficult to determine because a variety of classification systems (discussed in the second article in this continuing medical education series) have historically been used to diagnose the condition. Epidemiologic studies report incidence rates for the IIMs of 2.47-7.8 per 100,000 person-years and prevalence rates of 9.54 to 32.74 per 100,000 individuals.¹⁻³ DM-specific prevalence has been estimated at 1 to 6 per 100,000 adults in the United States.³ DM is the most common of the IIMs with a recent analysis of 3067 patients in the Euromyositis registry identifying DM in 31% of patients.⁴ DM affects both genders with a 2:1 female:male ratio. All ethnic groups are affected, but it is more common in African Americans.^{5,6} Population-based data suggest that clinically amyopathic DM (CADM) occurs in ≥20% of adults with DM.⁷

The average age of diagnosis of DM is bimodal, with juvenile DM (JDM) most commonly diagnosed between 4 and 14 years of age and adult DM diagnosed between 40 and 60 years of age.⁶ JDM is the most common inflammatory myopathy of childhood but remains rare, with an estimated incidence of 3.2 cases per million children per year.⁸ Rates of clinically amyopathic JDM are not well established.⁹ In a recent series of patients with clinically amyopathic JDM, 25% eventually developed muscle involvement.¹⁰

CUTANEOUS MANIFESTATIONS

Cutaneous manifestations of DM may be variable,¹¹ and precise skin criteria for DM diagnosis is

an area of ongoing research. Traditionally, skin findings have been divided into pathognomonic (Gottron papules, Gottron sign, and heliotrope rash), characteristic, compatible, less common, rare, and nonspecific (Table I).^{12,13} Patients may present with 1 or a combination of DM-related skin changes (Figs 1-8). The clinical course of DM skin lesions does not necessarily parallel that of muscle disease and may precede or follow myositis. Lesions are often pruritic or burning and are usually photosensitive.¹⁴ Persistent severe pruritus can significantly impact patients' quality of life.^{15,16} The cutaneous manifestations of DM associated with MSAs will be discussed in detail below.

MUSCLE MANIFESTATIONS

Approximately 80% of patients with DM have myopathy. The classic muscular manifestation is acute or subacute onset of symmetric, proximal muscle weakness. The myopathy is usually painless, and while elevations of creatine kinase, aspartate aminotransferase, and alanine aminotransferase are common, laboratory indicators of muscle activity may also be normal.^{14,17} Dysphagia, dysphonia, and symptoms of aspiration indicate possible involvement of striated muscle of the pharynx and esophagus and are associated with a poor prognosis.¹⁸ Notably, DM is not associated with sensory loss, ptosis, involvement of the extraocular muscles, or abnormal reflexes, which can help differentiate it from other neuromuscular disorders.⁵

Those with DM-consistent skin findings but without myopathy have what is termed CADM. CADM may be hypomyopathic (no objective weakness but evidence of subclinical muscle involvement on laboratory testing, biopsy, or imaging) or amyopathic (no evidence of muscle involvement on examination or workup).¹⁹

SYSTEMIC MANIFESTATIONS

Table II lists systemic manifestations of DM in adults and children. Specific manifestations and malignancy associations will be discussed in the context of MSAs to best reflect how these manifestations present in clinical practice. The clinical subsets associated with MSAs will be discussed separately for adult and juvenile DM because the significance of each antibody depends on the age of the affected individual.

HISTOPATHOLOGY

Skin

Skin biopsy specimens obtained from patients with DM are characterized by hyperkeratosis, epidermal atrophy, vacuolar interface dermatitis,

Table I. Cutaneous manifestations of adult dermatomyositis

Category	Finding	Clinical description ^{8,9,12,17,71}	Additional features
Pathognomonic	Gottron papules	Violaceous papules and plaques, sometimes with subtle scale, overlying the MCP and ICP joints of the hands	Dyspigmentation, atrophy, and scarring possible when lesions resolve ¹⁰⁶
	Gottron sign	Erythematous macules or patches over extensor surfaces of elbows, knuckles, knees, and ankles	Slight scale may be present ¹³
	Heliotrope rash	Periorbital erythema with edema, most often of the upper eyelids	May also involve cheeks and nose ¹²
Characteristic	Nailfold changes	Periungual erythema and telangiectasias, dystrophic cuticles, and hemorrhagic nailfold infarcts	Nailfold capillaroscopy may be useful adjunctive tool for monitoring disease activity ¹⁰⁷⁻¹⁰⁹
	Shawl sign	Violaceous or erythematous macules and patches over posterior shoulders, neck, upper back, and possibly lateral upper arms	Poikiloderma may also be present in same distribution ¹³
	V sign	Erythematous, confluent macules and patches over lower anterior neck and upper chest	Skin may also appear atrophic ¹³
Compatible	Holster sign	Symmetric poikiloderma of hips and lateral thighs below the greater trochanter	May be reticulated, livedoid, or linear and is reported to be highly specific for DM ¹³
	Scalp involvement	Atrophic, erythematous, sometimes pruritic scaly plaques	May be misdiagnosed as psoriasis or seborrheic dermatitis ¹¹⁰
	Poikiloderma	Hypo- or hyperpigmentation, telangiectasia, and atrophy, usually found on upper chest and lateral upper arms	May be referred to as "poikiloderma atrophicans vasculare" or "poikilodermatomyositis" ¹³
Less common	Periorbital edema and facial swelling	Edema with or without erythema	
	Vesiculobullous, necrotic, or ulcerative lesions	Variable	Often associated with cutaneous vasculitis, ¹³ ulceration associated with anti-MDA5 antibodies ⁹³
	Cutaneous vasculitis	Variable, but may include petechiae, palpable purpura, livedo reticularis, and ulceration	More common in JDM
Rare	Calcinosis cutis	Superficial white papules or nodules, most commonly over bony surfaces or at sites of inflammation	Rare in adult DM (estimated 4% of adult DM patients ⁴)
	Mechanic's hands	Hyperkeratotic, scaling, and fissuring of fingers and/or palms	More common in patients with anti-MDA5 antibodies ⁵³ and antisynthetase syndrome ^{53,111}
	Flagellate erythema	Linear erythematous macules and patches on the back	Associated with absence of MSAs on serological testing ⁵⁶ or presence of anti-Mi2 antibodies ⁷⁰
	Deck chair sign	Erythematous eruption sparing transverse skin folds	May be first cutaneous sign preceding classic DM skin findings ^{*112}
	Follicular hyperkeratosis ("wong-type DM")	Follicular, hyperkeratotic papules on extensor surfaces resembling pityriasis rubra pilaris	Hair follicle destruction and follicular hyperkeratosis on histopathology plus interface changes of DM ¹¹³

Continued

Table I. Cont'd

Category	Finding	Clinical description ^{8,9,12,17,71}	Additional features
Nonspecific	Panniculitis	Painful, indurated nodules of buttocks, arms, thighs, and abdomen	Associated with anti-MDA5 antibodies ⁹³
	Mucinosis	Variable, frequently plaques appearing in a reticular pattern	
	Erythroderma	Widespread erythema	Associated with malignancy ¹²
	Oral mucosal changes	Variable, but gingival telangiectasias, erosions, ulcers, and leukoplakia-like lesions reported	Ovoid palatal patch associated with anti-TIF1 antibodies ⁸⁰
	Raynaud phenomenon	Episodic vasospasm of fingers and toes in response to cold with triphasic color change ¹¹⁴	More common in antisynthetase syndrome ⁵

DM, Dermatomyositis; ICP, intercarpal phalangeal; JDM, juvenile dermatomyositis; MCP, metacarpal phalangeal; MDA5, anti-melanoma differentiation-associated protein 5; MSA, myositis-specific antibody; TIF1, transcription intermediary factor 1.

*S. Madsen et al, unpublished data, 2019.



Fig 1. **A** and **B**, Gottron papules and the Gottron sign on the dorsal surfaces of the hands of two patients with dermatomyositis.

basement membrane thickening, dermal edema, pigmentary incontinence, mucin deposits, and a perivascular infiltrate composed of CD4⁺ lymphocytes.⁶ Endothelial cell damage, loss of capillaries, and vascular dilatation may also be seen.²⁰

Muscle

Biopsy specimens of muscle from patients with DM are hallmark by perifascicular atrophy.^{14,21} However, atrophy may be patchy,²² which can cause false negatives. A 2017 study estimated the sensitivity of perifascicular atrophy to be only 47% (though it is 98% specific).²³ Recent studies suggest that expression of myxovirus resistance protein A in myofiber cytoplasm may be a better indicator of muscle involvement,^{23,24} with a sensitivity of 71% and specificity of 98%.²³ Other abnormalities observed in DM muscle include deposition of complement on endomysial capillaries⁵ (35% sensitive and 93% specific)⁶ and decreased capillary density. Inflammatory infiltrates are both perimysial and perivasculär and consist of macrophages, CD20⁺ B cells, CD4⁺ T cells,



Fig 2. Heliotrope rash on the face of a patient with dermatomyositis.

CD25⁺ plasma cells, and plasmacytoid dendritic cells.^{5,25} Increased perifascicular expression of major histocompatibility complex class I has also been reported.^{14,26}

Special considerations in JDM

There is considerable histologic overlap between DM in adults and children, but perifascicular atrophy seen on a biopsy specimen of muscle may be more reliably identified in JDM.¹⁷ In addition, vascular



Fig 3. Holster sign on the (A) right lateral thigh and (B) right lateral hip of two patients with dermatomyositis.



Fig 4. Characteristic nailfold changes of dermatomyositis. Dermoscopic image shows periungual erythema and telangiectasias and dystrophic cuticles.

involvement in JDM is often more prominent.²⁷ Specific features of a muscle biopsy specimen and their associated JDM phenotypes are outlined in Table III.

PATHOGENESIS

The pathogenesis of DM is multifactorial, complex, and incompletely understood. Genetic, environmental, and immune mechanisms (including the recently discovered autoantibodies discussed below), are thought to play a role in both adult DM and JDM development.

Genetic risk factors

DM has a strong genetic component. Multiple genotyping studies have demonstrated associations between major histocompatibility complex polymorphisms and DM development,^{28,29} and particular human leukocyte antigen (HLA) alleles have been



Fig 5. Ulcerative lesion on the antecubital fossa of a patient with dermatomyositis.

correlated with autoantibody production in both adults^{30,31} and children.^{32,33} In addition, the International Genetics Consortium in Myositis has identified cytokine and lymphocyte signaling alleles associated with disease development, disease severity, calcinosis, and ulceration in genome-wide analyses of juvenile IIMs.²⁸ Epigenetic modification, including DNA methylation, histone modification, and microRNA activity, may also play a role in DM pathogenesis.^{34,35}

Environmental risk factors

Multiple environmental factors may trigger chronic immune activation in genetically susceptible individuals.^{30,36} Proposed triggers for DM include ultraviolet radiation, viral infections, medications,



Fig 6. Characteristic poikiloderma on the lateral arm of a patient with dermatomyositis.

and smoking. Ultraviolet exposure has been linked with DM and anti-Mi2 antibodies in adult women³⁷ and with JDM and anti-transcription intermediary factor 1 (TIF1) antibodies in children.³⁸ Viral infections may play a role in triggering immune activation or disrupting immune tolerance,³⁹ but attempts to isolate viruses from DM muscle samples have been unsuccessful.¹⁴ A 2017 study found that DM/JDM flares were associated with ultraviolet exposure, infections, and some medications, although only sun exposure (odds ratio, 2.2) and recent nonsteroidal antiinflammatory drug use (odds ratio, 1.9) remained significant predictors in multivariable analysis.⁴⁰ Smoking has been associated with DM and the development of interstitial lung disease (ILD), dysphagia, malignancy, and cardiac involvement.⁴ Other potential environmental triggers are less well established, including a recent report of CADM developing after receiving a tattoo⁴¹ and a case series of 3 patients who developed an acute onset or flare of DM after ingesting the herbal supplement IsaLean.⁴²

Immune mechanisms

The sequence of immune activation in DM remains incompletely understood although it likely results from inappropriate complement activation.^{43,44} It remains controversial whether this activation is antibody-dependent or whether it results



Fig 7. Scalp dark purpuric hyperpigmentation equivalent to erythema and subtle frontal diffuse alopecia in a patient with Fitzpatrick skin type V and dermatomyositis.

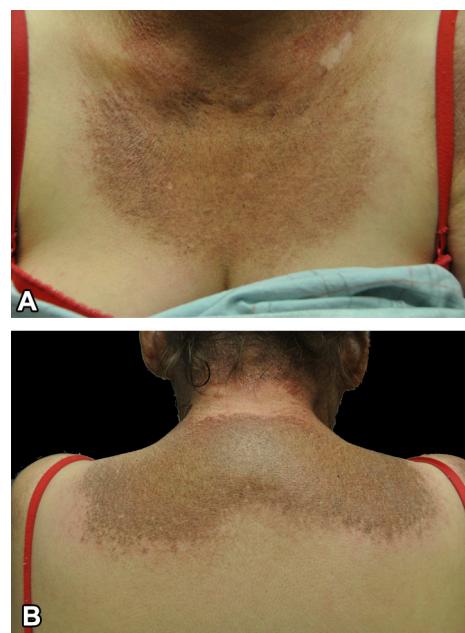


Fig 8. **A**, V sign with erythema and poikiloderma and **(B)** shawl sign in a patient with dermatomyositis.

from initiation of the classical complement cascade. Regardless, this activation results in capillary destruction that leads to ischemia and microinfarction, hypoperfusion, and perifascicular atrophy.¹⁴ Altered expression of myogenic regulatory factors

Table II. Systemic manifestations of dermatomyositis in adults and children

Organ system	Adult DM	JDM
Pulmonary	Varying degrees of ILD most common, ¹⁷ ILD is associated with anti-MDA5 antibodies, ¹⁹ may be rapidly progressive, especially in Asian populations ⁸⁹ ; pulmonary hypertension or serositis also possible ¹⁷	ILD rare (6% of cases), associated with anti-MDA5 antibodies ^{4,71} ; respiratory muscle weakness affecting ventilation possible ⁷¹ and not correlated with other clinical measures of muscle weakness ¹¹⁵
Cardiac	Cardiovascular risk factors are increased in patients with DM ¹¹⁶ ; subclinical diastolic dysfunction is common ¹¹⁶ ; myocarditis, myocardial fibrosis, arrhythmias, and congestive heart failure are all possible ¹¹⁶ ; cardiac involvement does not correlate with disease severity and may develop at any time ¹¹⁷	Clinically significant involvement uncommon, but systolic and diastolic dysfunction possible ¹¹⁸ ; increased rates of hypertension, dyslipidemia, ¹¹⁶ and ECG abnormalities ^{116,119} ; decreased heart rate variability ^{116,119} , pericarditis and myositis occur rarely ¹¹⁶
Gastrointestinal	Dysphagia related to dysfunction of the pharynx or esophagus ¹²⁰ ; gastric and small intestinal motility may be affected ¹²⁰ ; rarely, vasculopathy may lead to GI tract infarction or perforation ¹²¹	GI involvement in 5-37% of JDM cases ¹²² ; dysphagia, dysmotility, vasculitis-related bowel pathology possible ¹²² ; weakness affecting swallowing does not correlate with other clinical measures of muscle weakness ¹²³
Endocrine		Lipodystrophy in 10-30% of patients ¹²⁴ ; growth failure in 10% of cases ¹²⁵ ; bone mineral density may be reduced ⁷¹
Vascular	Cutaneous vasculopathy may cause ulcerations, especially in patients with anti-MDA5 antibodies ^{92,93}	Vasculitis more common in JDM, especially involving the skin and small vessels ¹²² ; GI involvement may lead to malabsorption, ulceration, or perforation ¹²⁶ ; central nervous system ¹²² and retinal involvement ¹²⁷ also reported; nailfold capillaroscopy may be useful tool ¹⁰⁷⁻¹⁰⁹

DM, Dermatomyositis; ECG, electrocardiographic; GI, gastrointestinal; ILD, interstitial lung disease; JDM, juvenile dermatomyositis; MDA5, anti-melanoma differentiation-associated protein 5.

(demonstrated in JDM muscle) may also contribute to atrophy because of impaired cell differentiation and maturation.⁴⁵

In addition, there is considerable evidence that interferons (IFNs) play a role in DM and JDM. Marked upregulation of the type I IFN pathway has been demonstrated in the muscle, skin, and blood of patients with DM,^{20,34,46-48} and cutaneous activity in adult DM has been shown to correlate with a type I IFN gene signature.⁴⁶ In patients with JDM, type I IFN score, type II IFN score, and tumor necrosis factor-alpha expression correlate with disease activity.⁴⁹ A persistent IFN response (perpetuated by chronic stimulation of antigen-presenting cells) has been implicated in multiple autoimmune diseases; the resulting T and B cell activation may be responsible for autoantibody production.⁵⁰ In DM and JDM, however, the pathogenic role of these autoantibodies remains unclear. The recent identification of antiendothelial cell antibodies in the plasma of children with JDM supports the conceptualization of JDM as an antibody-mediated vasculopathy.⁵¹

MYOSITIS-SPECIFIC ANTIBODIES

MSAs are antibodies that are exclusively associated with a diagnosis of an IIM.⁵² DM-specific antibodies include anti-Mi2, anti-melanoma differentiation-associated protein 5 (MDA5), anti-NXP2, anti-TIF1, and anti-small ubiquitin-like modifier activating enzyme (SAE). Except for anti-Jo1, which is present in antisynthetase syndrome, MSAs have not yet been incorporated into the diagnostic criteria for IIMs. However, MSAs are potentially helpful to the dermatologist because: 1) they may facilitate diagnosis in the absence of a biopsy specimen of muscle and in clinically atypical DM cases^{53,54}; 2) they impact prognosis and can help guide management⁵⁵⁻⁵⁸; and 3) they allow for clinical studies to select patients based on serologies, which may help further elucidate the significance of MSAs and improve the generalizability of these studies in clinical practice.⁵⁴

The current limitations of MSAs are twofold: 1) there is still a “serologic gap,” with a significant proportion of DM patients presenting without MSAs;

Table III. Biopsy features and associated phenotypes in juvenile dermatomyositis^{71,128,129}

Phenotype	Muscle biopsy features
Severe disease course	Lymphoid follicles including networks of fDCs and high endothelial venules; high levels of CXCL13 and lymphotaxins; resident naïve CD45RA ⁺ T cells, and maternally derived B cells and pDCs
Chronic disease course with ulcerations	Severe arteriopathic changes, positive arterial direct immunofluorescence, severe capillary loss, endomysial fibrosis, and muscle infarcts
Chronic disease course	Extensive active myopathic changes and central nuclei without basophilia

fDC, Follicular dendritic cell; pDC, plasmacytoid dendritic cell.

and 2) clinically available laboratory tests for MSAs can vary in their sensitivity and specificity. Results of laboratory testing for MSAs vary depending on the testing technique used, and estimated rates of MSA positivity in DM range from 20% to 50%.⁵⁹⁻⁶¹ Using commercial laboratories, it is not uncommon for MSA testing to be negative, even after a diagnosis of DM has been clinically confirmed⁶¹; this may be partially attributable to the variability in the accuracy of available commercial testing. Nonetheless, the clinical utility of MSA testing is increasing as commercial testing improves and is standardized, especially with recent studies suggesting that MSAs alone can accurately subdivide patients into their appropriate clinical diagnoses.⁵³ Although laboratory testing for MSAs and their use to classify IIMs remain somewhat exploratory, we believe this is a promising area of research. A summary of MSAs and their clinical associations in both adults and children is presented in Table IV.

Mi-2

Anti-Mi2 antibodies are directed against a nuclear DNA helicase involved in transcription.³⁴ The prevalence of anti-Mi2 antibodies among adult patients with DM varies based on ethnicity, geographic location, and method of testing,⁶² but estimates in the literature range from 4% to 35%.^{34,63-68} These patients present with “classic dermatomyositis” characterized by the development of pathognomonic cutaneous manifestations.^{58,69} The cutaneous manifestations disproportionately associated with Mi-2 DM in adults include facial dermatosis, shawl sign, poikiloderma, and flagellate erythema.⁷⁰ Other more

severe cutaneous features of DM, such as calcinosis and ulcerative vasculopathy, are not commonly seen in this clinical subset.

In addition, Mi-2 DM characteristically presents with proximal symmetric muscle weakness. Despite having clinically mild myopathy, these patients frequently have creatine kinase elevations that are out of proportion to their degree of muscle involvement. Fortunately, this form of DM is usually responsive to treatment. Mi-2 DM portends a benign prognosis and is not associated with an increased risk of development of malignancy or interstitial lung disease.⁵⁸

Anti-Mi2 antibodies are identified in 4% to 10% of patients with JDM, and the clinical manifestations and prognostic implications are similar in adults and children. Anti-Mi2 antibodies are more common in Hispanic children who are older at disease onset (median age 11 years).^{71,72} As in adults, clinical features include symmetric, proximal muscle weakness and pathognomonic cutaneous findings, and these patients tend to respond well to treatment.⁷¹⁻⁷³

TIF1

TIF1 (previously p155/140) is a tumor suppressor protein that is responsible for serving as a transcriptional corepressor.^{24,55} There are 3 subunits of the TIF1 protein (alpha, beta, and gamma), with each subunit having its own respective auto-antibodies.^{74,75} Antibodies to this family of proteins were first identified in 2006⁷⁶ and are found in 18% to 23% of adult patients with DM.⁵⁵ The primary clinical significance of anti-TIF1-gamma DM is its strong association with underlying malignancy. Identification of anti-TIF1 antibodies has a positive predictive value of 58% and a negative predictive value of 95% for cancer-associated DM (odds ratio, 27.26).⁷⁷ TIF1 antibodies are associated with the development of both solid and hematologic malignancies. Tumor rates reported in the literature are variable but range from 20% to 65%.^{55,78} It has been hypothesized that anti-TIF1 antibodies are generated during an antitumor immune response.^{24,55,79}

Anti-TIF1 DM has multiple other key clinical associations in adults: 1) severe, photosensitive cutaneous disease with heliotrope rash, v sign, and Gottron papules; 2) unique mucocutaneous findings, such as palmar hyperkeratosis, psoriasiform plaques, ovoid palatal patches, and atrophic hypopigmented patches with overlying telangiectasias; 3) hypomyopathic disease; 4) gastrointestinal involvement; and 5) a lack of other systemic

Table IV. Dermatomyositis-associated myositis-specific antibodies and their associated clinical features

Antibody	Target antigen	Incidence	Associated clinical features	Malignancy association
Anti-Mi2	Nuclear DNA helicase involved in transcription	Adult DM 4-35% JDM 4-10%	"Classic" cutaneous findings, facial dermatosis, shawl sign, poikiloderma, flagellate erythema; proximal, symmetric muscle weakness with highly elevated CK; treatment responsive	None
			More common in Hispanic patients, older at disease onset; clinical features similar to adults	None
Anti-TIF1 (previously anti-p155/140)	Tumor suppressor protein that acts as transcriptional corepressor	Adult DM 18-23% JDM 18-35%	Severe, photosensitive cutaneous disease, palmar hyperkeratosis, psoriasisiform plaques, ovoid palatal patches, atrophic hypopigmented patches with overlying telangiectasias; often hypomyopathic; GI involvement	Strongly associated with malignancy
			More common in white patients, younger at disease onset; severe, treatment-refractory cutaneous disease, ulceration, muscle weakness, lipodystrophy, chronic disease course	None
Anti-MDA5 (previously CADM140)	RNA-specific helicase involved in antiviral immune response	Adult DM 10-30% JDM 7-50%	Clinically amyopathic disease; interstitial lung disease (may be rapidly progressive); cutaneous ulceration, painful palmar papules, panniculitis	None
			Ulcerative skin and mucosal lesions; interstitial lung disease; milder muscle involvement; arthritis	None
Anti-NXP2	Nuclear protein involved in regulation of transcription and RNA metabolism	Adult DM 2-25% (varies by ethnicity) JDM 20-25%	Classic cutaneous findings; peripheral edema; calcinosis and ulceration rare	Increased risk of malignancy
			Calcinosis cutis; disabling myopathy; GI bleeding related to vasculopathy	None
Anti-SAE	Nuclear enzyme involved in posttranslation modification of proteins	Adult DM 8% (varies by ethnicity) JDM 2-8%	Strong HLA associations; severe cutaneous disease; progressive muscle disease with dysphagia; fever and weight loss	Unknown
			Severe cutaneous disease, minimal muscle disease	Unknown

CK, Creatine kinase; DM, dermatomyositis; GI, gastrointestinal; HLA, human leukocyte antigen; MCP, intercarpal phalangeal; JDM, juvenile dermatomyositis; MCP, metacarpal phalangeal; MDA5, anti-melanoma differentiation-associated protein 5; MSA, myositis-specific antibody; NXP2, nuclear matrix protein 2; RNA, ribonucleic acid; SAE, small ubiquitin-like modifier activating enzyme; TIF1, anti-transcription intermediary factor 1.

Table V. Non–dermatomyositis-associated myositis-specific antibodies

Antibody	Disease entity	Clinical association(s)
Anti-ARS (includes anti-Jo1 [histidyl], anti-PL7 [alanyl], anti-PL12 [glycyl], anti-EJ [isoleucyl], anti-OJ [isoleucyl], anti-KS [asparaginyl], anti-Zo [phenylalanyl], and anti-YRS/HA [tyrosyl])	Antisynthetase syndrome	Myositis with ILD, polyarthritis, Raynaud phenomenon, and cutaneous findings (Gottron papules, "mechanic's hands") ¹⁰⁴ ; more severe ILD and poorer prognosis with non-Jo1 antibodies ⁸⁵
Anti-SRP	Necrotizing myopathy (anti-SRP antibody syndrome)	Sudden, severe, and progressive muscle weakness, often with cardiac involvement and/or dysphagia ^{59,104} ; treatment resistant ⁸⁵ ; no increased risk of malignancy ¹³⁰
Anti-HMGCR	Immune-mediated necrotizing myopathy	Increased risk of malignancy compared with the general population ¹³⁰ ; statin-induced myopathy ¹³¹
CN1A	Inclusion body myositis	Progressive weakness and functional impairment in older patients (typically >50 years of age) ¹³²

ARS, Aminoacyl tRNA synthetase; CN1A, cytosolic 5'nucleotidase 1A; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; ILD, interstitial lung disease; SRP, signal recognition particle.

manifestations, such as interstitial lung disease, Raynaud phenomenon, and arthritis.^{58,80-82}

In children with JDM, the frequency of anti-TIF1 antibodies is estimated to be 18% to 35%.⁷¹ These antibodies are more common in white patients^{71,72} with a younger age at disease onset (median 7 years).⁷¹ Unlike in adult DM, anti-TIF1 antibodies in children are not associated with malignancy.⁵⁵ Clinical associations include severe, treatment-refractory, photodistributed cutaneous disease, cutaneous ulceration, greater muscle weakness, lipodystrophy, and a chronic disease course.^{71,72}

MDA5

MDA5 (previously CADM140) is a RNA-specific helicase involved in antiviral immune response (including the production of type I IFN).^{24,83} Autoantibodies against MDA5 are identified in the majority of adults and children with CADM^{84,85} and in 10% to 30% of patients with DM overall.⁵⁷ This subset is identified most frequently in Asian patients, with the associated clinical significance demonstrating some degree of regional/ethnic variability.⁸⁶⁻⁸⁸ Anti-MDA5 DM is associated with an increased risk of developing ILD, which in some cases may be rapidly progressive (RP-ILD).

RP-ILD is characterized by short-interval (<4 weeks) progression of ILD by subjective symptoms or objective metrics (eg, ground glass opacity on computed tomography, worsening PaO₂).⁹⁰ The presence of anti-MDA5 antibodies has an estimated sensitivity of 77% and specificity of 86% for the

development of DM-associated RP-ILD.⁹¹ The associated 6-month mortality is approximately 59%.⁹¹

Anti-MDA5 DM also presents with several unique cutaneous findings in both adults and children that are thought to be attributable to the development of cutaneous vasculopathy.^{92,93} These include: 1) cutaneous ulceration frequently at the site of Gottron papules and the lateral nail folds; 2) painful palmar papules (termed inverse Gottron papules); and 3) panniculitis.^{19,93-95}

Anti-MDA5 antibodies are the third most common MSA detected in children with JDM after anti-TIF1 and anti-nuclear matrix protein 2 (NXP-2).⁷¹ The exact prevalence of anti-MDA5 antibodies in JDM is unknown, although estimates range from 7.4% per the United Kingdom Juvenile Dermatomyositis Registry⁹⁶ to near 50% in Japanese children with JDM.^{96,97} Like their adult counterparts, children with anti-MDA5 DM have an elevated risk of developing ILD as well as ulcerative skin and mucosal lesions.^{71,96} RP-ILD is less common in children, but rates of RP-ILM are higher in Asian JDM patients with anti-MDA5 antibodies.^{71,96} Patients with JDM with these antibodies frequently demonstrate milder muscle involvement⁹⁶ (though less commonly amyopathic disease) and arthritis.⁷¹

NXP-2

NXP-2 is a protein involved in multiple nuclear functions, including regulation of transcription and RNA metabolism.²⁴ Anti NXP-2 antibodies (formerly anti-MJ) are detected in a relatively small percentage of adults with DM, although prevalence varies by ethnicity (14-25% in U.S. populations and 2-5% in

Japanese populations).^{58,78,84,98-100} Like anti-TIF1-gamma DM, adults with anti-NXP-2 DM are at an elevated risk of underlying malignancy, although the tumor rate associated with NXP-2 antibodies (37.5%) is less than that conferred by anti-TIF1-gamma seropositivity.⁵⁷ This subset of DM patients typically presents with classic cutaneous findings. Peripheral edema may be seen in $\leq 35\%$ of patients,^{58,99} and calcinosis and distal ulcerations are observed in adults with anti-NXP-2 DM on occasion.⁵⁸ Calcinosis is a much less frequent finding in adults than it is in children with this antibody.

Anti-NXP2 antibodies are the second most common autoantibody in patients with JDM, with a frequency of 20% to 25%.^{58,72} Like anti-TIF1 antibodies, anti-NXP2 antibodies are more common in younger, white patients (median age at disease onset 6 years).^{71,72} NXP-2 JDM portends a poor prognosis and requires more aggressive management than other forms of JDM. The cutaneous hallmark of this subset is the development of calcinosis cutis, which occurs in $>40\%$ of NXP-2 antibody-positive individuals.^{101,102} This form of JDM also presents with severe myopathy that frequently causes functional impairment and results in contracture development.⁵⁸ The severe myopathy associated with NXP-2 seropositivity develops secondary to vasculopathy-induced muscle ischemia.⁷¹ This vasculopathy also predisposes individuals with NXP-2 antibodies to gastrointestinal bleeding.⁷² Children with NXP-2 JDM do not have associated malignancies.

Anti-SAE

Anti-SAE DM is a more recently described subset of DM that occurs in $\sim 8\%$ of adults though frequency varies by ethnicity.⁵⁹ This subtype of DM is strongly associated with HLA-DQB1*03. HLA-DRB1*04 and 03-DQB1*03 are also risk factors.¹⁰³ Patients with this subset of DM present initially with severe cutaneous disease and minimal myopathy. These individuals typically develop progressive muscle involvement over time and frequently develop severe dysphagia.¹⁰⁴ Some case series have also suggested that patients with anti-SAE DM frequently have systemic symptoms, such as fever and weight loss.¹⁰³ The association of this subset of DM with malignancy and ILD is still unknown. Notably, the presence of anti-SAE antibodies has been reported to be predictive of hydroxychloroquine drug eruptions.¹⁰⁵ In children, anti-SAE JDM comprises only a small segment of JDM cases (6-8% in European cohorts and 2% in Asian cohorts) and is typically characterized by severe cutaneous

involvement and minimal muscle disease in a manner analogous to adults.⁷¹

Other MSAs

Other MSAs occur in immune-mediated necrotizing myositis, inclusion body myositis, and antisynthetase syndrome. These antibodies may be identified during a work-up of a patient for DM. Table V lists these other MSAs and their associated clinical features.

In conclusion, the recent discovery of MSAs has revealed that DM is comprised of a heterogeneous group of closely related clinical subtypes that can be distinguished from one another based on serology. Understanding the clinical implications of MSAs in DM will become increasingly important as more studies are done and autoantibody testing is standardized. The first article in this continuing medical education series provided readers with an understanding of the clinical significance of MSAs that will be essential for understanding the approaches to diagnosis, work-up, and management discussed in the second article in this series.

REFERENCES

1. Smoyer-Tomic KE, Amato AA, Fernandes AW. Incidence and prevalence of idiopathic inflammatory myopathies among commercially insured, Medicare supplemental insured, and Medicaid enrolled populations: an administrative claims analysis. *BMC Musculoskeletal Disord.* 2012;13:103.
2. Bernatsky S, Joseph L, Pineau CA, et al. Estimating the prevalence of polymyositis and dermatomyositis from administrative data: age, sex and regional differences. *Ann Rheum Dis.* 2009;68:1192-1196.
3. Furst DE, Amato AA, Iorga SR, Gajria K, Fernandes AW. Epidemiology of adult idiopathic inflammatory myopathies in a U.S. managed care plan. *Muscle Nerve.* 2012;45:676-683.
4. Lilleker JB, Vencovsky J, Wang G, et al. The EuroMyositis registry: an international collaborative tool to facilitate myositis research. *Ann Rheum Dis.* 2018;77:30-39.
5. Findlay AR, Goyal NA, Mozaffar T. An overview of polymyositis and dermatomyositis. *Muscle Nerve.* 2015;51:638-656.
6. Aussy A, Boyer O, Cordel N. Dermatomyositis and immune-mediated necrotizing myopathies: a window on autoimmunity and cancer. *Front Immunol.* 2017;8:992.
7. Bendewald MJ, Wetter DA, Li X, Davis MDP. Incidence of dermatomyositis and clinically amyopathic dermatomyositis: a population-based study in Olmsted County, Minnesota. *Arch Dermatol.* 2010;146:26-30.
8. Mendez EP, Lipton R, Ramsey-Goldman R, et al. US incidence of juvenile dermatomyositis, 1995-1998: results from the National Institute of Arthritis and Musculoskeletal and Skin Diseases Registry. *Arthritis Rheum.* 2003;49:300-305.
9. Kim S, Kahn P, Robinson AB, et al. Childhood Arthritis and Rheumatology Research Alliance consensus clinical treatment plans for juvenile dermatomyositis with skin predominant disease. *Pediatr Rheumatol Online J.* 2017;15:1.
10. Gerami P, Walling HW, Lewis J, Doughty L, Sontheimer RD. A systematic review of juvenile-onset clinically amyopathic dermatomyositis. *Br J Dermatol.* 2007;157:637-644.

11. Patel B, Khan N, Werth VP. Applicability of EULAR/ACR classification criteria for dermatomyositis to amyopathic disease. *J Am Acad Dermatol.* 2018;79:77-83.e1.
12. Mainetti C, Terzioli Beretta-Piccoli B, Selmi C. Cutaneous manifestations of dermatomyositis: a comprehensive review. *Clin Rev Allergy Immunol.* 2017;53:337-356.
13. Bogdanov I, Kazandjieva J, Darlenski R, Tsankov N. Dermatomyositis: current concepts. *Clin Dermatol.* 2018;36:450-458.
14. Dalakas MC. Inflammatory muscle diseases. *N Engl J Med.* 2015;372:1734-1747.
15. Hundley JL, Carroll CL, Lang W, et al. Cutaneous symptoms of dermatomyositis significantly impact patients' quality of life. *J Am Acad Dermatol.* 2006;54:217-220.
16. Goreshi R, Chock M, Foering K, et al. Quality of life in dermatomyositis. *J Am Acad Dermatol.* 2011;65:1107-1116.
17. Schmidt J. Current classification and management of inflammatory myopathies. *J Neuromuscul Dis.* 2018;5:109-129.
18. Ogawa-Momohara M, Muro Y, Kono M, Akiyama M. Prognosis of dysphagia in dermatomyositis. *Clin Exp Rheumatol.* 2019;37:165.
19. Moghadam-Kia S, Oddis CV, Sato S, Kuwana M, Aggarwal R. Antimelanoma differentiation-associated gene 5 antibody: expanding the clinical spectrum in North American patients with dermatomyositis. *J Rheumatol.* 2017;44:319-325.
20. Wong D, Kea B, Pesich R, et al. Interferon and biologic signatures in dermatomyositis skin: specificity and heterogeneity across diseases. *PLoS One.* 2012;7:e29161.
21. De Bleecker JL, De Paepe B, Aronica E, et al. 205th ENMC International Workshop: pathology diagnosis of idiopathic inflammatory myopathies part II 28–30 March 2014, Naarden, The Netherlands. *Neuromuscul Disord.* 2015;25:268-272.
22. Iaccarino L, Ghirardello A, Bettio S, et al. The clinical features, diagnosis and classification of dermatomyositis. *J Autoimmun.* 2014;48-49:122-127.
23. Uruha A, Nishikawa A, Tsuburaya RS, et al. Sarcoplasmic MxA expression: a valuable marker of dermatomyositis. *Neurology.* 2017;88:493-500.
24. Suzuki S, Uruha A, Suzuki N, Nishino I. Integrated Diagnosis Project for Inflammatory Myopathies: an association between autoantibodies and muscle pathology. *Autoimmun Rev.* 2017;16:693-700.
25. Lahoria R, Selcen D, Engel AG. Microvascular alterations and the role of complement in dermatomyositis. *Brain.* 2016;139(pt 7):1891-1903.
26. Hoogendoijk JE, Amato AA, Lecky BR, et al. 119th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10–12 October 2003, Naarden, The Netherlands. *Neuromuscul Disord.* 2004;14:337-345.
27. Pestronk A. Acquired immune and inflammatory myopathies: pathologic classification. *Curr Opin Rheumatol.* 2011;23:595-604.
28. Miller FW, Cooper RG, Vencovský J, et al. Genome-wide association study of dermatomyositis reveals genetic overlap with other autoimmune disorders. *Arthritis Rheum.* 2013;65:3239-3247.
29. Rothwell S, Cooper RG, Lundberg IE, et al. Dense genotyping of immune-related loci in idiopathic inflammatory myopathies confirms HLA alleles as the strongest genetic risk factor and suggests different genetic background for major clinical subgroups. *Ann Rheum Dis.* 2016;75:1558-1566.
30. O'Hanlon TP, Carrick DM, Targoff IN, et al. Immunogenetic risk and protective factors for the idiopathic inflammatory myopathies: distinct HLA-A, -B, -Cw, -DRB1, and -DQA1 allelic profiles distinguish European American patients with different myositis autoantibodies. *Medicine (Baltimore).* 2006;85:111-127.
31. Chen Z, Wang Y, Kuwana M, et al. HLA-DRB1 Alleles as genetic risk factors for the development of anti-MDA5 antibodies in patients with dermatomyositis. *J Rheumatol.* 2017;44:1389-1393.
32. Wedderburn LR, Rider LG. Juvenile dermatomyositis: new developments in pathogenesis, assessment and treatment. *Best Pract Res Clin Rheumatol.* 2009;23:665-678.
33. Rider LG, Nistala K. The juvenile idiopathic inflammatory myopathies: pathogenesis, clinical and autoantibody phenotypes, and outcomes. *J Intern Med.* 2016;280:24-38.
34. Gao S, Luo H, Zhang H, Zuo X, Wang L, Zhu H. Using multi-omics methods to understand dermatomyositis/polymyositis. *Autoimmun Rev.* 2017;16:1044-1048.
35. Gao S, Zhang H, Zuo X, et al. Integrated comparison of the miRNAome and mRNAome in muscles of dermatomyositis and polymyositis reveals common and specific miRNA-mRNAs. *Epigenomics.* 2019;11:23-33.
36. Miller FW. Environmental agents and autoimmune diseases. *Adv Exp Med Biol.* 2011;711:61-81.
37. Love LA, Weinberg CR, McConaughay DR, et al. Ultraviolet radiation intensity predicts the relative distribution of dermatomyositis and anti-Mi-2 autoantibodies in women. *Arthritis Rheum.* 2009;60:2499-2504.
38. Shah M, Targoff IN, Rice MM, Miller FW, Rider LG, Childhood Myositis Heterogeneity Collaborative Study Group. Brief report: ultraviolet radiation exposure is associated with clinical and autoantibody phenotypes in juvenile myositis. *Arthritis Rheum.* 2013;65:1934-1941.
39. Pignone A, Fiori G, Del Rosso A, Generini S, Matucci-Cerinic M. The pathogenesis of inflammatory muscle diseases: on the cutting edge among the environment, the genetic background, the immune response and the dysregulation of apoptosis. *Autoimmun Rev.* 2002;1:226-232.
40. Mamyrava G, Rider LG, Ehrlich A, et al. Environmental factors associated with disease flare in juvenile and adult dermatomyositis. *Rheumatology (Oxford).* 2017;56:1342-1347.
41. Han B, Guo Q. Clinically amyopathic dermatomyositis caused by a tattoo. *Case Rep Rheumatol.* 2018;2018:7384681.
42. Zeidi M, Chansky PB, Werth VP. Acute onset/flare of dermatomyositis following ingestion of IsaLean herbal supplement: clinical and immunostimulatory findings. *J Am Acad Dermatol.* 2019;80:801-804.
43. Emslie-Smith AM, Engel AG. Microvascular changes in early and advanced dermatomyositis: a quantitative study. *Ann Neurol.* 1990;27:343-356.
44. Dalakas MC. Immunotherapy of myositis: issues, concerns and future prospects. *Nat Rev Rheumatol.* 2010;6:129-137.
45. Baumann M, Gumpold C, Mueller-Felber W, et al. Pattern of myogenesis and vascular repair in early and advanced lesions of juvenile dermatomyositis. *Neuromuscul Disord.* 2018;28:973-985.
46. Huard C, Gullà SV, Bennett DV, Coyle AJ, Vleugels RA, Greenberg SA. Correlation of cutaneous disease activity with type 1 interferon gene signature and interferon β in dermatomyositis. *Br J Dermatol.* 2017;176:1224-1230.
47. Greenberg SA, Higgs BW, Morehouse C, et al. Relationship between disease activity and type 1 interferon- and other cytokine-inducible gene expression in blood in dermatomyositis and polymyositis. *Genes Immun.* 2012;13:207-213.
48. Xie S, Luo H, Zhang H, Zhu H, Zuo X, Liu S. Discovery of key genes in dermatomyositis based on the gene expression

- omnibus database. *DNA Cell Biol.* 2019. <https://doi.org/10.1089/dna.2018.4256> [Epub ahead of print].
49. Moneta GM, Pires Marafon D, Marasco E, et al. Muscle expression of type I and type II interferons is increased in juvenile dermatomyositis and related to clinical and histologic features. *Arthritis Rheumatol.* 2019;71:1011-1021.
 50. Ivashkiv LB, Donlin LT. Regulation of type I interferon responses. *Nat Rev Immunol.* 2014;14:36-49.
 51. Karasawa R, Tamaki M, Sato T, et al. Multiple target autoantigens on endothelial cells identified in juvenile dermatomyositis using proteomics. *Rheumatology (Oxford).* 2018;57:671-676.
 52. Gunawardena H. The clinical features of myositis-associated autoantibodies: a review. *Clin Rev Allergy Immunol.* 2017;52:45-57.
 53. Mariampillai K, Granger B, Amelin D, et al. Development of a new classification system for idiopathic inflammatory myopathies based on clinical manifestations and myositis-specific autoantibodies. *JAMA Neurol.* 2018;75:1528-1537.
 54. Bottai M, Tjärnlund A, Santoni G, et al. EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups: a methodology report. *RMD Open.* 2017;3:e000507.
 55. Fujimoto M, Hamaguchi Y, Kaji K, et al. Myositis-specific anti-155/140 autoantibodies target transcription intermediary factor 1 family proteins. *Arthritis Rheum.* 2012;64:513-522.
 56. Best M, Jachiet M, Molinari N, et al. Distinctive cutaneous and systemic features associated with specific antimyositis antibodies in adults with dermatomyositis: a prospective multicentric study of 117 patients. *J Eur Acad Dermatol Venereol.* 2018;32:1164-1172.
 57. Fujimoto M, Watanabe R, Ishitsuka Y, Okiyama N. Recent advances in dermatomyositis-specific autoantibodies. *Curr Opin Rheumatol.* 2016;28:636-644.
 58. Wolstencroft PW, Fiorentino DF. Dermatomyositis clinical and pathological phenotypes associated with myositis-specific autoantibodies. *Curr Rheumatol Rep.* 2018;20:28.
 59. Betteridge Z, McHugh N. Myositis-specific autoantibodies: an important tool to support diagnosis of myositis. *J Intern Med.* 2016;280:8-23.
 60. O'Connor A, Mulhall J, Harney SMJ, et al. investigating idiopathic inflammatory myopathy; initial cross specialty experience with use of the extended myositis antibody panel. *Clin Pract.* 2017;7:922.
 61. Gandiga PC, Zhang J, Sangani S, Thomas P, Werth VP, George MD. Utilization patterns and performance of commercial myositis autoantibody panels in routine clinical practice. *Br J Dermatol.* 2019. <https://doi.org/10.1111/bjd.18133> [Epub ahead of print].
 62. Ghirardello A, Bassi N, Palma L, et al. Autoantibodies in polymyositis and dermatomyositis. *Curr Rheumatol Rep.* 2013;15:335.
 63. Kang EH, Nakashima R, Mimori T, et al. Myositis autoantibodies in Korean patients with inflammatory myositis: anti-140-kDa polypeptide antibody is primarily associated with rapidly progressive interstitial lung disease independent of clinically amyopathic dermatomyositis. *BMC Musculoskeletal Disord.* 2010;11:223.
 64. Ikeda N, Takahashi K, Yamaguchi Y, Inasaka M, Kuwana M, Ikezawa Z. Analysis of dermatomyositis-specific autoantibodies and clinical characteristics in Japanese patients. *J Dermatol.* 2011;38:973-979.
 65. Ghirardello A, Rampudda M, Ekholm L, et al. Diagnostic performance and validation of autoantibody testing in myositis by a commercial line blot assay. *Rheumatology (Oxford).* 2010;49:2370-2374.
 66. Petri MH, Satoh M, Martin-Marquez BT, et al. Implications in the difference of anti-Mi-2 and -p155/140 autoantibody prevalence in two dermatomyositis cohorts from Mexico City and Guadalajara. *Arthritis Res Ther.* 2013;15:R48.
 67. Targoff IN, Reichlin M. The association between Mi-2 antibodies and dermatomyositis. *Arthritis Rheum.* 1985;28:796-803.
 68. Shamim EA, Rider LG, Pandey JP, et al. Differences in idiopathic inflammatory myopathy phenotypes and genotypes between Mesoamerican Mestizos and North American Caucasians: ethnogeographic influences in the genetics and clinical expression of myositis. *Arthritis Rheum.* 2002;46:1885-1893.
 69. Muro Y, Sugiura K, Akiyama M. Cutaneous manifestations in dermatomyositis: key clinical and serological features-a comprehensive review. *Clin Rev Allergy Immunol.* 2016;51:293-302.
 70. Daly ML, Gordon PA, Creamer D. Cutaneous features of dermatomyositis associated with myositis-specific antibodies. *Br J Dermatol.* 2017;176:1662-1665.
 71. Wu Q, Wedderburn LR, McCann LJ. Juvenile dermatomyositis: latest advances. *Best Pract Res Clin Rheumatol.* 2017;31:535-557.
 72. Rider LG, Shah M, Mamyoava G, et al. The myositis autoantibody phenotypes of the juvenile idiopathic inflammatory myopathies. *Medicine (Baltimore).* 2013;92:223-243.
 73. Deakin CT, Yasin SA, Simou S, et al. Muscle biopsy findings in combination with myositis-specific autoantibodies aid prediction of outcomes in juvenile dermatomyositis. *Arthritis Rheumatol.* 2016;68:2806-2816.
 74. Kim Y, Song KS, Sohn EH, et al. Anti-TIF1 γ antibody and the expression of TIF1 γ in idiopathic inflammatory myopathies. *Int J Rheum Dis.* 2019;22:314-320.
 75. Fiorentino D, Casciola-Rosen L. TIF1 autoantibodies in dermatomyositis shed insight into the cancer-myositis connection. *Arthritis Rheum.* 2012;64:346-349.
 76. Targoff IN, Mamyoava G, Trieu EP, et al. A novel autoantibody to a 155-kd protein is associated with dermatomyositis. *Arthritis Rheum.* 2006;54:3682-3689.
 77. Trallero-Araguás E, Rodrigo-Pendás JA, Selva-O'Callaghan A, et al. Usefulness of anti-p155 autoantibody for diagnosing cancer-associated dermatomyositis: a systematic review and meta-analysis. *Arthritis Rheum.* 2012;64:523-532.
 78. Fiorentino DF, Chung LS, Christopher-Stine L, et al. Most patients with cancer-associated dermatomyositis have antibodies to nuclear matrix protein NXP-2 or transcription intermediary factor 1 γ . *Arthritis Rheum.* 2013;65:2954-2962.
 79. Casciola-Rosen L, Nagaraju K, Plotz P, et al. Enhanced autoantigen expression in regenerating muscle cells in idiopathic inflammatory myopathy. *J Exp Med.* 2005;201:591-601.
 80. Bernet LL, Lewis MA, Rieger KE, Casciola-Rosen L, Fiorentino DF. Ovoid palatal patch in dermatomyositis: a novel finding associated with anti-TIF1 γ (p155) antibodies. *JAMA Dermatol.* 2016;152:1049-1051.
 81. Fiorentino DF, Kuo K, Chung L, Zaba L, Li S, Casciola-Rosen L. Distinctive cutaneous and systemic features associated with antitranscriptional intermediary factor-1 γ antibodies in adults with dermatomyositis. *J Am Acad Dermatol.* 2015;72:449-455.
 82. Casal-Dominguez M, Pinal-Fernandez I, Mego M, et al. High-resolution manometry in patients with idiopathic inflammatory myopathy: elevated prevalence of esophageal

- involvement and differences according to autoantibody status and clinical subset. *Muscle Nerve*. 2017;56:386-392.
83. Sato S, Hoshino K, Satoh T, et al. RNA helicase encoded by melanoma differentiation-associated gene 5 is a major autoantigen in patients with clinically amyopathic dermatomyositis: association with rapidly progressive interstitial lung disease. *Arthritis Rheum*. 2009;60:2193-2200.
 84. Sato S, Hirakata M, Kuwana M, et al. Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. *Arthritis Rheum*. 2005;52:1571-1576.
 85. Satoh M, Tanaka S, Ceribelli A, Calise SJ, Chan EKL. A comprehensive overview on myositis-specific antibodies: new and old biomarkers in idiopathic inflammatory myopathy. *Clin Rev Allergy Immunol*. 2017;52:1-19.
 86. Chen Z, Hu W, Wang Y, Guo Z, Sun L, Kuwana M. Distinct profiles of myositis-specific autoantibodies in Chinese and Japanese patients with polymyositis/dermatomyositis. *Clin Rheumatol*. 2015;34:1627-1631.
 87. Ceribelli A, Fredi M, Taraborelli M, et al. Prevalence and clinical significance of anti-MDA5 antibodies in European patients with polymyositis/dermatomyositis. *Clin Exp Rheumatol*. 2014;32:891-897.
 88. Lin JM, Zhang YB, Peng QL, et al. Genetic association of HLA-DRB1 multiple polymorphisms with dermatomyositis in Chinese population. *HLA*. 2017;90:354-359.
 89. Ortiz-Santamaria V, Babot A, Ferrer C. Anti-MDA5-positive dermatomyositis: an emerging entity with a variable clinical presentation. *Scand J Rheumatol*. 2017;46:509-511.
 90. Morisset J, Johnson C, Rich E, Collard HR, Lee JS. Management of myositis-related interstitial lung disease. *Chest*. 2016;150:1118-1128.
 91. Chen Z, Cao M, Plana MN, et al. Utility of anti-melanoma differentiation-associated gene 5 antibody measurement in identifying patients with dermatomyositis and a high risk for developing rapidly progressive interstitial lung disease: a review of the literature and a meta-analysis. *Arthritis Care Res (Hoboken)*. 2013;65:1316-1324.
 92. Ono N, Kai K, Maruyama A, et al. The relationship between type 1 IFN and vasculopathy in anti-MDA5 antibody-positive dermatomyositis patients. *Rheumatology (Oxford)*. 2019;58:786-791.
 93. Kurtzman DJB, Vleugels RA. Anti-melanoma differentiation-associated gene 5 (MDA5) dermatomyositis: a concise review with an emphasis on distinctive clinical features. *J Am Acad Dermatol*. 2018;78:776-785.
 94. Fiorentino D, Chung L, Zwerner J, Rosen A, Casciola-Rosen L. 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.
 95. Hall JC, Casciola-Rosen L, Samedy LA, et al. Anti-melanoma differentiation-associated protein 5-associated dermatomyositis: expanding the clinical spectrum. *Arthritis Care Res (Hoboken)*. 2013;65:1307-1315.
 96. Tansley SL, Betteridge ZE, Gunawardena H, et al. Anti-MDA5 autoantibodies in juvenile dermatomyositis identify a distinct clinical phenotype: a prospective cohort study. *Arthritis Res Ther*. 2014;16(4):R138.
 97. Kobayashi I, Okura Y, Yamada M, Kawamura N, Kuwana M, Ariga T. Anti-melanoma differentiation-associated gene 5 antibody is a diagnostic and predictive marker for interstitial lung diseases associated with juvenile dermatomyositis. *J Pediatr*. 2011;158:675-677.
 98. Albayda J, Pinal-Fernandez I, Huang W, et al. Antinuclear matrix protein 2 autoantibodies and edema, muscle disease, and malignancy risk in dermatomyositis patients. *Arthritis Care Res*. 2017;69:1771-1776.
 99. Rogers A, Chung L, Li S, Casciola-Rosen L, Fiorentino DF. Cutaneous and systemic findings associated with nuclear matrix protein 2 antibodies in adult dermatomyositis patients. *Arthritis Care Res (Hoboken)*. 2017;69:1909-1914.
 100. Ishikawa A, Muro Y, Sugiura K, Akiyama M. Development of an ELISA for detection of autoantibodies to nuclear matrix protein 2. *Rheumatology (Oxford)*. 2012;51:1181-1187.
 101. Tansley SL, Betteridge ZE, Shaddick G, et al. Calcinosis in juvenile dermatomyositis is influenced by both anti-NXP2 autoantibody status and age at disease onset. *Rheumatology (Oxford)*. 2014;53:2204-2208.
 102. Gunawardena H, Wedderburn LR, Chinoy H, et al. Autoantibodies to a 140-kd protein in juvenile dermatomyositis are associated with calcinosis. *Arthritis Rheum*. 2009;60(6):1807-1814.
 103. Betteridge ZE, Gunawardena H, Chinoy H, et al. Clinical and human leucocyte antigen class II haplotype associations of autoantibodies to small ubiquitin-like modifier enzyme, a dermatomyositis-specific autoantigen target, in UK Caucasian adult-onset myositis. *Ann Rheum Dis*. 2009;68:1621-1625.
 104. Merlo G, Clapasson A, Cozzani E, et al. Specific autoantibodies in dermatomyositis: a helpful tool to classify different clinical subsets. *Arch Dermatol Res*. 2017;309:87-95.
 105. Wolstencroft PW, Casciola-Rosen L, Fiorentino DF. Association between autoantibody phenotype and cutaneous adverse reactions to hydroxychloroquine in dermatomyositis. *JAMA Dermatol*. 2018;154:1199-1203.
 106. Auriemma M, Capo A, Meogrossi G, Amerio P. Cutaneous signs of classical dermatomyositis. *G Ital Dermatol Venereol*. 2014;149:505-517.
 107. Barth Z, Witczak BN, Flatø B, Koller A, Sjaastad I, Sanner H. Assessment of microvascular abnormalities by nailfold capillaroscopy in juvenile dermatomyositis after medium- to long-term followup. *Arthritis Care Res (Hoboken)*. 2018;70:768-776.
 108. Bertolazzi C, Cutolo M, Smith V, Gutierrez M. State of the art on nailfold capillaroscopy in dermatomyositis and polymyositis. *Semin Arthritis Rheum*. 2017;47:432-444.
 109. Manfredi A, Sebastiani M, Cassone G, et al. Nailfold capillaroscopic changes in dermatomyositis and polymyositis. *Clin Rheumatol*. 2015;34:279-284.
 110. Kasteler JS, Callen JP. Scalp involvement in dermatomyositis. Often overlooked or misdiagnosed. *JAMA*. 1994;272:1939-1941.
 111. Gusdorf L, Moruzzi C, Goetz J, Lipsker D, Sibilia J, Cribier B. Mechanics hands in patients with antisynthetase syndrome: 25 cases. *Ann Dermatol Venereol*. 2019;146:19-25.
 112. Wernham AGH, Fremlin GA, Orpin SD, Salim A. Physician, beware! The deckchair sign can be seen in dermatomyositis. *Clin Exp Dermatol*. 2016;41:919-920.
 113. Lupton JR, Figueiroa P, Berberian BJ, Sulica VI. An unusual presentation of dermatomyositis: the type Wong variant revisited. *J Am Acad Dermatol*. 2000;43(5 pt 2):908-912.
 114. Block JA, Sequeira W. Raynaud's phenomenon. *Lancet*. 2001;357:2042-2048.
 115. Pouessel G, Deschildre A, Le Bourgeois M, et al. The lung is involved in juvenile dermatomyositis. *Pediatr Pulmonol*. 2013;48:1016-1025.
 116. Schwartz T, Diederichsen LP, Lundberg IE, Sjaastad I, Sanner H. Cardiac involvement in adult and juvenile idiopathic inflammatory myopathies. *RMD Open*. 2016;2:e000291.

117. Jayakumar D, Zhang R, Wasserman A, Ash J. Cardiac manifestations in idiopathic inflammatory myopathies: an overview. *Cardiol Rev.* 2019;27:131-137.
118. Schwartz T, Sanner H, Gjesdal O, Flato B, Sjaastad I. In juvenile dermatomyositis, cardiac systolic dysfunction is present after long-term follow-up and is predicted by sustained early skin activity. *Ann Rheum Dis.* 2014;73:1805-1810.
119. Barth Z, Nomeland Witczak B, Schwartz T, et al. In juvenile dermatomyositis, heart rate variability is reduced, and associated with both cardiac dysfunction and markers of inflammation: a cross-sectional study median 13.5 years after symptom onset. *Rheumatology (Oxford).* 2016;55:535-543.
120. Gadiparthi C, Hans A, Potts K, Ismail MK. Gastrointestinal and hepatic disease in the inflammatory myopathies. *Rheum Dis Clin North Am.* 2018;44:113-129.
121. Kibbi N, Bekui A, Buckley LM. Colonic vasculopathy and perforation in the initial presentation of adult dermatomyositis in a patient with improving muscle weakness. *BMJ Case Rep.* 2016;2016. <https://doi.org/10.1136/bcr-2015-213460>.
122. Papadopoulou C, McCann LJ. The vasculopathy of juvenile dermatomyositis. *Front Pediatr.* 2018;6:284.
123. Enders FB, Bader-Meunier B, Baildam E, et al. Consensus-based recommendations for the management of juvenile dermatomyositis. *Ann Rheum Dis.* 2017;76:329-340.
124. McCann LJ, Juggins AD, Maillard SM, et al. The Juvenile Dermatomyositis National Registry and Repository (UK and Ireland)—clinical characteristics of children recruited within the first 5 yr. *Rheumatology (Oxford).* 2006;45:1255-1260.
125. Sanner H, Gran JT, Sjaastad I, Flato B. Cumulative organ damage and prognostic factors in juvenile dermatomyositis: a cross-sectional study median 16.8 years after symptom onset. *Rheumatology (Oxford).* 2009;48:1541-1547.
126. Mamyrova G, Kleiner DE, James-Newton L, Shaham B, Miller FW, Rider LG. Late-onset gastrointestinal pain in juvenile dermatomyositis as a manifestation of ischemic ulceration from chronic endarteropathy. *Arthritis Rheum.* 2007;57:881-884.
127. Starr MR, Softing Hataye AL, Bakri SJ. Asymptomatic multifocal paracentral acute middle maculopathy associated with juvenile dermatomyositis: optical coherence angiography findings. *Retin Cases Brief Rep.* 2019 [Epub ahead of print].
128. López De Padilla CM, Vallejo AN, Lacomis D, McNallan K, Reed AM. Extranodal lymphoid microstructures in inflamed muscle and disease severity of new-onset juvenile dermatomyositis. *Arthritis Rheum.* 2009;60:1160-1172.
129. Miles L, Bove KE, Lovell D, et al. Predictability of the clinical course of juvenile dermatomyositis based on initial muscle biopsy: a retrospective study of 72 patients. *Arthritis Rheum.* 2007;57:1183-1191.
130. Allenbach Y, Keraen J, Bouvier AM, et al. High risk of cancer in autoimmune necrotizing myopathies: usefulness of myositis specific antibody. *Brain.* 2016;139(pt 8):2131-2135.
131. Tiniakou E, Christopher-Stine L. Immune-mediated necrotizing myopathy associated with statins: history and recent developments. *Curr Opin Rheumatol.* 2017;29:604-611.
132. Tawara N, Yamashita S, Zhang X, et al. Pathomechanisms of anti-cytosolic 5'-nucleotidase 1A autoantibodies in sporadic inclusion body myositis. *Ann Neurol.* 2017;81:512-525.

Answers to CME examination

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Dermatomyositis: Diagnosis and treatment

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Learning objectives

After completing this learning activity, participants should be able to describe initial workup for a suspected case of DM (including the role of auto-antibody testing) as well as recently updated diagnostic criteria; identify appropriate screening measures for both adults and children with DM; choose appropriate treatment for adults and children with DM and discuss the potential roles of emerging immunologic therapies in DM.

Disclosures

Editors

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The second article in this continuing medical education series reviews the initial evaluation of patients with suspected dermatomyositis (DM), the relevant work-up for malignancy and interstitial lung disease once a diagnosis of DM is made, and treatment recommendations for patients with DM based on disease severity, the presence of systemic symptoms, and myositis-specific antibody (MSA) profiles. This review emphasizes the emerging role of MSAs in the diagnosis of DM and highlights how MSAs can be used to guide the appropriate work-up for malignancy and interstitial lung disease. The treatment approach proposed by this continuing medical education series discusses both established and novel therapies for DM and highlights the importance of considering lesion type, degree of muscle involvement, presence of systemic symptoms, presence of MSAs, and patient age when determining the best treatment approach for a patient with DM. (J Am Acad Dermatol 2020;82:283-96.)

Key words: anti-MDA5 dermatomyositis; cancer-associated dermatomyositis; dermatomyositis; juvenile dermatomyositis.

The evaluation and management of patients with suspected dermatomyositis (DM) is evolving. The second article in this continuing medical education series reviews the

initial evaluation of patients with suspected DM and the relevant work-up for systemic manifestations once a diagnosis is made. Recommendations for treatment based on disease severity, the presence of

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Abbreviations used:

EULAR/ACR:	European League Against Rheumatism/American College of Rheumatology
ILD:	interstitial lung disease
IVIG:	intravenous immunoglobulin
JDM:	juvenile dermatomyositis
JKI:	Janus kinase inhibitor
MMF:	mycophenolate mofetil
MSA:	myositis-specific antibody
MTX:	methotrexate
RP-ILD:	rapidly progressive interstitial lung disease

systemic symptoms, the presence of myositis-specific antibodies (MSAs), and patient age will be given. The integration of MSAs into the management of patients with DM will be emphasized. Treatment recommendations include a discussion of emerging therapies.

THE INITIAL APPROACH: DIAGNOSING DERMATOMYOSITIS

The initial evaluation of patients with suspected DM must include a total body skin examination, objective muscle strength examination, and a laboratory work-up.¹ In equivocal cases, obtaining a biopsy specimen of the skin or muscle or muscle imaging may clarify the diagnosis.² Historically, a diagnosis of DM was made based on criteria proposed by Bohan and Peter in 1975.³ Many new classification systems have subsequently been proposed (Table I). Most recently, the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) developed the first validated classification criteria with a reported sensitivity of 87% and specificity of 82% for a diagnosis of DM. However, the sensitivity of these guidelines is poor for diagnosing amyopathic DM because only limited types of cutaneous lesions are included in their scoring system.^{4,5} In addition, the only MSA included in the EULAR/ACR criteria is anti-Jo-1, because other antibodies were not widely available at the time the guidelines were formed.¹

We have modified the EULAR/ACR diagnostic approach to incorporate the use of multiple newly available MSAs (Table II and Fig 1). The incorporation of MSAs into diagnostic criteria of DM is beneficial for several reasons: 1) it facilitates the diagnosis of DM, especially in cases of clinically amyopathic DM (CADM); 2) it separates patients with DM into clinically relevant subsets (which helps tailor the additional work-up for systemic

manifestations based on an individual's MSA profile); and 3) it obfuscates the need for obtaining a biopsy specimen of the muscle in many cases. A 2018 study in *JAMA Neurology* supports the use of MSAs in diagnosis; in this study, patients with idiopathic inflammatory myopathies were appropriately classified as having DM, inclusion body myositis, immune-mediated necrotizing myositis, or antisynthetase syndrome based solely on MSA profile and clinical manifestations.⁶

EVALUATION FOR SYSTEMIC MANIFESTATIONS

Once a diagnosis of DM has been confirmed, patients must undergo additional work-up to identify systemic manifestations. This work-up should be directed by the patient's MSA profile. An in-depth review of the clinical manifestations associated with each MSA is provided in the first article in this continuing medical education series. Dermatologists using MSAs as part of their clinical decision making must ensure that they are ordering a testing assay that reliably detects and discriminates between relevant MSAs because some assays perform less reliably than others.^{7,8}

Malignancy work-up

The estimated prevalence of malignancy in adult patients with DM is 20%. The risk of developing malignancy is highest within a year of diagnosis and remains elevated for ≤ 5 years.⁹ Malignancy risk is also increased for males and those > 45 years of age at the time of diagnosis.^{9,10} In juvenile dermatomyositis (JDM), malignancy is extremely uncommon with no cases of malignancy-associated JDM identified in the EuroMyositis registry.¹¹ As highlighted in the first article in this continuing medical education series, malignancy-associated DM primarily occurs in adults who are either anti-transcription intermediary factor 1- or anti-nuclear matrix protein 2-positive.^{11,12}

Patients with JDM do not require any work-up for malignancy.¹¹ A suggested algorithm for appropriate malignancy screening in newly diagnosed adult patients with DM is detailed in Fig 2. Adult patients with DM who are both anti-transcription intermediary factor 1- and anti-nuclear matrix protein 2-negative (ie, who have a low risk of malignancy-associated DM) require history, physical examination, "age-appropriate" cancer screening, and symptom-targeted cancer screening alone because there is not strong evidence to suggest that individuals without these antibodies are at an appreciably elevated risk for malignancy compared with the general population.¹² Aggressive work-up for

Table I. Classification systems for idiopathic inflammatory myopathies

Classification system	Criteria included	Entities defined	Benefits and limitations
Bohan and Peter (1975) ^{3,80}	Clinical: skin rash (heliotrope rash or Gottron sign) and symmetric proximal muscle weakness Laboratory: elevation of skeletal muscle enzymes Other: EMG and muscle biopsy specimen findings	Definite DM, probable DM, possible DM, definite PM, probable PM, and possible PM	High sensitivity but low specificity ⁸¹ ; outdated conceptualization of DM and PM as related entities on a spectrum of inflammatory myopathy ⁸² ; does not specify how to exclude other forms of myopathy ⁸¹
Tanimoto et al (1995) ⁸³	Clinical: skin rash (heliotrope rash or Gottron sign or linear extensor erythema), proximal muscle weakness, muscle pain on grasping or spontaneous pain, nondestructive arthritis or arthralgia, and fever Laboratory: elevated CK or aldolase, elevated CRP or ESR, and positive anti-Jo-1 antibodies Other: abnormal EMG and muscle biopsy specimen findings	DM and PM	High sensitivity but low specificity ⁸¹
Targoff et al (1997) ⁸⁴	Clinical: skin rash (heliotrope rash or Gottron sign) and symmetric proximal muscle weakness Laboratory: elevation of skeletal muscle enzymes and presence of any MSA Other: EMG and muscle biopsy specimen findings	Definite IIM, probable IIM, possible IIM, subclassifies DM, IBM, JDM, and ADM	Sensitivity 93% and specificity 89% using EULAR/ACR dataset ⁸¹
Dalakas and Hohlfeld (2003) ⁸⁵	Clinical: skin rash (or calcinosis) and myopathic muscle weakness Laboratory: elevated muscle enzymes Other: EMG and muscle biopsy specimen findings	Definite PM, probable PM, definite DM, probable DM, and definite ADM	High specificity but low sensitivity using EULAR/ACR dataset ⁸¹
Hoogendoijk et al (2003) ⁸⁶	Clinical: age, muscle weakness (specifies time course and pattern), and skin rash (heliotrope, periorbital edema, Gottron papules/sign, V sign, shawl sign, holster sign) Laboratory: elevated CK and detection of MSAs Other: EMG, MRI, and muscle biopsy specimen findings	Definite DM, probable DM, ADM, DM sine dermatitis, definite PM, probable PM, nonspecific myositis, and IMNM	High specificity but low sensitivity using EULAR/ACR dataset ⁸¹

Continued

Table I. Cont'd

Classification system	Criteria included	Entities defined	Benefits and limitations
EULAR/ACR (2017) ⁸¹	Clinical: age, muscle weakness, and skin rash (heliotrope rash, Gottron papules, and Gottron sign) Laboratory: positive anti-Jo-1 antibody and elevated CK, LDH, AST, and ALT Other: muscle biopsy specimen findings	Algorithm determines IIM probability; subclassifies PM, IBM, DM, ADM, and JDM	Large dataset; sensitivity 93%, specificity 88% (with muscle biopsy data); sensitivity 87%, specificity 82% (without muscle biopsy data); subclassification limited by small sample size for some entities; requires additional validation in Asian and African populations; can diagnose DM without muscle biopsy when typical skin findings are present
Mariampillai et al (2018) ⁶	47 variables used in multiple correspondence analysis, included sociodemographic variables, skin lesions, biological variables (including CK levels and MSAs), histologic variables, clinical muscular variables, and extramuscular variables	DM, IBM, IMNM, and ASS	

ADM, Amyopathic dermatomyositis; ALT, alanine aminotransferase; ASS, antisynthetase syndrome; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; DM, dermatomyositis; EMG, electromyographic; ESR, erythrocyte sedimentation rate; EULAR/ACR, European League Against Rheumatism/American College of Rheumatology; IBM, inclusion body myositis; IIM, idiopathic inflammatory myopathy; IMNM, immune-mediated necrotizing myositis; JDM, juvenile dermatomyositis; LDH, lactate dehydrogenase; MSA, myositis-specific antibody; PM, polymyositis.

Table II. Initial workup for suspected dermatomyositis based on European League Against Rheumatism/American College of Rheumatology criteria

Examination	History and physical examination	Total body skin examination, manual strength testing of bilateral extremities and neck flexors
Baseline laboratory testing	Muscle enzymes	Creatine kinase, lactate dehydrogenase, aspartate aminotransferase, and aldolase
Autoantibody testing	DM-specific autoantibodies Antisynthetase syndrome autoantibodies IMNM autoantibodies (if indicated clinically) Other connective tissue disease-related autoantibodies (if indicated clinically)	Mi2, TIF1, MDA5, NXP2, and SAE Jo-1, PL-7, PL-12, EJ, and OJ SRP and HMGCR Antinuclear antibody, Ro/La, dsDNA, anti-Sm, and Scl-70
Additional testing	If the above testing is equivocal If diagnosis remains uncertain	T2-weighted MRI of area of weakness Obtain biopsy specimen of muscle from affected area identified on MRI

DM, Dermatomyositis; dsDNA, double-stranded DNA; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IMNM, immune-mediated necrotizing myositis; MDA5, anti-melanoma differentiation-associated protein 5; MRI, magnetic resonance imaging; NXP2, nuclear matrix protein 2; SAE, small ubiquitin-like modifier activating enzyme; Scl-70, topoisomerase 1; SRP, signal recognition particle; TIF1, transcription intermediary factor 1.

malignancy in these patients is likely to be costly and invasive, and the available evidence suggests that it is unlikely to improve outcomes. Possible exceptions to this recommendation are: 1) anti-small ubiquitin-like modifier activating enzyme-positive individuals, because some studies have demonstrated a risk

for malignancy in these patients, although this finding has not been uniformly reproducible; and 2) MSA-negative patients, because a recent large, retrospective study suggested that these patients have a threefold elevated risk of developing malignancy over matched control subjects.¹²

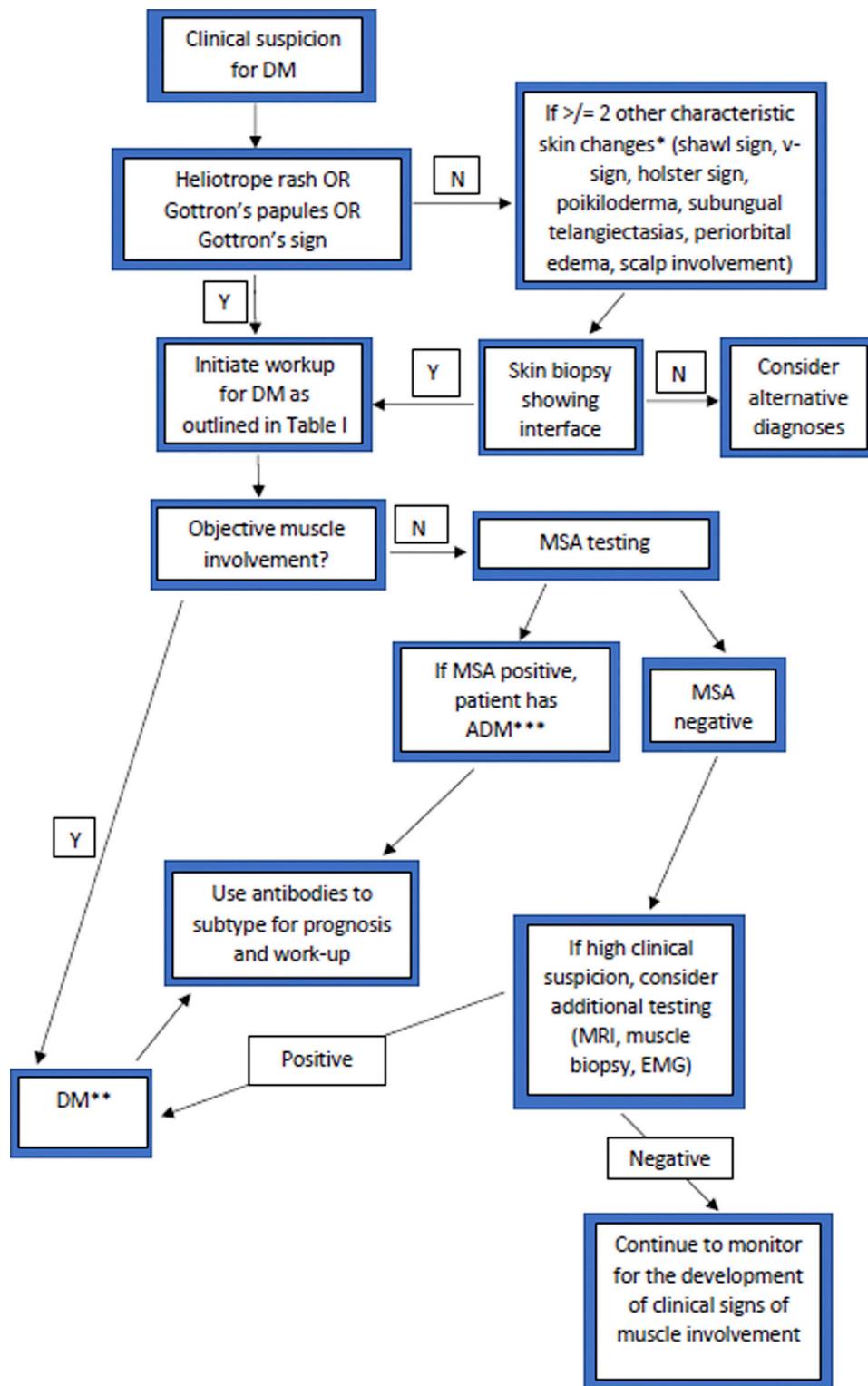


Fig 1. Diagnostic algorithm for adult and juvenile dermatomyositis (DM). *As indicated in the first article in this continuing medical education series Table I. **Pts <18 years of age at the time of symptom onset are considered to have juvenile dermatomyositis (JDM). ***Patients with amyopathic DM should be monitored regularly for the development of muscle involvement. *EMG*, Electromyography; *MRI*, magnetic resonance imaging; *MSA*, myositis-specific antibody.

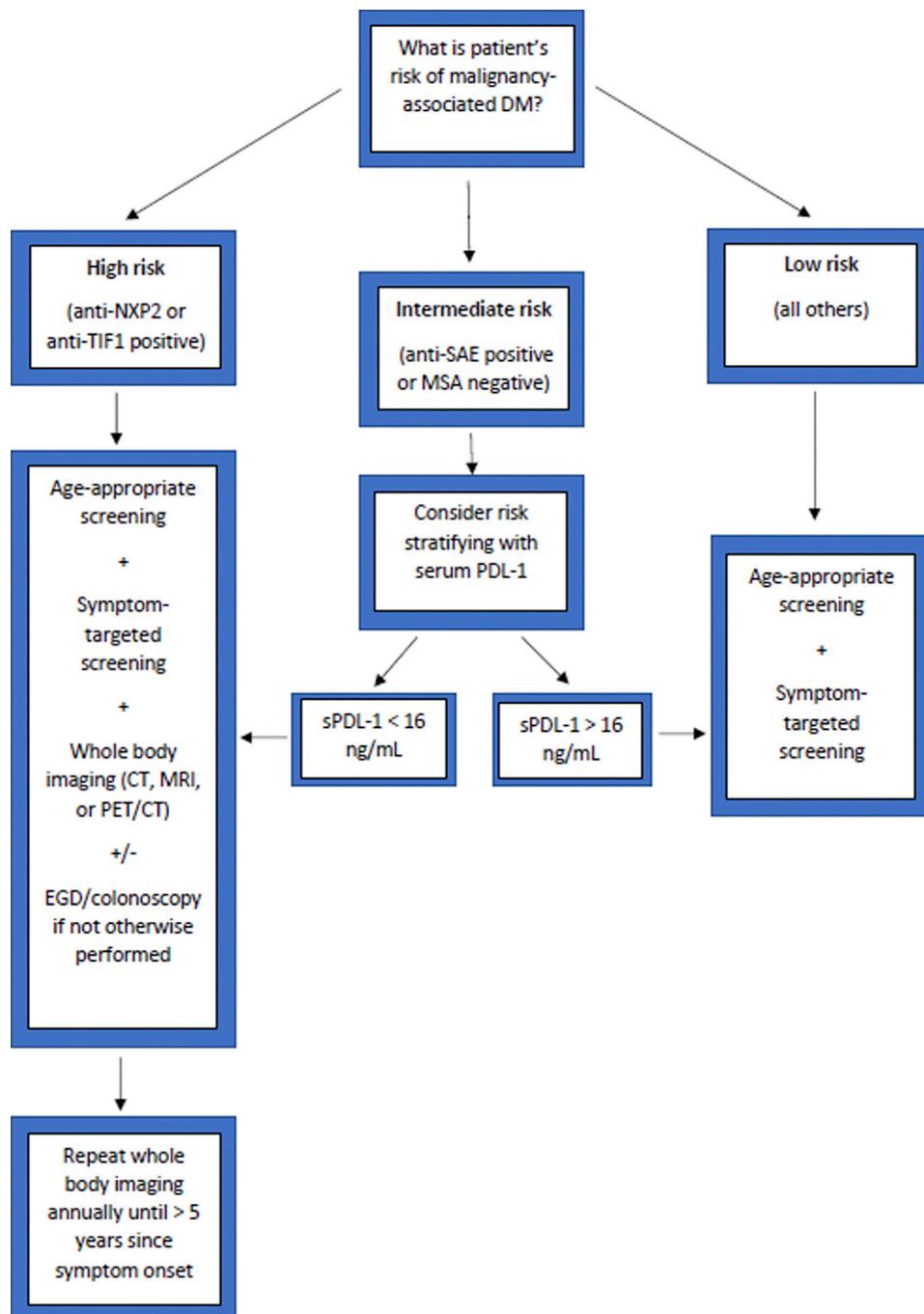


Fig 2. Malignancy work-up for newly diagnosed patients with dermatomyositis (DM). *CT*, Computed tomography; *MRI*, magnetic resonance imaging; *NXP2*, nuclear matrix protein 2; *PET-CT*, positron emission tomography-computed tomography; *SAE*, small ubiquitin-like modifier activating enzyme; *sPDL*, soluble programmed death ligand-1; *TIF1*, anti-transcription intermediary factor 1.

Given the paucity of data about cancer risk in these 2 subpopulations, it may be reasonable to further stratify cancer risk with serum biomarkers, although such an approach has never been studied or suggested for this “intermediate-risk” population

specifically. Annual soluble programmed death ligand-1 measurements can be considered, because extremely elevated levels of soluble programmed death ligand-1 have been associated with malignancy in patients with DM.^{13,14} The use of cancer

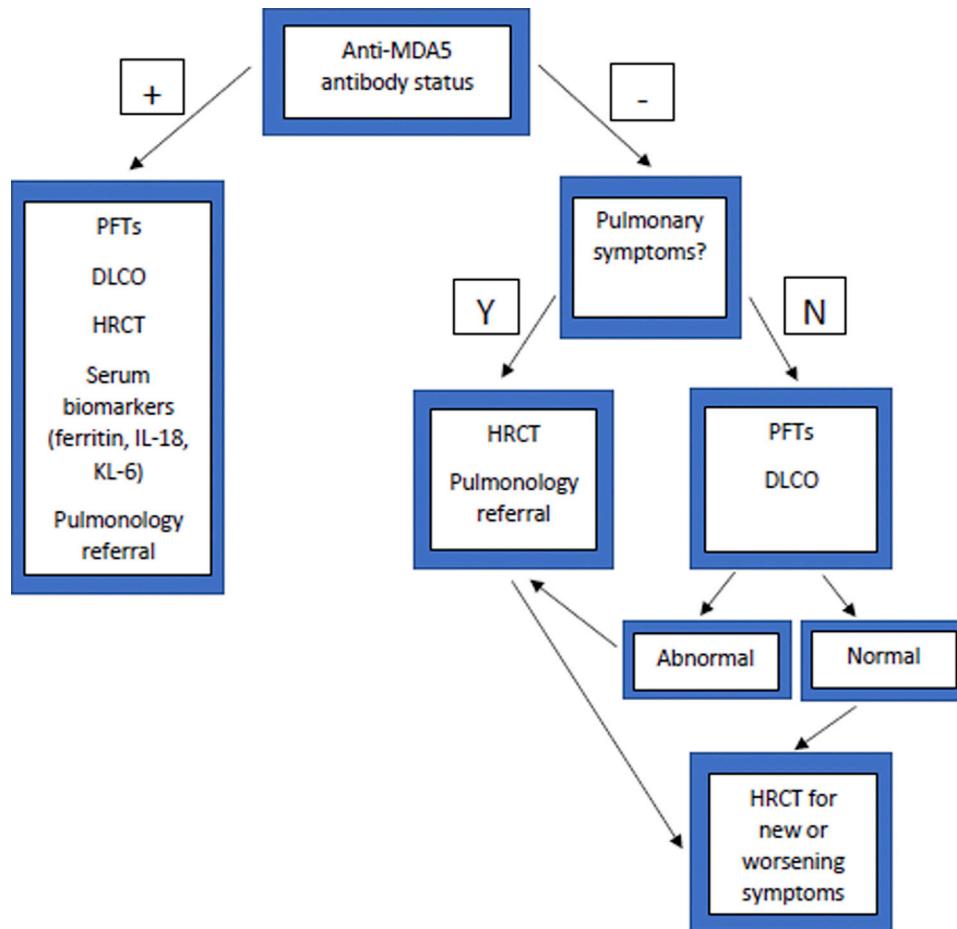


Fig 3. Interstitial lung disease work-up for newly diagnosed patients with dermatomyositis (DM). *DLCO*, Diffusion capacity of the lung for carbon monoxide; *HRCT*, high-resolution computed tomography; *IL-18*, interleukin-18; *KL-6*, Krebs von den Lungen-6; *MDA5*, anti-melanoma differentiation-associated protein 5; *PFT*, pulmonary function testing.

serum biomarkers (eg, CEA, CA 19-9) other than prostate-specific antigen, a potential component of age-appropriate screening, has not been demonstrated to be effective for detecting malignancy in patients with DM.¹⁵

In addition to age-appropriate and symptom-targeted malignancy screening, individuals who are anti-transcription intermediary factor 1– or anti-nuclear matrix protein 2–positive (ie, high-risk for malignancy-associated DM) should undergo whole body imaging with either computed tomography (CT), magnetic resonance imaging, or positron emission tomography CT.^{13,16} These modalities have been proven to detect DM-associated malignancies that would be missed by age-appropriate and symptom-targeted screening.¹⁷ No study has compared superiority of one imaging modality over the others. Studies that have failed to demonstrate benefit with the use of whole-body imaging have not subselected for high-risk patients.¹⁸

The appropriate reimaging interval in high-risk individuals who had an initially negative work-up for malignancy has not been studied. As an increased malignancy risk is present for ≤ 5 years after DM onset, some authorities recommend annual imaging until that time point is reached.¹³ Finally, high-risk individuals who would not receive upper and lower endoscopy as part of their age-appropriate screening and who do not have malignancy identified on other work-ups should consider undergoing this testing.¹³

Interstitial lung disease work-up

Evaluation for interstitial lung disease (ILD) in patients with a new diagnosis of DM involves identifying whether a patient has ILD and, if so, whether a patient has a poor prognosis subset of ILD termed rapidly progressive ILD (RP-ILD). The early identification of RP-ILD is essential because it is fatal in ≤ 6 months in 50% of cases and the prognosis can be improved if treatment is initiated before the

development of abnormalities on high-resolution CT.^{19,20}

Fig 3 provides an algorithm for evaluating patients with DM for ILD. All patients require pulmonary function testing and diffusion capacity of the lung for carbon monoxide at the time of diagnosis.²¹ In asymptomatic patients with restrictive physiology present on pulmonary function testing and decreased diffusion capacity of the lung for carbon monoxide, or in patients with symptoms suggestive of ILD, high-resolution CT is indicated.²¹ If ILD is not present on an initial work-up, patients can be monitored clinically with a plan to repeat high-resolution CT if new or worsening pulmonary symptoms develop.²¹ All patients with evidence of ILD require an urgent pulmonology evaluation.

Anti-melanoma differentiation-associated protein 5 (MDA5) antibodies are present in at least half of all cases of DM-associated ILD and >80% of cases of DM-associated RP-ILD.^{20,22,23} In JDM, anti-MDA5 positivity is also predictive of ILD and RP-ILD with an estimated sensitivity of ~70% for ILD.²⁴ Because RP-ILD can evade imaging during its early stages, testing serum biomarkers that correlate with the presence of ILD and that are elevated before imaging changes should be considered.^{25,26} Elevated levels of serum ferritin, interleukin-18, Krebs von den Lungen-6, and anti-MDA5 antibodies themselves have been associated with the presence of ILD, and laboratory testing for these biomarkers should be considered in all patients with anti-MDA5 dermatomyositis.²⁷⁻³¹

Other systemic work-up

The first article in this continuing medical education series discussed the many other potential systemic manifestations of DM and JDM. Given their relative infrequency, screening for these manifestations with a targeted review of symptoms is reasonable.

GENERAL TREATMENT APPROACH

Management of DM is nuanced; dermatologists frequently diagnose the disease and have primary responsibility for the cutaneous manifestations of the disease, but myopathy and other systemic manifestations often drive therapy. The appropriate treatment approach is determined by consideration of 5 factors:

- 1) Lesion type—Is the lesion nonvasculopathic (eg, shawl sign, heliotrope rash), vasculopathic (digital pulp ulcers, inverse Gottron papules), or calcinotic?
- 2) Degree of muscle involvement—Is the patient amyopathic/hypomyopathic? Does the patient have persistent cutaneous symptoms despite

having controlled myopathy? Is the patient postmyopathic (ie, have the patient's muscle symptoms resolved despite being off treatment but residual cutaneous disease is still present)?

- 3) Presence of systemic symptoms—Are other organ systems involved? Is there an associated malignancy?
- 4) Presence of MSAs—What clinical subset does the patient have as suggested by the presence of MSAs?
- 5) Patient age—Does the patient have adult or juvenile dermatomyositis?

We discuss each of these factors with an emphasis on the use of a multidisciplinary approach in settings where muscle involvement or systemic symptoms are present.

Considering lesion type

Nonvasculopathic cutaneous disease. Three layers of therapy should be used for all patients with nonvasculopathic disease: sun protection, topical therapy with corticosteroids or calcineurin inhibitors, and systemic therapy.^{32,33} This section will focus on systemic therapies. A treatment algorithm for adult DM is shown in **Fig 4**.

Systemic corticosteroids. Systemic corticosteroids are the gold standard initial treatment for DM-related myopathy. However, they should not be used in patients with CADM and should not be used as a monotherapy because this approach is frequently ineffective and associated with the development of unacceptable long-term adverse effects.³⁴⁻³⁶ Similarly, in cases where a patient's myopathy is controlled with corticosteroids but cutaneous symptoms persist, a dose increase in corticosteroids alone is not recommended. A combination of systemic corticosteroids with oral immunosuppressants or biologics should be used at disease onset in patients with myopathy or other systemic symptoms, similar to how combination therapy is used in patients with bullous disorders to limit systemic corticosteroid use.^{34,37}

Antimalarials. Traditional treatment algorithms have emphasized hydroxychloroquine as the first-line systemic agent for cutaneous DM. However, recent evidence suggests that patients treated with hydroxychloroquine are more likely to flare their cutaneous disease than they are to achieve satisfactory disease control from hydroxychloroquine monotherapy.^{35,36,38,39} Patient MSA profiles may predict risk of cutaneous flare after hydroxychloroquine initiation with anti-small ubiquitin-like modifier activating enzyme-positive patients at the highest risk and anti-MDA5 patients without

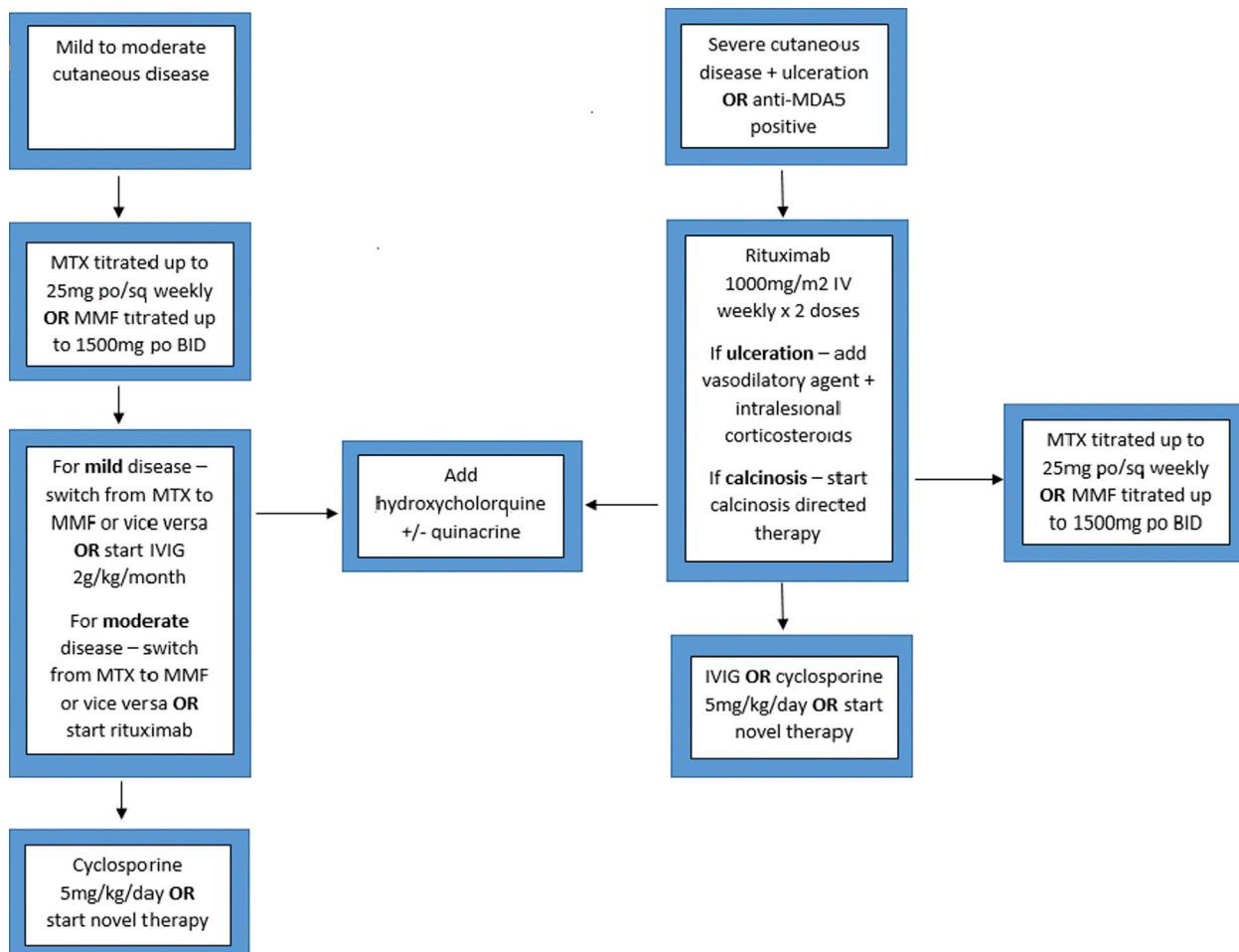


Fig 4. Adult dermatomyositis treatment algorithm. *BID*, Twice daily; *IV*, intravenous; *IVIG*, intravenous immunoglobulin; *MDA-5*, anti-melanoma differentiation-associated protein 5; *MMF*, mycophenolate mofetil; *MTX*, methotrexate.

demonstrable risk.⁴⁰ Furthermore, unlike other systemic therapies, none of the antimalarials have an effect on the noncutaneous manifestations of DM (eg, myopathy and ILD).^{41,42} Given the favorable side effect profile of antimalarials, they can be considered as adjuvants when disease control is inadequate with other systemic agents.^{35,36,42,43}

Mycophenolate mofetil and methotrexate. In the absence of vasculopathic or calcinotic lesions, the first-line systemic therapies for nonvasculopathic DM are mycophenolate mofetil (MMF) and methotrexate (MTX).^{38,44-48} Both of these medications often require high dosing, with many adults requiring 3 g of MMF daily or 25 mg of MTX weekly. These medications should be started in conjunction with systemic corticosteroids when myopathy is present. However, systemic corticosteroids do not need to be used in conjunction with these medications when treating CADM or postmyopathic cutaneous disease.

There are no head-to-head studies comparing MMF and MTX, but several considerations may favor the use of one agent over the other; MTX often has faster onset (~4 weeks) and has clinical trial data supporting its use as a steroid-sparing agent. In addition, MMF is effective for treating ILD.^{37,49,50} Treatment failure with one agent is not predictive of treatment failure with the other.

Rituximab. In cases where a combination of systemic corticosteroids and an oral immunosuppressant fail, rituximab is the appropriate next step in therapy.⁵¹⁻⁵³ In individuals with vasculopathic or calcinotic lesions, adults with anti-MDA5 positivity, or children with NXP-2 positivity, rituximab plus systemic corticosteroids can be considered first-line treatment.⁵⁴⁻⁵⁶ Support for the use of rituximab comes from the largest clinical trial ever conducted for idiopathic inflammatory myopathies, the Rituximab in Myositis trial.⁵¹ This trial demonstrated that 83% of children and adults with DM who

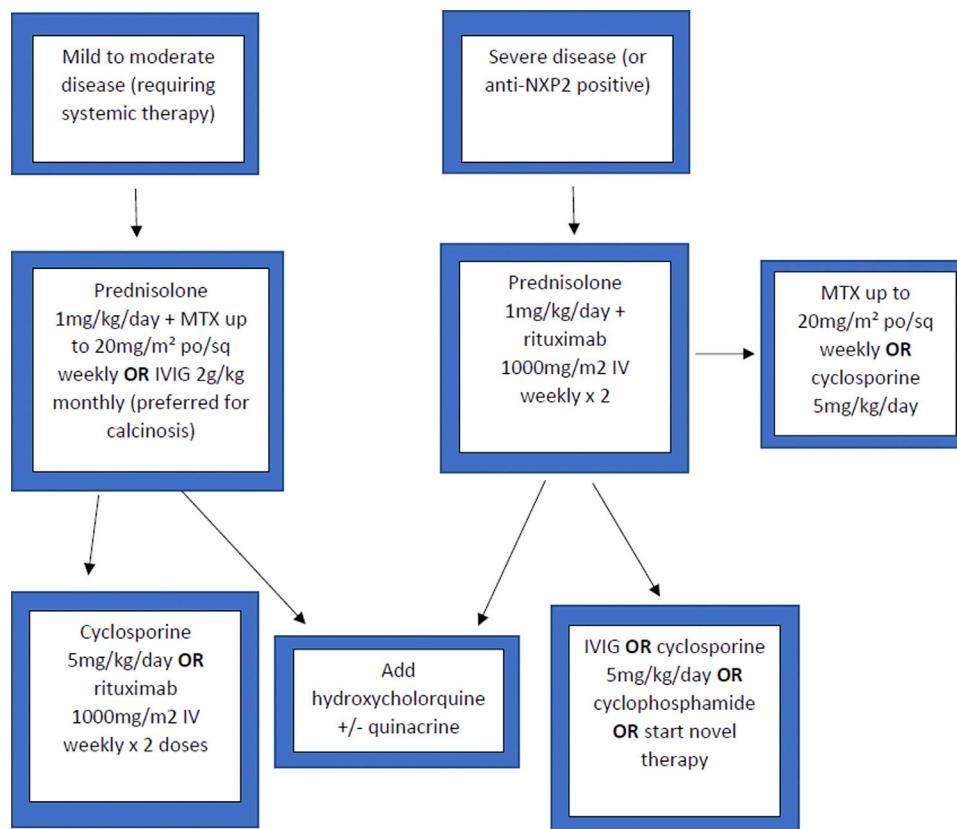


Fig 5. Juvenile dermatomyositis treatment algorithm. *IV*, Intravenous; *IVIG*, intravenous immunoglobulin; *MTX*, methotrexate; *NXP2*, nuclear matrix protein 2.

Table III. Emerging treatments for dermatomyositis

Drug	Route of administration	Mechanism of action	Ongoing clinical trial (Y/N)
Tocilizumab	IV	IL-6 inhibitor	Y
Aletuzumab	IV	Anti-CD52	N
Abatacept	IV	Costimulatory modulator	Y
Infliximab	IV	TNF inhibitor	Y
Anakinra	SubQ	IL-1 inhibitor	N
Eculizumab	IV	C5-blocking agent	N
Apremilast	PO	PDE4 inhibitor	Y

IL, Interleukin; *IV*, intravenous; *PDE4*, phosphodiesterase 4; *PO*, per os; *SubQ*, subcutaneous; *TNF*, tumor necrosis factor.

previously failed systemic corticosteroids and ≥ 1 immunosuppressant improved with rituximab and were tapered off systemic steroids more quickly.⁵¹ MSA-positive individuals had a greater chance of responding favorably to rituximab than MSA-negative individuals.⁵¹

In addition, several recent findings suggest that rituximab may have disease-modifying properties.

Rituximab is the only treatment associated with improvement in nailfold capillary abnormalities that may represent prevention of pathogenic vessel damage. In cases where MSAs are presumed to be pathogenic (eg, anti-MDA5 DM), rituximab likely works through a similar mechanism as in pemphigus (a condition in which it has been shown to be disease-modifying).^{51,57} The 2 major limitations to the use of rituximab are that it has a slow onset and a risk of serious infection >6%.^{51,56}

The frequency with which individuals receiving rituximab should undergo an additional round of treatment is unknown. In the Rituximab in Myositis trial, CD19⁺ numbers rebounded above 5 cells/uL at weeks 32 to 36 on average.⁵¹ Based on the pemphigus literature, it may be reasonable to trend peripheral B cell concentrations to guide therapy.⁵⁸

Intravenous immunoglobulin. A reasonable treatment option in patients who have failed or who are intolerant of rituximab is intravenous immunoglobulin (IVIG).^{43,59,60} It is also recommended for patients with controlled myopathy but persistent cutaneous disease.⁶¹ In cases with severe disease that is refractory to IVIG, subcutaneous immunoglobulin administration can be considered if available.⁶²

Calcineurin inhibitors. Calcineurin inhibitors (typically cyclosporine and less frequently tacrolimus) are reasonable third-line options or are useful in cases in which myopathy is controlled but other immunosuppressants are not controlling cutaneous disease.⁴⁸ Although cyclosporine is as effective as MTX based on Pediatric Rheumatology International Trials Organization data, MTX and MMF are preferred because the Pediatric Rheumatology International Trials Organization trial demonstrated that cyclosporine use was associated with a greater risk of serious adverse effects.³⁷ Calcineurin inhibitors are also a reasonable choice in patients with comorbid interstitial lung disease.^{63,64}

Other traditional therapies. Other therapies that can be considered include infliximab, azathioprine, and cyclophosphamide. However, these should be reserved for refractory cases given the plethora of superior options listed above.⁶⁵⁻⁶⁷

Vasculopathic cutaneous disease. Vasculopathic skin lesions include ulceration, inverse Gottron papules, and nailfold capillary abnormalities. These lesions are notoriously refractory to immunosuppressive therapy and confer significant morbidity even in the absence of other cutaneous disease. The only systemic agent with robust data supporting its use for vasculopathic lesions is rituximab. However, rituximab alone is often ineffective for treating ulceration.^{56,68} Intralesional corticosteroids are frequently used for treating ulcerations and inverse Gottron papules and may be effective, but recent evidence supports using vasodilatory agents. Case studies suggest that nifedipine, sildenafil, intravenous prostaglandins, and bosentan should be added as early adjuncts given the otherwise refractory nature of these lesions.⁶⁹

Calcinosis cutis. Like vasculopathic lesions, calcinotic lesions are typically refractory to immunosuppressive therapy. Patients with JDM and calcinosis should be preferentially treated with IVIG because it has the best data supporting its use for calcinosis specifically.^{59,70,71} For a detailed discussion of calcinosis cutis-directed therapies, we encourage readers to review the continuing medical education series on calcinosis cutis.⁷²

Considering degree of muscle involvement

Patients with myopathy should be managed in conjunction with a rheumatologist or neurologist. Controlled cutaneous disease is not predictive of controlled myopathy and vice versa. Unlike in patients with CADM (for whom monotherapy with oral immunosuppressants is a reasonable first-line therapy), first-line therapy for management of the myopathy component of DM is the simultaneous initiation of corticosteroids and a steroid-sparing

immunosuppressant (eg, MMF or MTX).³⁷ Subsequent treatment choices in individuals with recalcitrant myopathy are similar to those highlighted above for the treatment of refractory cutaneous disease.

The appropriate treatment for persistent cutaneous involvement in patients with controlled myopathy depends on the treatment the patient is currently receiving and the degree of severity of the cutaneous involvement.⁷³ Dose escalations of an oral immunosuppressant, initiation of hydroxychloroquine, initiation of IVIG, or initiation of rituximab can all be reasonable next steps depending on the clinical scenario.⁶¹ Postmyopathic cutaneous disease can be managed similarly to CADM.

Considering systemic symptoms

Treatment of the systemic symptoms associated with DM is beyond the scope of this continuing medical education series and should be addressed as part of a multidisciplinary approach.

Considering MSAs. MSAs will undoubtedly be used to personalize treatment decisions for patients with DM in the future. However, currently there is a paucity of data supporting such an approach. Several anecdotally supported treatment considerations have been mentioned above.

Considering age. Only 2 clinical trials have specifically evaluated patients with JDM (the Pediatric Rheumatology International Trials Organization and Rituximab in Myositis trials), but consensus opinions are also available from the Childhood Arthritis and Rheumatology Research Alliance and Single Hub and Access Point for Pediatric Rheumatology in Europe registries.^{37,51,56,74,75} Review of these pivotal studies supports the approach to JDM proposed in Fig 5. All patients should at least be started on a combination of systemic corticosteroids with either MTX or IVIG to decrease the long-term steroid burden.^{37,75} In patients who fail first-line treatment, have severe disease with ulceration, calcinosis, or lipodystrophy at the time of presentation, or have poor-prognosis NXP-2 disease, rituximab plus systemic corticosteroids can be considered.⁵⁶ Other biologics, cyclophosphamide, and Janus kinase inhibitors can be considered in patients with refractory disease.^{65,67,76}

Emerging treatments

Several novel approaches to DM have recently garnered significant interest. Janus kinase inhibitors (JAKIs) will be discussed below because they have the most robust evidence for the treatment of cutaneous DM. Other emerging treatments are listed in Table III.

JAKIs. DM is driven by type I interferons. Both in vivo and in vitro data have shown that JAKIs

decrease levels of type I interferons in individuals with DM.⁷⁷ Case series have shown that several JKIs are effective for treating refractory cutaneous disease.⁷⁸ One series has also shown that JKIs may be an effective add-on therapy in patients with RP-ILD.⁷⁹ There is an ongoing clinical trial assessing the efficacy of tofacitinib in refractory DM that is assessing both skin and muscle outcomes.

In conclusion, a thorough initial assessment of patients with suspected DM is essential to making a diagnosis with as little delay and morbidity as possible. The management of DM is nuanced and requires a constant assessment for the development of systemic symptoms. A multi-disciplinary approach is recommended.

REFERENCES

- Bottai M, Tjärnlund A, Santoni G, et al. EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups: a methodology report. *RMD Open*. 2017;3:e000507.
- Ran J, Ji S, Morelli JN, Wu G, Li X. T2 mapping in dermatomyositis/polymyositis and correlation with clinical parameters. *Clin Radiol*. 2018;73:1057.e13-1057.e18.
- Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med*. 1975;292:344-347.
- Hočevar A, Rotar Z, Krosel M, Čučnik S, Tomšič M. Performance of the 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies in clinical practice. *Ann Rheum Dis*. 2018;77:e90.
- Patel B, Khan N, Werth VP. Applicability of EULAR/ACR classification criteria for dermatomyositis to amyopathic disease. *J Am Acad Dermatol*. 2018;79:77-83.e1.
- Mariampillai K, Granger B, Amelin D, et al. Development of a new classification system for idiopathic inflammatory myopathies based on clinical manifestations and myositis-specific autoantibodies. *JAMA Neurol*. 2018;75:1528-1537.
- Ghirardello A, Rampudda M, Ekholm L, et al. Diagnostic performance and validation of autoantibody testing in myositis by a commercial line blot assay. *Rheumatology (Oxford)*. 2010;49:2370-2374.
- Victor J, Zanardo L, Héron-Mermin D, et al. Retrospective analysis of anti-TIF1gamma, anti-NXP2 and anti-SAE1/2 antibodies carriers at Bordeaux university hospital from November 2014 to February 2017 [in French]. *Rev Med Interne*. 2019;40:70-81.
- Qiang JK, Kim WB, Baibergenova A, Alhusayen R. Risk of malignancy in dermatomyositis and polymyositis. *J Cutan Med Surg*. 2017;21:131-136.
- Yang Z, Lin F, Qin B, Liang Y, Zhong R. Polymyositis/dermatomyositis and malignancy risk: a metaanalysis study. *J Rheumatol*. 2015;42:282-291.
- Lilleker JB, Vencovsky J, Wang G, et al. The EuroMyositis registry: an international collaborative tool to facilitate myositis research. *Ann Rheum Dis*. 2018;77:30-39.
- Yang H, Peng Q, Yin L, et al. Identification of multiple cancer-associated myositis-specific autoantibodies in idiopathic inflammatory myopathies: a large longitudinal cohort study. *Arthritis Res Ther*. 2017;19:259.
- Selva-O'Callaghan A, Martínez-Gómez X, Trallero-Araguás E, Pinal-Fernández I. The diagnostic work-up of cancer-associated myositis. *Curr Opin Rheumatol*. 2018;30:630-636.
- Chen H, Peng Q, Yang H, et al. Increased levels of soluble programmed death ligand 1 associate with malignancy in patients with dermatomyositis. *J Rheumatol*. 2018;45:835-840.
- Lim CH, Tseng CW, Lin CT, et al. The clinical application of tumor markers in the screening of malignancies and interstitial lung disease of dermatomyositis/polymyositis patients: a retrospective study. *SAGE Open Med*. 2018;6, 2050312118781895.
- Li Y, Zhou Y, Wang Q. Multiple values of 18F-FDG PET/CT in idiopathic inflammatory myopathy. *Clin Rheumatol*. 2017;36: 2297-2305.
- Leatham H, Schadt C, Chisolm S, et al. Evidence supports blind screening for internal malignancy in dermatomyositis: data from 2 large US dermatology cohorts. *Medicine (Baltimore)*. 2018;97:e9639.
- Maliha PG, Hudson M, Abikhzer G, Singerman J, Probst S. 18F-FDG PET/CT versus conventional investigations for cancer screening in autoimmune inflammatory myopathy in the era of novel myopathy classifications. *Nucl Med Commun*. 2019;40: 377-382.
- Kurasawa K, Arai S, Namiki Y, et al. Tofacitinib for refractory interstitial lung diseases in anti-melanoma differentiation-associated 5 gene antibody-positive dermatomyositis. *Rheumatology (Oxford)*. 2018;57:2114-2119.
- Chen Z, Cao M, Plana MN, et al. Utility of anti-melanoma differentiation-associated gene 5 antibody measurement in identifying patients with dermatomyositis and a high risk for developing rapidly progressive interstitial lung disease: a review of the literature and a meta-analysis. *Arthritis Care Res*. 2013;65:1316-1324.
- Vij R, Strek ME. Diagnosis and treatment of connective tissue disease-associated interstitial lung disease. *Chest*. 2013;143: 814-824.
- Li L, Wang H, Wang Q, et al. Myositis-specific autoantibodies in dermatomyositis/polymyositis with interstitial lung disease. *J Neurol Sci*. 2019;397:123-128.
- Ikeda S, Arita M, Morita M, et al. Interstitial lung disease in clinically amyopathic dermatomyositis with and without anti-MDA-5 antibody: to lump or split? *BMC Pulm Med*. 2015; 15:159.
- Tansley SL, Betteridge ZE, Gunawardena H, et al. Anti-MDA5 autoantibodies in juvenile dermatomyositis identify a distinct clinical phenotype: a prospective cohort study. *Arthritis Res Ther*. 2014;16:R138.
- Nishioka A, Tsunoda S, Abe T, et al. Serum neopterin as well as ferritin, soluble interleukin-2 receptor, KL-6 and anti-MDA5 antibody titer provide markers of the response to therapy in patients with interstitial lung disease complicating anti-MDA5 antibody-positive dermatomyositis. *Mod Rheumatol*. 2018;1-7.
- Kurtzman DJB, Vleugels RA. Anti-melanoma differentiation-associated gene 5 (MDA5) dermatomyositis: a concise review with an emphasis on distinctive clinical features. *J Am Acad Dermatol*. 2018;78:776-785.
- Hanaoka M, Katsumata Y, Kawasumi H, Kawaguchi Y, Yamanaka H. KL-6 is a long-term disease-activity biomarker for interstitial lung disease associated with polymyositis/dermatomyositis, but is not a short-term disease-activity biomarker. *Mod Rheumatol*. 2019;29:625-632.
- Li L, Wang Q, Wen X, et al. Assessment of anti-MDA5 antibody as a diagnostic biomarker in patients with dermatomyositis-associated interstitial lung disease or rapidly progressive interstitial lung disease. *Oncotarget*. 2017;8: 76129-76140.
- Yang Y, Yin G, Hao J, Xie Q, Liu Y. serum interleukin-18 level is associated with disease activity and interstitial lung disease in

- patients with dermatomyositis. *Arch Rheumatol.* 2017;32:181-188.
30. Kobayashi N, Takezaki S, Kobayashi I, et al. Clinical and laboratory features of fatal rapidly progressive interstitial lung disease associated with juvenile dermatomyositis. *Rheumatol (Oxford).* 2015;54:784-791.
31. Sato S, Uejima Y, Nanbu M, et al. Clinical analysis and outcome of interstitial lung disease complicated with juvenile dermatomyositis and juvenile polymyositis. *Mod Rheumatol.* 2017;27:652-656.
32. Muro Y, Sugiura K, Akiyama M. Cutaneous manifestations in dermatomyositis: key clinical and serological features-a comprehensive review. *Clin Rev Allergy Immunol.* 2016;51:293-302.
33. Yoshimasu T, Ohtani T, Sakamoto T, Oshima A, Furukawa F. Topical FK506 (tacrolimus) therapy for facial erythematous lesions of cutaneous lupus erythematosus and dermatomyositis. *Eur J Dermatol.* 2002;12:50-52.
34. Kohsaka H, Mimori T, Kanda T, et al. Treatment consensus for management of polymyositis and dermatomyositis among rheumatologists, neurologists and dermatologists. *Mod Rheumatol.* 2019;29:1-19.
35. Anyanwu CO, Chansky PB, Feng R, Carr K, Okawa J, Werth VP. The systemic management of cutaneous dermatomyositis: results of a stepwise strategy. *Int J Womens Dermatol.* 2017;3:189-194.
36. Pinard J, Femia AN, Roman M, et al. Systemic treatment for clinically amyopathic dermatomyositis at 4 tertiary care centers. *JAMA Dermatol.* 2019;155:494-496.
37. Ruperto N, Pistorio A, Oliveira S, et al. Prednisone versus prednisone plus cyclosporin versus prednisone plus methotrexate in new-onset juvenile dermatomyositis: a randomised trial. *Lancet.* 2016;387:671-678.
38. Galimberti F, Li Y, Fernandez AP. Clinically amyopathic dermatomyositis: clinical features, response to medications and malignancy-associated risk factors in a specific tertiary-care-centre cohort. *Br J Dermatol.* 2016;174:158-164.
39. Pelle MT, Callen JP. Adverse cutaneous reactions to hydroxychloroquine are more common in patients with dermatomyositis than in patients with cutaneous lupus erythematosus. *Arch Dermatol.* 2002;138:1231-1233.
40. Dalakas MC, Illia I, Dambrosia JM, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med.* 1993;329:1993-2000.
41. Piguet V, Choy E. Dermatomyositis: a slow path towards targeted therapies or will conventional therapies prevail? *Br J Dermatol.* 2018;179:1233-1234.
42. Woo TY, Callen JP, Voorhees JJ, Bickers DR, Hanno R, Hawkins C. Cutaneous lesions of dermatomyositis are improved by hydroxychloroquine. *J Am Acad Dermatol.* 1984;10:592-600.
43. Callander J, Robson Y, Ingram J, Piguet V. Treatment of clinically amyopathic dermatomyositis in adults: a systematic review. *Br J Dermatol.* 2018;179:1248-1255.
44. Olivo Pallo PA, de Souza FHC, Miossi R, Shinjo SK. Mycophenolate mofetil in patients with refractory systemic autoimmune myopathies: case series. *Adv Rheumatol.* 2018;58:34.
45. Edge JC, Outland JD, Dempsey JR, Callen JP. Mycophenolate mofetil as an effective corticosteroid-sparing therapy for recalcitrant dermatomyositis. *Arch Dermatol.* 2006;142:65-69.
46. Gelber AC, Nousari HC, Wigley FM. Mycophenolate mofetil in the treatment of severe skin manifestations of dermatomyositis: a series of 4 cases. *J Rheumatol.* 2000;27:1542-1545.
47. Mainetti C, Terzioli Beretta-Piccoli B, Selmi C. Cutaneous manifestations of dermatomyositis: a comprehensive review. *Clin Rev Allergy Immunol.* 2017;53:337-356.
48. Isak V, Jorizzo JL. Recent developments on treatment strategies and the prognosis of dermatomyositis: a review. *J Dermatol Treat.* 2018;29:450-459.
49. Waldman R, Strober BE. Laboratory monitoring requirements during mycophenolate mofetil therapy for dermatologic conditions: a single institution retrospective chart review. *J Am Acad Dermatol.* 2019. <https://doi.org/10.1016/j.jaad.2019.02.040> [Epub ahead of print].
50. Hayashi M, Kikuchi T, Takada T. Mycophenolate mofetil for the patients with interstitial lung diseases in amyopathic dermatomyositis with anti-MDA-5 antibodies. *Clin Rheumatol.* 2017;36:239-240.
51. Oddis CV, Reed AM, Aggarwal R, et al. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. *Arthritis Rheum.* 2013;65:314-324.
52. Dinh HV, McCormack C, Hall S, Prince HM. Rituximab for the treatment of the skin manifestations of dermatomyositis: a report of 3 cases. *J Am Acad Dermatol.* 2007;56:148-153.
53. de Souza FHC, Miossi R, de Moraes JCB, Bonfá E, Shinjo SK. Favorable rituximab response in patients with refractory idiopathic inflammatory myopathies. *Adv Rheumatol.* 2018;58:31.
54. So H, Wong VTL, Lao VWN, Pang HT, Yip RML. Rituximab for refractory rapidly progressive interstitial lung disease related to anti-MDA5 antibody-positive amyopathic dermatomyositis. *Clin Rheumatol.* 2018;37:1983-1989.
55. Vargas Lebrón C, Ruiz Montesino MD, Moreira Navarrete V, Toyos Sainz de Miera FJ. Treatment with rituximab in juvenile dermatomyositis: effect on calcinosis. *Reumatol Clin.* 2019. <https://doi.org/10.1016/j.reuma.2018.06.010>. [in Spanish; Epub ahead of print].
56. Aggarwal R, Loganathan P, Koontz D, Qi Z, Reed AM, Oddis CV. Cutaneous improvement in refractory adult and juvenile dermatomyositis after treatment with rituximab. *Rheumatol (Oxford).* 2017;56:247-254.
57. Argobi Y, Smith GP. Tracking changes in nailfold capillaries during dermatomyositis treatment. *J Am Acad Dermatol.* 2019;81:275-276.
58. Albers LN, Liu Y, Bo N, Swerlick RA, Feldman RJ. Developing biomarkers for predicting clinical relapse in pemphigus patients treated with rituximab. *J Am Acad Dermatol.* 2017;77:1074-1082.
59. Galimberti F, Kooistra L, Li Y, Chatterjee S, Fernandez AP. Intravenous immunoglobulin is an effective treatment for refractory cutaneous dermatomyositis. *Clin Exp Dermatol.* 2018;43:906-912.
60. Anh-Tu Hoa S, Hudson M. Critical review of the role of intravenous immunoglobulins in idiopathic inflammatory myopathies. *Semin Arthritis Rheum.* 2017;46:488-508.
61. Danieli MG, Calcabrini L, Calabrese V, Marchetti A, Logullo F, Gabrielli A. Intravenous immunoglobulin as add on treatment with mycophenolate mofetil in severe myositis. *Autoimmun Rev.* 2009;9:124-127.
62. de Inocencio J, Enríquez-Merayo E, Casado R, González-Granado LI. Subcutaneous immunoglobulin in refractory juvenile dermatomyositis. *Pediatrics.* 2016;137. <https://doi.org/10.1542/peds.2015-3537>.
63. Kotani T, Makino S, Takeuchi T, et al. Early intervention with corticosteroids and cyclosporin A and 2-hour postdose blood concentration monitoring improves the prognosis of acute/subacute interstitial pneumonia in dermatomyositis. *J Rheumatol.* 2008;35:254-259.
64. Shimojima Y, Ishii W, Matsuda M, Kishida D, Ikeda SI. Effective use of calcineurin inhibitor in combination therapy for

- interstitial lung disease in patients with dermatomyositis and polymyositis. *J Clin Rheumatol.* 2017;23:87-93.
65. Schiffenbauer A, Garg M, Castro C, et al. A randomized, double-blind, placebo-controlled trial of infliximab in refractory polymyositis and dermatomyositis. *Semin Arthritis Rheum.* 2018;47:858-864.
 66. Bunch TW, Worthington JW, Combs JJ, Ilstrup DM, Engel AG. Azathioprine with prednisone for polymyositis. A controlled, clinical trial. *Ann Intern Med.* 1980;92:365-369.
 67. Deakin CT, Campanillo-Marques R, Simou S, et al. Efficacy and safety of cyclophosphamide treatment in severe juvenile dermatomyositis shown by marginal structural modeling. *Arthritis Rheumatol.* 2018;70:785-793.
 68. Clotti A, Laffitte E, Prins C, Chizzolini C. Response of mucocutaneous lesions to rituximab in a case of melanoma differentiation antigen 5-related dermatomyositis. *Dermatology.* 2012;225:376-380.
 69. Combalia A, Giavedoni P, Tamez L, Grau-Junyent JM, Mascaró JM. Bosentan for cutaneous ulcers in anti-MDA5 dermatomyositis. *JAMA Dermatol.* 2018;154:371-373.
 70. Schanz S, Ulmer A, Fierlbeck G. Response of dystrophic calcification to intravenous immunoglobulin. *Arch Dermatol.* 2008;144:585-587.
 71. Shahani L. Refractory calcinosis in a patient with dermatomyositis: response to intravenous immune globulin. *BMJ Case Rep.* 2012;2012. <https://doi.org/10.1136/bcr-2012-006629>.
 72. Reiter N, El-Shabrawi L, Leinweber B, Berghold A, Aberer E. Calcinosis cutis: part II. Treatment options. *J Am Acad Dermatol.* 2011;65:15-22.
 73. Huber AM, Kim S, Reed AM, et al. Childhood Arthritis and Rheumatology Research Alliance consensus clinical treatment plans for juvenile dermatomyositis with persistent skin rash. *J Rheumatol.* 2017;44:110-116.
 74. Spencer CH, Rouster-Stevens K, Gewanter H, et al. Biologic therapies for refractory juvenile dermatomyositis: five years of experience of the Childhood Arthritis and Rheumatology Research Alliance in North America. *Pediatr Rheumatol Online J.* 2017;15:50.
 75. Enders FB, Bader-Meunier B, Baildam E, et al. Consensus-based recommendations for the management of juvenile dermatomyositis. *Ann Rheum Dis.* 2017;76:329-340.
 76. Papadopoulou C, Hong Y, Omoyinmi E, Brogan PA, Eleftheriou D. Janus kinase 1/2 inhibition with baricitinib in the treatment of juvenile dermatomyositis. *Brain.* 2019;142:e8.
 77. Ladislau L, Suárez-Calvet X, Toquet S, et al. JAK inhibitor improves type I interferon induced damage: proof of concept in dermatomyositis. *Brain J Neurol.* 2018;141:1609-1621.
 78. Kurtzman DJB, Wright NA, Lin J, et al. Tofacitinib citrate for refractory cutaneous dermatomyositis: an alternative treatment. *JAMA Dermatol.* 2016;152:944-945.
 79. Kato M, Ikeda K, Kageyama T, et al. Successful treatment for refractory interstitial lung disease and pneumomediastinum with multidisciplinary therapy including tofacitinib in a patient with anti-MDA5 antibody-positive dermatomyositis. *J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis.* 2019. <https://doi.org/10.1097/RHU.0000000000000984> [Epub ahead of print].
 80. Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). *N Engl J Med.* 1975;292:403-407.
 81. Lundberg IE, Tjärnlund A, Bottai M, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann Rheum Dis.* 2017;76:1955-1964.
 82. Suzuki S, Uruha A, Suzuki N, Nishino I. Integrated Diagnosis Project for Inflammatory Myopathies: an association between autoantibodies and muscle pathology. *Autoimmun Rev.* 2017;16:693-700.
 83. Tanimoto K, Nakano K, Kano S, et al. Classification criteria for polymyositis and dermatomyositis. *J Rheumatol.* 1995;22:668-674.
 84. Targoff IN, Miller FW, Medsger TA, Oddis CV. Classification criteria for the idiopathic inflammatory myopathies. *Curr Opin Rheumatol.* 1997;9:527-535.
 85. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. *Lancet.* 2003;362:971-982.
 86. Hoogendoijk JE, Amato AA, Lecky BR, et al. 119th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10-12 October 2003, Naarden, The Netherlands. *Neuromuscul Disord.* 2004;14:337-345.

Ectoparasites



Scabies

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Learning objectives

After completing this learning objective participants should be able to describe the cutaneous manifestations of scabies and complications of secondary bacterial infection; recognize novel diagnostic tools for the identification of scabies; explain scabies treatment strategies in the context of current evidence; and discuss public health strategies for the control of scabies.

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Scabies is an ectoparasitic dermatosis caused by *Sarcoptes scabiei* var. *hominis* and is a public health issue in all countries regardless of socioeconomic status. In high-income countries, delays in diagnosis can lead to institutional outbreaks; in low- and middle-income countries, poor access to health care contributes to disease undertreatment and long-term systemic sequelae. With scabies now recognized as a neglected tropical disease by the World Health Organization, increased awareness and systematic efforts are addressing gaps in diagnosis and treatment that impede scabies control. This review summarizes the available data and provides an update on scabies epidemiology, clinical features, diagnosis, management, and public health considerations. (J Am Acad Dermatol 2020;82:533-48.)

Key words: crusted scabies; homeless; impetigo; infestation; ivermectin; mass drug administration; neglected tropical disease; optical coherence tomography; permethrin; poststreptococcal glomerulonephritis; pruritus; reflectance confocal microscopy; refugee; rheumatic fever; rheumatic heart disease; *Sarcoptes scabiei*; scabies; *Staphylococcus aureus*; *Streptococcus pyogenes*.

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Abbreviations used:

APSGN:	acute poststreptococcal glomerulonephritis
DALY:	disability-adjusted life year
MDA:	mass drug administration
RCM:	reflectance confocal microscopy

EPIDEMIOLOGY**Key points**

- Scabies affects around 200 million people worldwide
- The prevalence is highest in low- and middle-income tropical countries
- Population crowding and skin-to-skin contact promotes transmission among children, homeless individuals, and displaced groups

Scabies is caused by *Sarcoptes scabiei* var. *hominis* (*S. scabiei*), an obligate microscopic parasitic mite that lives its entire 10- to 14-day life cycle in the human epidermis (Fig 1).¹ Female mites burrow into the stratum corneum, inducing a cutaneous

hypersensitivity reaction to the mite and its products. In classic scabies, prolonged skin-to-skin contact, including sexual contact, is the primary mode of transmission, and fomite-mediated transmission is uncommon.^{2,3} Transmission via fomites may be more important in profuse and crusted scabies (formerly known as Norwegian scabies), wherein mites are more numerous and survive in shedded scale.⁴

In the 2015 Global Burden of Disease Study, the global prevalence of scabies was 204 million.⁵ Disease burden was measured using the disability-adjusted life year (DALY), calculated as the sum of life years lost because of premature mortality and disability; greater DALYs represent a higher disease burden.⁵ Scabies burden was greatest in tropical regions, including east Asia, southeast Asia, south Asia, Oceania, and tropical Latin America.⁶ Although the prevalence in North America was lower than in other regions, age-standardized DALYs from scabies have increased.⁶ Scabies contributed more age-standardized DALYs than atrial fibrillation/flutter or acute lymphocytic leukemia.⁷ Notably, scabies was presumed to carry zero mortality, and thus the

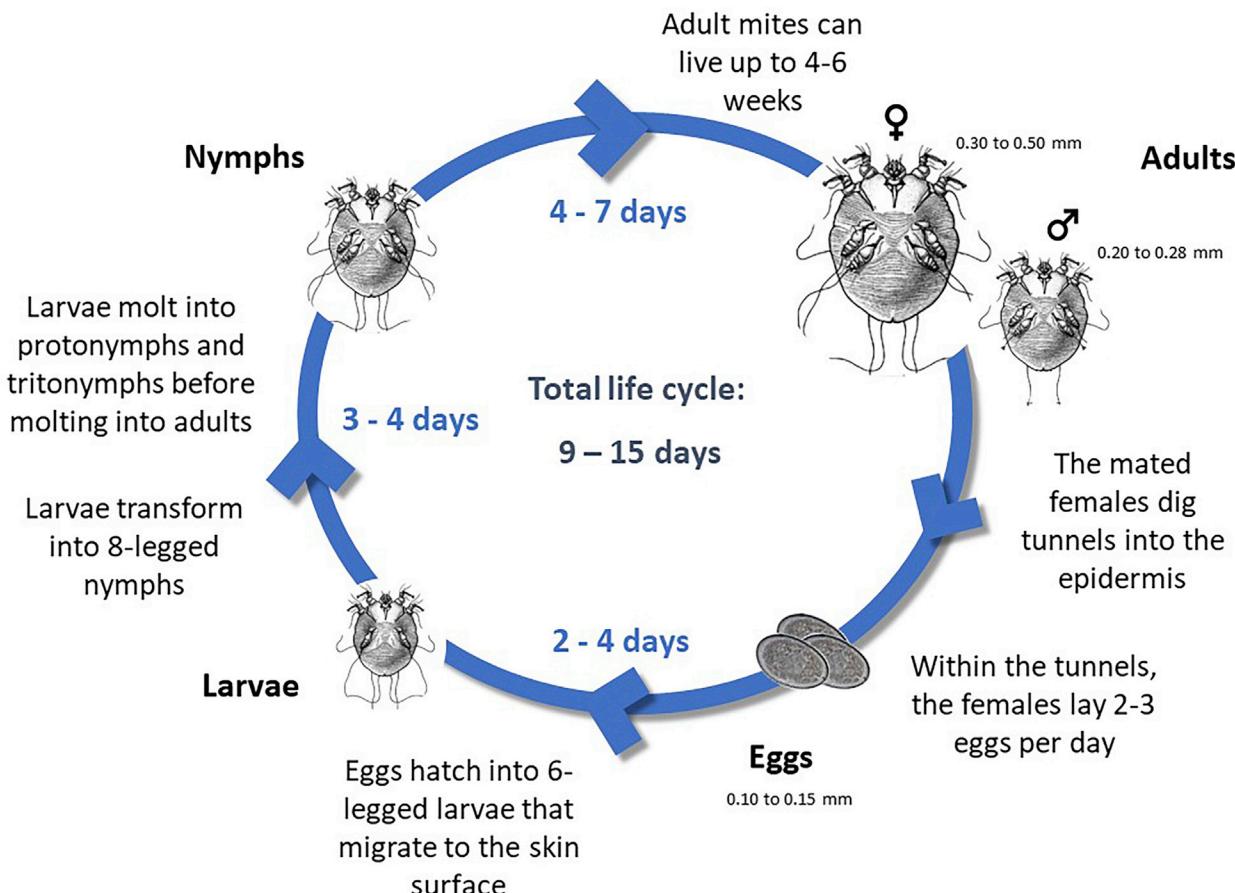


Fig 1. *Sarcoptes scabiei* life cycle. (Adapted with permission of Elsevier from Bernigaud C, Chosidow O. Scabies [in French]. Rev Prat 2018;1:63-8.)



Fig 2. Scabies. **A**, Papules and scaling on the fingers and webspaces (courtesy of Aileen Chang, MD). **B**, Erythematous papules and nodules on the penile shaft and glans penis (courtesy of Timothy Berger, MD). **C**, Acral crusted papules and scaling in an infant (courtesy of Timothy Berger, MD). **D**, Red-brown nodules on the trunk of an infant (courtesy of Ilona Frieden, MD). **E**, Hyperkeratosis on the sole and interdigital webspaces in crusted scabies (courtesy of Timothy Berger, MD). **F**, Pustules and papules with overlying honey-colored crust on the dorsal surface of the hand in impetiginized scabies (courtesy of Wendemagegn Enbiale, MD, MPH).

estimated DALYs reflect only years lived with disability.^{6,8} However, high mortality has been reported from scabies-related *Staphylococcus aureus* (*S. aureus*) bacteremia in a majority indigenous Australian population.⁹

Certain subpopulations with increased skin-to-skin contact are at higher risk of infestation. In high-income countries, outbreaks frequently occur in institutional settings, homeless populations, and groups living in crowded conditions after displacement. For example, scabies was diagnosed in 56.5% of dermatologic consultations in a majority homeless population in Paris and 58% of infectious/dermatologic consultations in migrants arriving to Italy.^{10,11} Outbreaks also occur in natural disaster victims after drought,¹² flooding,^{13,14} and earthquakes.^{15,16} In low- and middle-income countries and tropical regions, scabies disproportionately affects children.^{17,18} In the Solomon Islands, 25.7% of children 1 to 4 years of age were diagnosed with scabies.¹⁹ Overcrowding,²⁰ bed sharing,²¹ high reinfection rates,²² and disease underrecognition²³ may account for higher prevalence in children. In tropical regions, DALY burden is greatest in children 1 to 4 years of

age, gradually decreases from 5 to 24 years of age,⁶ drops in adulthood, and rises after 70 years of age.⁶

CLINICAL FEATURES

Key points

- Classic scabies presents with pruritus and multiple skin lesion morphologies involving finger webspaces, hands, the volar surfaces of the wrists, axillae, buttocks, the areola in women, and genitalia in men
- Disease patterns may differ in infants, children, elderly, and the immunocompromised
- Crusted scabies most frequently occurs in immunocompromised patients, manifesting as hyperkeratosis with or without pruritus
- Complications include secondary impetigo, cellulitis, abscesses, poststreptococcal glomerulonephritis, rheumatic fever, and sepsis

Scabies presents with multiple morphologies (Fig 2), and the differential diagnosis varies by clinical subtype (Table 1). Generalized pruritus that is worse at night is a hallmark feature and may be mediated by nonhistaminergic itch mechanisms,

Table I. Differential diagnosis of scabies

Classic scabies	Arthropod bites Folliculitis Impetigo Papular urticaria Atopic dermatitis Contact dermatitis Nummular eczema Prurigo nodularis Bullous pemphigoid (urticular stage) Dermatitis herpetiformis Lice infestation Delusional parasitosis Morgellons disease
Infantile scabies	Arthropod bites Papular urticaria Atopic dermatitis Infantile acropustulosis Langerhans cell histiocytosis
Bullous scabies	Bullous arthropod bites Bullous impetigo Bullous pemphigoid Pemphigus vulgaris Incontinentia pigmenti (inflammatory stage)
Crusted scabies	Psoriasis Pityriasis rubra pilaris Seborrheic dermatitis Atopic dermatitis Contact dermatitis Palmoplantar keratoderma Darier disease Erythrodermic mycosis fungoides/ Sézary syndrome

including tryptase, its receptor protease-activated receptor-2, and ion channels transient receptor potential cation channel subfamily V member 1 and transient receptor potential cation channel subfamily A member 1.²⁴ Pruritus can be severe, negatively impacting quality of life.²⁵⁻²⁷ However, sensitization to mite antigens occurs 4 to 6 weeks after the initial infestation, and therefore asymptomatic carriage is common during this period.²⁸ With reinfection, itching begins within days, and presentations may be more severe. Pruritus may be absent in infants,²⁹ the elderly,³⁰ patients inappropriately treated with topical corticosteroids,^{31,32} or those taking immunosuppressive/antiinflammatory agents.³³

Classic scabies

In classic scabies, lesions favor the finger web-spaces, hands, the volar surfaces of the wrists, axillae, feet, waistline, lower buttocks, inner thighs, the areola in women, and genitalia in men. With an average mite load of 5 to 15 in classic scabies,²

pathognomonic burrows are only occasionally visible as short, linear, or wavy tracks culminating with an intact or eroded vesicle/pustule containing the mite. Most burrows are found on the hands/wrists but can be seen on the elbows, genitalia, buttocks, and axillae. More commonly, nonspecific secondary lesions are seen, including excoriated papules, eczematous plaques, and impetigo. Prolonged scratching can result in lichenification and prurigo nodularis.

Atypical scabies and subpopulations

Atypical findings include scalp involvement, nodules, bullous lesions, and crusted scabies. Scalp involvement is seen in infants, children, the elderly, and immunocompromised individuals. Firm red-brown or violaceous nodules can occur on the axillae, groin, male genitalia, and trunk (in infants) and often persist for months after treatment. Bullous scabies manifests as tense or flaccid bullae in typical locations with or without pruritus.

In crusted scabies, psoriasiform and hyperkeratotic lesions are generally widespread with head/neck involvement and accentuation over acral sites. Localized crusted scabies can occur on the scalp,^{3,34-36} face,^{3,34} fingers,^{3,34} toes/toenails,^{3,34,37} soles,^{3,34,38} and genitalia.^{3,39,40} Eosinophilia⁴¹ and generalized lymphadenopathy can be seen.³⁴ Despite high mite burden—estimated to be ≤ 4700 mites per gram of shedded skin⁴—lesions are not always pruritic. Crusted scabies is associated with immobility and immunocompromised states, including iatrogenic immunosuppression (topical/systemic glucocorticoids^{35,42,43} and biologic therapy^{44,45}), T-cell lymphoma/leukemia,^{46,47} HIV infection,⁴⁸ and human T-cell lymphotropic virus-1 infection^{41,48} but can occur in the absence of these risk factors.

Several subpopulations have distinct clinical presentations. In infants and young children, lesions are more widespread but favor the palms/soles, wrists, and ankles.²⁹ Impetiginization and eczematization are common. Infants may not scratch but rather feed poorly and appear irritable. In the elderly, atypical findings are common and though the inflammatory response may be subdued, pruritus is often still present. In bed-bound individuals, lesions may involve the back.³⁴

Local complications

Scabies infestation is often complicated by *Streptococcus pyogenes* (*S pyogenes*) or *S aureus* impetigo because of scratching-induced skin trauma (Fig 3). Mite and host immune system interactions, including mite production of complement-inhibiting proteins, promote *S pyogenes* survival and *S aureus* growth.⁴⁹⁻⁵³ Impetiginized scabies is common in areas with high

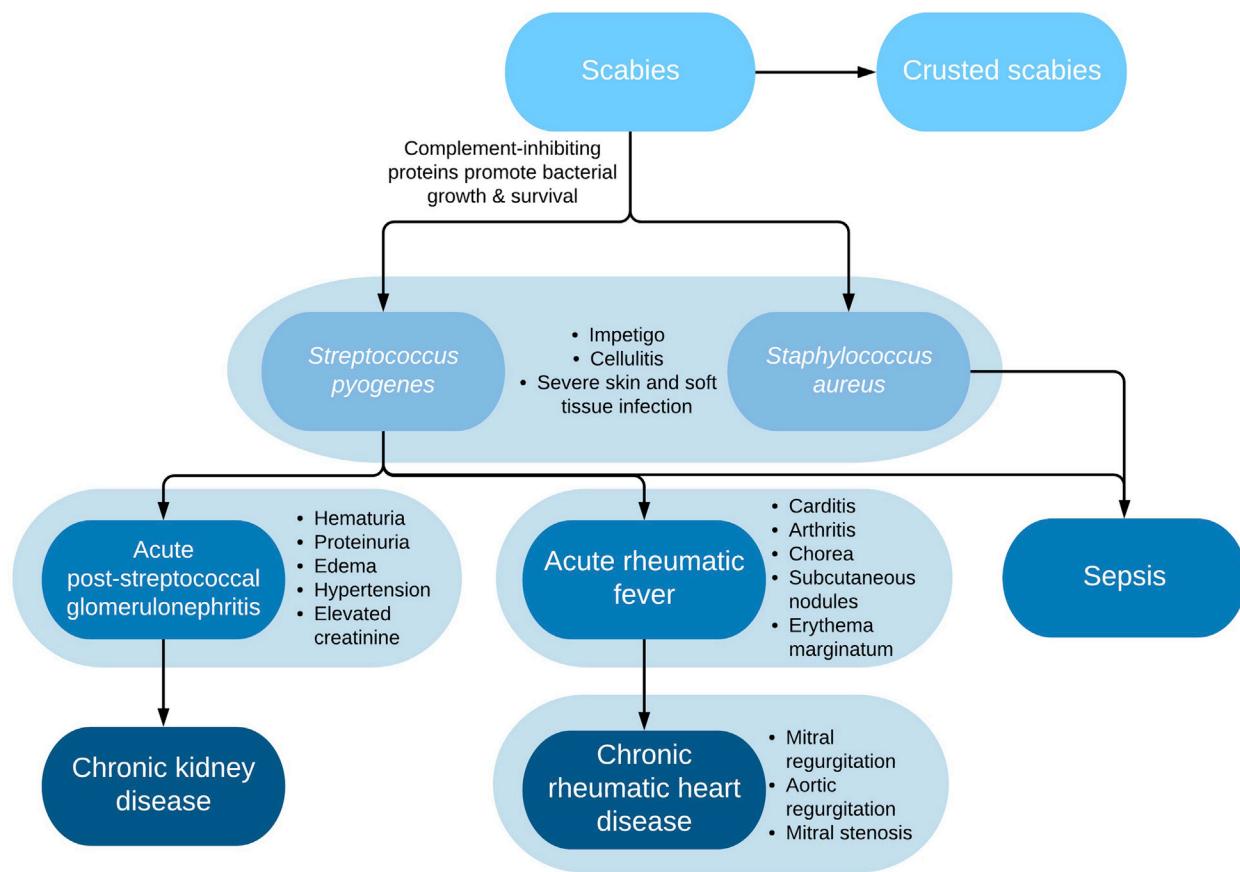


Fig 3. Systemic complications of scabies. (Adapted with permission of Elsevier from Engelman D, Kiang K, Chosidow O, et al. Toward the global control of human scabies: introducing the International Alliance for the Control of Scabies. PLoS Negl Trop Dis 2013;7:e2167.)

scabies prevalence.^{18,54-57} In Australia, Aboriginal children were 7 times more likely to have scabies and concomitant skin infections with *Spyogenes* or *Saureus* than skin infections alone.⁵⁸ In addition, scabies treatment alone decreases impetigo rates in areas with high scabies and impetigo prevalences.⁵⁹⁻⁶² Abscesses, cellulitis, and, rarely, necrotizing soft tissue infections can also occur as local complications.⁶³⁻⁶⁵

Systemic complications

Systemic complications of scabies are mainly caused by secondary bacterial infection (Fig 3). *S pyogenes* infection may lead to acute post-streptococcal glomerulonephritis (APSGN), and APSGN epidemics are linked to *S pyogenes* superinfection of scabies lesions.⁶⁶⁻⁶⁸ Although the immediate consequences of APSGN are limited, long-term effects, particularly chronic kidney disease, have substantial morbidity.⁶⁹ In the Aboriginal Australian community, high rates of end-stage renal disease are associated with scabies and secondary superinfection.⁷⁰

As with APSGN, streptococcal skin infection is likely an important driver of acute rheumatic fever and subsequent rheumatic heart disease in some settings, although this link has not been conclusively established.^{71,72} In New Zealand and Ethiopia, scabies diagnoses were associated with rheumatic fever and rheumatic heart disease development, supporting the potential role of scabies-associated impetigo in these high-morbidity conditions.^{73,74}

Secondary bacterial infections also predispose those with scabies to bacteremia and sepsis.^{9,75} Untreated crusted scabies carries a high risk of mortality from secondary sepsis.⁷⁶⁻⁷⁹

DIAGNOSIS

Key points

- Consensus diagnostic criteria can be used in various clinical settings
- Visualization of mites, eggs, or feces on microscopy of skin scrapings confirms diagnosis but has low sensitivity

Table II. 2018 International Alliance for the Control of Scabies diagnostic criteria for scabies⁸²

A: Confirmed scabies
At least one of:
A1: Mites, eggs, or feces on light microscopy of skin samples
A2: Mites, eggs, or feces visualized on individual using high-powered imaging device
A3: Mite visualized on individual using dermoscopy
B: Clinical scabies
At least one of:
B1: Scabies burrows
B2: Typical lesions affecting male genitalia
B3: Typical lesions in a typical distribution and 2 history features
C: Suspected scabies
One of:
C1: Typical lesions in a typical distribution and 1 history feature
C2: Atypical lesions or atypical distribution and 2 history features
History features
H1: Itch
H2: Close contact with an individual who has itch or typical lesions in a typical distribution

Diagnosis can be made at 1 of the 3 levels (A, B, or C). A diagnosis of clinical and suspected scabies should only be made if other differential diagnoses are considered less likely than scabies.

- Noninvasive diagnostic techniques include dermoscopy, videodermoscopy, reflectance confocal microscopy, and optical coherence tomography
- On dermoscopy, the “delta-wing jet” sign is a burrow ending in a mite

Diagnostic criteria

Scabies is commonly misdiagnosed. In a single-center retrospective study in the United States, 45% of scabies patients were previously misdiagnosed.⁸⁰ The lack of standardized diagnostic criteria poses challenges to both patient care and research.⁸¹ Recently, consensus diagnostic criteria were developed using the Delphi method (Table II) to enable standardization and comparison of findings, with validation studies ongoing.⁸²

Imaging diagnostics

Classically, diagnosis is confirmed by light microscopy with ex vivo visualization of mites, eggs, or feces from skin scrapings (Fig 4). To obtain a skin scraping sample, a drop of mineral oil is placed at the terminal end of a burrow, and the lesion and

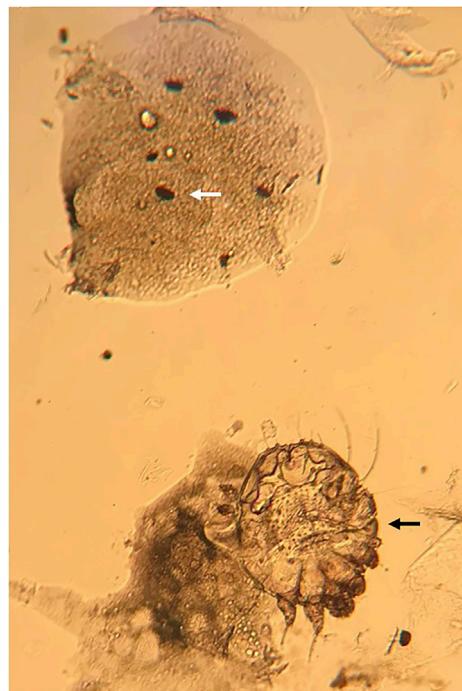


Fig 4. Mineral oil scraping showing *Sarcoptes scabiei* mite (black arrow) and feces (white arrow). (Courtesy of Kristen Corey, MD. Original magnification: ×10.)

underlying epidermis are gently scraped away with a surgical blade or sterile needle. Sensitivity can be low,⁸³ and testing is contingent on the availability of required equipment. Recently, several noninvasive *in vivo* diagnostic techniques have emerged (Fig 5).

Scabies can be rapidly diagnosed using dermoscopy. On 10× magnification, the mite head and trailing burrow can be visualized in the “delta-wing jet” sign.^{84,85} In 2 studies, the sensitivity of dermoscopy was equivalent to skin scraping (91% vs 90%, respectively) in high-resource settings and higher than skin scraping (83% vs 46%, respectively) in low-resource settings.^{83,84} Despite the ease and accuracy of dermoscopy, its use is limited by operator experience and low sensitivity in mild disease.⁸³

Videodermoscopy uses video cameras to provide up to 1000× magnification.⁸⁶ Low magnification enables burrow detection while mites, eggs, and feces are visualized on higher magnifications.⁸⁷ When dermoscopy cannot distinguish burrows from excoriations, videodermoscopy’s higher magnification is useful and contributes to its high specificity.⁸⁸

Reflectance confocal microscopy (RCM) uses cellular structure light reflectance to visualize the epidermis and papillary dermis *in vivo* at resolutions comparable to histology. Although most commonly used to detect cutaneous neoplasm, RCM also reliably detects and quantifies classic and crusted scabies.^{89–96} Comparisons between RCM and other

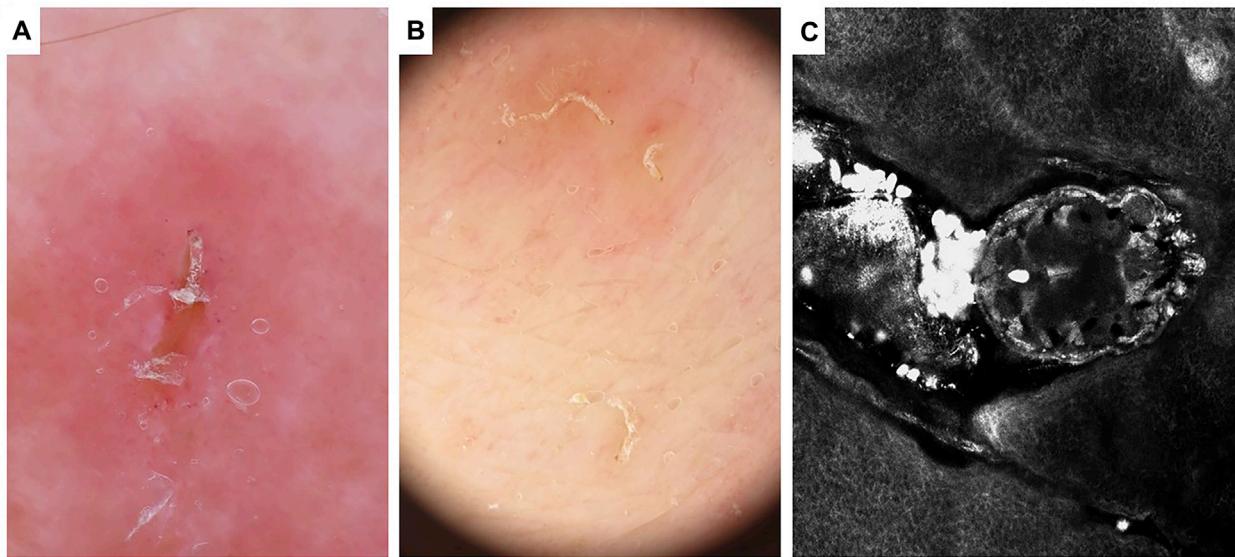


Fig 5. Noninvasive scabies diagnostic techniques. **A**, Dermoscopy showing the “delta-wing” sign composed of a burrow ending in a mite. (Reprinted with permission of Elsevier from Lallas A, Apalla Z, Lazaridou E, et al. Scabies escaping detection until dermoscopy was applied. *Dermatol Pract Concept* 2017; 7:49-50.) **B**, Videodermoscopy demonstrating burrows ending in mites. (Original magnification: $\times 20$. Reprinted with permission of John Wiley and Sons from Cinotti E, Labeille B, Cambazard F, et al. Videodermoscopy compared to reflectance confocal microscopy for the diagnosis of scabies. *J Eur Acad Dermatol Venereol* 2016;30:1573-7.) **C**, Reflectance confocal microscopy showing a mite with feces. (Reprinted with permission of Elsevier from Micali G, Lacarrubba F, Verzi A, et al. Scabies: advances in noninvasive diagnosis. *PLoS Negl Trop Dis* 2016;10:e0004691.)

diagnostic tools are sparse, but RCM accuracy is comparable to 70 \times magnification videodermoscopy.⁹⁷ RCM’s cost and time-intensiveness (approximately 10 minutes per lesion) limit widespread use, but it may have utility in research settings.⁹⁸

Optical coherence tomography uses light refraction to produce high-resolution cross-sectional images similar to ultrasonography.⁹⁹ With this technique, mites, eggs, feces, and burrow contents can be identified.¹⁰⁰ Similar to RCM, availability and cost are barriers.⁹⁸

MANAGEMENT

Key points

- **Topical permethrin and oral ivermectin are effective treatments**
- **Novel topical and systemic agents are being investigated**
- **Limited data exist on the role of environmental measures in scabies control**

Treatment

The traditional pillars of treatment are topical scabicides, most commonly 5% permethrin, and oral ivermectin (Table III). Despite the high burden of scabies globally, treatment efficacy and safety data are scarce. While a 2007 Cochrane review suggested

that 5% permethrin (1 or 2 applications) was the most effective treatment, a recent Cochrane review concluded that 5% permethrin and ivermectin were equally effective.^{101,102} Conflicting results are related to differences in study design, cure definition, and loss to follow-up.¹⁰³

Topical scabicides used globally include 5% permethrin, 10% to 25% benzyl benzoate, 2% to 10% precipitated sulfur, 10% crotamiton, 0.5% malathion, and 1% lindane. Because of its high efficacy and tolerability, 5% permethrin is considered the first-line treatment in many countries and has been approved by the U.S. Food and Drug Administration for scabies treatment in individuals >2 months of age. When permethrin is unavailable, 10% to 25% benzyl benzoate and 2% to 10% precipitated sulfur are effective alternatives. While not available in the United States or Canada, benzyl benzoate is considered an essential medicine by the World Health Organization and is widely available outside North America.¹⁰⁴ Topical 10% crotamiton and 0.5% malathion are less effective than other treatments, but well-designed studies are limited.^{101,105} Because of the risk of neurotoxicity, lindane is restricted in numerous countries and California.^{106,107} For most topical treatments, a second course after 7 to 14 days will improve efficacy.

Table III. Therapies for scabies

	Therapy	Mechanism of action	Instructions	Adverse events	Level of evidence*	Considerations
Topical	Permethrin 5% cream, approved by the FDA in 1989	Inhibits sodium channels, causing neurotoxicity, paralysis, and death	Apply for 8-14 hours, then rinse off; may repeat in 7-14 days [†]	Burning, pruritus, and erythema	IA ¹⁰²	First-line treatment in the US; not approved by the FDA for infants <2 months of age given the theoretical risk of neurotoxicity ¹⁵⁴ ; safe in pregnancy ¹⁵⁵
	Benzyl benzoate 10-25% lotion, not approved by the FDA	Inhibits respiratory spiracles causing asphyxiation	Apply for 24 hours, then rinse off; may repeat in 7-14 days [†]	Burning and eczematous eruptions	IB ¹⁵⁶	Safe in infancy ¹⁵⁷ and pregnancy ¹⁵⁵ ; dilute to 12.5% for children and 6.25% for infants to minimize irritation; widely used globally; not available in North America but is a WHO essential medicine ¹⁰⁴
	Sulfur 2-10% ointment or cream, not approved by the FDA	Keratolytic, thought to have direct scabicidal activity	Apply for 24 hours, then rinse off, repeat for 3 consecutive days; may repeat in 7-14 days [†]	Malodor and burning	IB ¹⁵⁸	Safe in infancy ¹⁵⁷ and pregnancy ¹⁵⁵ ; limited data on safety and efficacy
	Crotamiton 10% cream or lotion, approved by the FDA in 1949	Unknown	Apply for 24 hours, then rinse off, repeat for 2 consecutive days. Rinse off 48 hours after second application; may repeat in 7-14 days [†]	Pruritus and local irritation	IV ^{118,119†}	Safe in infancy ¹⁵⁷ and pregnancy ¹⁵⁵ ; least effective topical agent; resistance reported ¹¹⁵
	Malathion 0.5% lotion or aqueous liquid, not approved by the FDA	Organophosphate that inhibits acetylcholinesterase, causing paralysis and death	Apply for 24 hours; may repeat in 7-14 days [†]	Burning and local irritation	IIA ¹⁵⁹	Limited data in pediatric scabies, but contraindicated in infants <2 years of age for lice treatment ¹⁶⁰ ; safe in pregnancy ¹⁵⁵ ; classified by IARC as probably carcinogenic to humans ¹⁶¹

	Lindane 1% lotion, approved by the FDA in 1981	Central nervous system stimulant causing paralysis, seizures, and death	Apply for 8 hours, then rinse off	Seizures, aplastic anemia, eczematous eruptions	IB ¹⁶²	Contraindicated in infants, ¹⁵⁷ pregnancy/breastfeeding, ¹⁵⁵ patients with seizure history, crusted scabies, and skin conditions that increase absorption ¹⁶³ ; resistance reported ¹¹²⁻¹¹⁴ ; banned in several countries given risk of neurotoxicity ¹⁰⁶ ; classified by IARC as carcinogenic to humans ¹⁶⁴
Oral	Ivermectin, not approved by the FDA	Inhibits chloride and gamma-aminobutyric acid channels, causing neuronal hyperpolarization and death	Two doses of 200 µg/kg each, 7-14 days apart	Pruritus and headache	IA ¹⁰²	Insufficient safety data to recommend use in infants <15 kg, ¹⁰⁸ children <5 years of age, ¹⁰⁸ and pregnancy ^{109,165} ; suggested to be safe in breastfeeding of infants >7 days of age ¹⁶⁶ ; cytochrome P450 3A4 -mediated drug interactions ¹⁶⁷ ; resistance reported in crusted scabies ¹¹⁶
Environmental measures	Washing linens/clothing	Fomite removal	Wash clothes/linens in hot water, dry with high heat	None	IV ^{110,118,119}	Efficacy unknown
	Sealing linens/clothing in plastic bag	Fomite removal	Seal linens/clothing in plastic bag for 72 hours	None	IV ^{110,118,119}	Efficacy unknown

FDA, US Food and Drug Administration; IARC, International Agency for Research on Cancer; WHO, World Health Organization.

*Level IA, evidence from metaanalysis of randomized controlled trials; level IB, evidence from ≥1 randomized controlled trial; level IIA, evidence from ≥1 controlled study without randomization; level IIB, evidence from ≥1 other type of experimental study; level III, evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; level IV, evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

[†]Repeating treatment in 7 to 14 days likely improves efficacy, but the risks of unnecessary overtreatment should be considered.

[‡]Several studies have evaluated crotamiton compared with 5% permethrin^{105,168,169} and 1% lindane,¹⁶⁹ but crotamiton demonstrated inferior efficacy.

Oral ivermectin is a safe and efficacious systemic option with the benefit of simple administration. Ivermectin is not ovicidal, and therefore a second dose is required to kill newly hatched mites. Ivermectin is approved for scabies treatment in several countries but is not approved by the FDA. Although available data suggest safety and efficacy, ivermectin is not recommended for use in pregnant women or young children (<5 years of age or <15 kg) because of inadequate data.^{108,109}

Pruritus commonly persists for 1 to 4 weeks, even after effective treatment.³ This postscabetic pruritus, representing ongoing inflammation, can be managed with emollients, oral antihistamines, and low-potency topical corticosteroids.¹¹⁰ High-potency or oral corticosteroids should be avoided because of potential complications, including iatrogenic Cushing syndrome.¹¹¹ If symptoms persist despite treatment for scabies and postscabetic itch, the following should be considered: treatment-related factors (ie, incorrect treatment application, treatment nonadherence, or irritant or allergic contact dermatitis from topical medications), incorrect initial diagnosis, reinfection, or delusions of parasitosis. In rare cases, resistance to topical lindane,¹¹²⁻¹¹⁴ topical crotamiton,¹¹⁵ and oral ivermectin (in crusted scabies)¹¹⁶ can occur. With persistent pruritus and skin lesions in the absence of burrow, mite, egg, or feces identification, the diagnosis (Table I) must be reconsidered. Skin biopsy specimens obtained for histopathologic review and immunofluorescence studies can be helpful.

Crusted scabies requires repeated concomitant oral and topical treatments to decrease the high mite burden and penetrate thick scale.^{110,117-119} The Centers for Disease Control and Prevention recommend oral ivermectin in 3, 5, or 7 standard doses, topical permethrin or benzyl benzoate every 2 to 3 days for 1 to 2 weeks, and a keratolytic.¹²⁰ Isolation of the affected individual is important to prevent spread. Hospitalization may be considered to achieve isolation and optimize appropriate treatment.

For all scabies subtypes, close contacts may be asymptomatic carriers before mite sensitization. Accordingly, guidelines recommend that all close contacts, even if asymptomatic, be treated simultaneously with the index patient.^{110,118,119}

Novel systemic treatments

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.^{121,122} The FDA recently

approved moxidectin for onchocerciasis treatment in individuals >12 years of age.¹²³ Another promising oral drug class is the isoxazolines, including afoxolaner and fluralaner, which demonstrated efficacy as single-dose regimens in animal models.^{124,125} Notably, the FDA issued an alert regarding potential neurotoxicity with these agents.¹²⁶

Novel topical agents

Tea tree oil, a known antimicrobial, has demonstrated scabicidal activity.¹²⁷ Other agents with demonstrated scabicidal activity include *Tinospora cordifolia*,¹²⁸ *Ligularia virgaurea*,¹²⁹ and eugenols.¹³⁰ With increasing concern for drug resistance, permethrin synergists that evade resistance mechanisms are also under investigation.^{131,132} Efficacy and safety data for these agents are limited.

Environmental measures

Although environmental measures, including hot water/high heat linen laundering and sealing linens in a plastic bag for at least 72 hours, are recommended in many treatment guidelines, little data exist on their efficacy.^{118,119} Fomite-mediated transmission does not play a major role in classic scabies. In fact, several mass drug administration (MDA) studies in low-resource settings achieved scabies control without concomitant environmental decontamination.^{61,62,133} Therefore, in settings where linen washing above 50°C is feasible, it is reasonable to recommend doing so. However, in low-resource settings, these measures may be impractical.

PUBLIC HEALTH CONSIDERATIONS

Key points

- In the United States, outbreaks are reportable events
- Outbreaks are common in institutional settings
- In high-prevalence settings, MDA decreases the prevalence of scabies and impetigo
- Global scabies control requires multidisciplinary collaborations involving dermatologists

Reporting and surveillance

Scabies is not a national notifiable infectious disease as determined by the Centers for Disease Control and Prevention; however, outbreaks are reportable events. The Council for Outbreak Response: Healthcare-Associated Infections and Antimicrobial-Resistant Pathogens has published guidelines for scabies outbreak detection and reporting.¹³⁴

Institutional outbreaks

Solitary scabies cases can quickly become outbreaks in institutional settings, including health care facilities, residential care facilities, prisons, dormitories, and shelters. Several risk factors predispose institutionalized individuals to scabies and subsequent outbreaks. In health care and residential care facilities, index patients are more likely to be immunosuppressed through iatrogenic means or because of immunosenescence.¹³⁻¹³⁷ Crusted scabies is also associated with institutional outbreaks and was reported in 83% of index cases in 1 study.¹³⁸ Another common feature of outbreaks is delayed diagnosis of the index patient because of clinician unfamiliarity with scabies, atypical presentations caused by inappropriate treatment (eg, topical corticosteroid use), or patients' inability to complain of, or desire to hide, their symptoms.^{30,138-140}

Several strategies exist for controlling scabies outbreaks. Patient and staff information campaigns¹⁴¹ and mass treatment of affected individuals and contacts with ivermectin,¹⁴² 5% permethrin,¹⁴³ and 25% benzyl benzoate¹⁴⁴ have halted outbreaks. Public health authorities at local and state levels publish guidelines for outbreak management.¹⁴⁵

Mass drug administration

MDA is a public health strategy whereby treatment is administered to an entire population in high disease-prevalent areas, regardless of disease status. Scabies-targeted MDA has demonstrated efficacy in reducing scabies prevalence, decreasing secondary bacterial infection, and preventing systemic complications.

MDA of lindane lotion,¹⁴⁶ benzyl benzoate lotion,¹⁴⁷ permethrin cream,^{59,61,148} and oral ivermectin^{60,61,147} have decreased scabies prevalence in endemic regions. In the only controlled study published, 2051 participants in Fiji were randomized at the island-level to receive standard care (individuals diagnosed with scabies and their contacts referred for permethrin treatment), permethrin MDA, or ivermectin 200 µg/kg MDA. In the MDA groups, those diagnosed with scabies at baseline received a second dose of either permethrin or ivermectin 7 to 14 days later. Of these 3 interventions, ivermectin MDA most effectively reduced scabies prevalence (by 94%, from 32.1% to 1.9%) at 12 months.⁶¹ Similar results were demonstrated in 2 other trials of ivermectin-based MDA in the Solomon Islands.^{62,149} Along with scabies, impetigo prevalence falls with ivermectin MDA^{60,61} and permethrin MDA.⁵⁹ Similarly, long-term renal sequelae of streptococcal superinfection are suspected to decline with MDA given reduced hematuria prevalence in

children in the Solomon Islands after ivermectin MDA.⁶⁰ While MDA shows promising results in high-prevalence island settings, efficacy may be lower in areas with lower prevalence.¹⁵⁰ Highly transmissible crusted scabies cases also limit MDA effectiveness.¹⁵¹ Routine surveillance and case identification after MDA is needed to ensure sustained responses. MDA has been used for scabies control in institutional outbreaks and refugee and migrant centers/camps, but fewer data exist to guide recommendations.^{30,142,144}

Scabies as a World Health Organization neglected tropical disease

To highlight the need for global scabies control, WHO added scabies to its list of neglected tropical diseases, a group of primarily communicable diseases in tropical/subtropical regions.¹⁵² Achieving scabies control requires dedicated groups of health personnel worldwide. In 2012, a worldwide collaboration of clinicians, researchers, and public health practitioners formed the International Alliance for the Control of Scabies to improve scabies control and promote the wellbeing of those affected.¹⁵³ A multidisciplinary approach involving dermatologists is essential to achieving successful scabies control worldwide.

In conclusion, scabies remains a public health priority globally. Novel diagnostic techniques and therapeutics may improve scabies management. In the global scabies control effort, dermatologists play a key role in diagnosing and treating scabies and its highly morbid complications.

REFERENCES

1. Walton S, Holt D, Currie B, et al. Scabies: new future for a neglected disease. *Adv Parasitol.* 2004;57:309-376.
2. Mellanby K. The development of symptoms, parasitic infection and immunity in human scabies. *Parasitology.* 1944;35: 197-206.
3. Chosidow O. Clinical practices. Scabies. *N Engl J Med.* 2006; 354:1718-1727.
4. Walton S, MacBroom J, Mathews J, et al. Crusted scabies: a molecular analysis of *Sarcoptes scabiei* variety *hominis* populations from patients with repeated infestations. *Clin Infect Dis.* 1999;29:1226-1230.
5. Global Burden of Disease 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* 2016;388: 1545-1602.
6. Karimkhani C, Colombara D, Drucker A, et al. The global burden of scabies: a cross-sectional analysis from the Global Burden of Disease Study 2015. *Lancet Infect Dis.* 2017;17: 1247-1254.
7. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315

- diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* 2016;388:1603-1658.
8. Chosidow O, Fuller L. Scratching the itch: is scabies a truly neglected disease? *Lancet Infect Dis.* 2017;17:1220-1221.
 9. Lynam S, Currie BJ, Baird R. Scabies and mortality. *Lancet Infect Dis.* 2017;17:1234.
 10. Arfi C, Dehen L, Benissaia E, et al. Dermatologic consultation in a precarious situation: a prospective medical and social study at the Hôpital Saint-Louis in Paris. *Ann Dermatol Venereol.* 1999;126:682-686.
 11. Di Meco E, Di Napoli A, Amato LM, et al. Infectious and dermatological diseases among arriving migrants on the Italian coasts. *Eur J Public Health.* 2018;28:910-916.
 12. World Health Organization. Drought and disease outbreaks in Ethiopia: partner update and funding request, 2016. Available at: http://www.afro.who.int/sites/default/files/2017-05/160208-ethiopia_partner-engagement-1_jan2016_final_ap.pdf. Accessed June 8, 2018.
 13. World Health Organization. Floods in Pakistan. Pakistan Health Cluster. Available at: <http://www.who.int/hac/crises/pak/sitreps/16august2010/en/>. Accessed June 16, 2018.
 14. Dayrit J, Bintanjoyo L, Andersen L, et al. Impact of climate change on dermatological conditions related to flooding: update from the International Society of Dermatology Climate Change Committee. *Int J Dermatol.* 2018;57:901-910.
 15. Shah N, Abro MA, Khan A, et al. Disease pattern in earthquake affected areas of Pakistan: data from Kaghan valley. *J Ayub Med Coll Abbottabad.* 2010;22:81-86.
 16. Malla T, Malla KK, Singh SK, et al. Analysis of post earthquake disease pattern in a camp at Gyampesal Gorkha. *Kathmandu Univ Med J.* 2016;14:249-253.
 17. World Health Organization. *Epidemiology and management of common skin diseases in children in developing countries.* Geneva: World Health Organization; 2005. Available at: https://apps.who.int/iris/bitstream/handle/10665/69229/WHO_FCH_CAH_05.12_eng.pdf?sequence=1. Accessed June 10, 2018.
 18. Romani L, Steer A, Whitfeld M, et al. Prevalence of scabies and impetigo worldwide: a systematic review. *Lancet Infect Dis.* 2015;15:960-967.
 19. Mason D, Marks M, Sokana O, et al. The prevalence of scabies and impetigo in the Solomon Islands: a population-based survey. *PLoS Negl Trop Dis.* 2016;10:e0004803.
 20. Karim S, Anwar K, Khan M, et al. Socio-demographic characteristics of children infested with scabies in densely populated communities of residential madrashas (Islamic education institutes) in Dhaka, Bangladesh. *Public Health.* 2007;121:923-934.
 21. Sara J, Haji Y, Gebretsadik A. Scabies outbreak investigation and risk factors in East Badewacho District, Southern Ethiopia: unmatched case control study. *Dermatol Res Pract.* 2018;2018:7276938.
 22. Edison L, Beaudoin A, Goh L, et al. Scabies and bacterial superinfection among American Samoan children, 2011-2012. *PLoS One.* 2015;10:e0139336.
 23. Yeoh D, Anderson A, Cleland G, et al. Are scabies and impetigo "normalised"? A cross-sectional comparative study of hospitalised children in northern Australia assessing clinical recognition and treatment of skin infections. *PLoS Negl Trop Dis.* 2017;11:e0005726.
 24. Sanders K, Natkemper L, Rosen J, et al. Non-histaminergic itch mediators elevated in the skin of a porcine model of scabies and of human scabies patients. *J Invest Dermatol.* 2019;139:971-973.
 25. Worth C, Heukelbach J, Fengler G, et al. Impaired quality of life in adults and children with scabies from an impoverished community in Brazil. *Int J Dermatol.* 2012;51:275-282.
 26. Jin-gang A, Sheng-xiang X, Sheng-bin X, et al. Quality of life of patients with scabies. *J Eur Acad Dermatol Venereol.* 2010;24:1187-1191.
 27. Walker SL, Lebas E, De Sario V, et al. The prevalence and association with health-related quality of life of tungiasis and scabies in schoolchildren in southern Ethiopia. *PLoS Negl Trop Dis.* 2017;11:e0005808.
 28. Walton S. The immunology of susceptibility and resistance to scabies. *Parasite Immunol.* 2010;32:532-540.
 29. Boralevi F, Diallo A, Miquel J, et al. Clinical phenotype of scabies by age. *Pediatrics.* 2014;133:e910-e916.
 30. Cassell J, Middleton J, Nalabanda A, et al. Scabies outbreaks in ten care homes for elderly people: a prospective study of clinical features, epidemiology, and treatment outcomes. *Lancet Infect Dis.* 2018;18:894-902.
 31. Jaramillo-Ayerbe F, Berrio-Muñoz J. Ivermectin for crusted Norwegian scabies induced by use of topical steroids. *Arch Dermatol.* 1998;134:143-145.
 32. Gach J, Heagerty A. Crusted scabies looking like psoriasis. *Lancet.* 2000;356:650.
 33. Venning V, Millard P. Recurrent scabies with unusual clinical features in a renal transplant recipient. *Br J Dermatol.* 1992;126:204-205.
 34. Chosidow O. Scabies and pediculosis. *Lancet.* 2000;355:819-826.
 35. Yee B, Carlos C, Hata T. Crusted scabies of the scalp in a patient with systemic lupus erythematosus. *Dermatol Online J.* 2014;20.
 36. Lewis E, Connolly S, Crutchfield C, et al. Localized crusted scabies of the scalp and feet. *Cutis.* 1998;61:87-88.
 37. Arico M, Noto G, La Rocca E, et al. Localized crusted scabies in the acquired immunodeficiency syndrome. *Clin Exp Dermatol.* 1992;17:339-341.
 38. Bitman L, Rabinowitz A. Hyperkeratotic plantar plaques in an HIV-positive patient. Crusted scabies, localized to the soles. *Arch Dermatol.* 1998;134, 1019:1022-1023.
 39. Bongiorno M, Ferro G, Aricò M. Norwegian (crusted) scabies of glans penis in an immunocompetent patient. *Br J Dermatol.* 2009;161:195-197.
 40. Perna A, Bell K, Rosen T. Localised genital Norwegian scabies in an AIDS patient. *Sex Transm Dis.* 2004;80:72-73.
 41. Roberts L, Huffam S, Walton S, et al. Crusted scabies: clinical and immunological findings in seventy-eight patients and a review of the literature. *J Infect.* 2005;50:375-381.
 42. Bilan P, Colin-Gorski A-M, Chapelon E, et al. Crusted scabies induced by topical corticosteroids: a case report. *Arch Pediatr.* 2015;22:1292-1294.
 43. Marlène V, Roul S, Labrèze C, et al. Crusted (Norwegian) scabies induced by use of topical corticosteroids and treated successfully with ivermectin. *J Pediatr.* 1999;135:122-124.
 44. Saillard C, Darrieux L, Safa G. Crusted scabies complicates etanercept therapy in a patient with severe psoriasis. *J Am Acad Dermatol.* 2013;68:e138-e139.
 45. Pipitone MA, Adams B, Sheth A, et al. Crusted scabies in a patient being treated with infliximab for juvenile rheumatoid arthritis. *J Am Acad Dermatol.* 2005;52:719-720.
 46. Yonekura K, Kanekura T, Kanzaki T, et al. Crusted scabies in an adult T-cell leukemia/lymphoma patient successfully treated with oral ivermectin. *J Dermatol.* 2006;33:139-141.
 47. Takeshita T, Takeshita H. Crusted (Norwegian) scabies in a patient with smoldering adult T-cell leukemia. *J Dermatol.* 2000;27:677-679.

48. Brites C, Weyll M, Pedroso C, et al. Severe and Norwegian scabies are strongly associated with retroviral (HIV-1/HTLV-1) infection in Bahia, Brazil. *AIDS*. 2002;16:1292-1293.
49. Swe P, Reynolds S, Fischer K. Parasitic scabies mites and associated bacteria joining forces against host complement defence. *Parasite Immunol*. 2014;36:585-593.
50. Reynolds S, Pike R, Mika A, et al. Scabies mite inactive serine proteases are potent inhibitors of the human complement lectin pathway. *PLoS Negl Trop Dis*. 2014;8:e2872.
51. Swe P, Fischer K. A scabies mite serpin interferes with complement-mediated neutrophil functions and promotes staphylococcal growth. *PLoS Negl Trop Dis*. 2014;8:e2928.
52. Swe P, Zakrazewski M, Kelly A, et al. Scabies mites alter the skin microbiome and promote growth of opportunistic pathogens in a porcine model. *PLoS Negl Trop Dis*. 2014;8:e2897.
53. Swe PM, Christian LD, Lu HC, et al. Complement inhibition by *Sarcoptes scabiei* protects *Streptococcus pyogenes* - an in vitro study to unravel the molecular mechanisms behind the poorly understood predilection of *S. pyogenes* to infect mite-induced skin lesions. *PLoS Negl Trop Dis*. 2017;11:e0005437.
54. Steer AC, Jenney AWJ, Kado J, et al. High burden of impetigo and scabies in a tropical country. *PLoS Negl Trop Dis*. 2009;3:e467.
55. Bowen AC, Mahé A, Hay RJ, et al. The global epidemiology of impetigo: a systematic review of the population prevalence of impetigo and pyoderma. *PLoS One*. 2015;10:e0136789.
56. Yeoh DK, Bowen AC, Carapetis JR. Impetigo and scabies – disease burden and modern treatment strategies. *J Infect*. 2016;72(suppl):S61-S67.
57. Romani L, Whitfeld MJ, Koroivueta J, et al. The epidemiology of scabies and impetigo in relation to demographic and residential characteristics: baseline findings from the skin health intervention Fiji Trial. *Am J Trop Med Hyg*. 2017;97:845-850.
58. Kearns T, Clucas D, Connors C, et al. Clinic attendances during the first 12 months of life for aboriginal children in five remote communities of Northern Australia. *PLoS One*. 2013;8:e58231.
59. Taplin D, Meinking T, Porcelain S, et al. Community control of scabies: a model based on use of permethrin cream. *Lancet*. 1991;337:1016-1018.
60. Lawrence G, Leafasia J, Sheridan J, et al. Control of scabies, skin sores and haematuria in children in the Solomon Islands: another role for ivermectin. *Bull World Heal Organ*. 2005;83:34-42.
61. Romani L, Whitfeld M, Koroivueta J, et al. Mass drug administration for scabies control in a population with endemic disease. *N Engl J Med*. 2015;373:2305-2313.
62. Marks M, Toloka H, Baker C, et al. Randomised trial of community treatment with azithromycin and ivermectin mass drug administration for control of scabies and impetigo. *Clin Infect Dis*. 2018;68:927-933.
63. Krüger R, Hanitsch L, Leistner R, et al. Scabies, periorbital cellulitis and recurrent skin abscesses due to Panton-Valentine Leukocidin-positive *Staphylococcus aureus* mimic hyper IgE syndrome in an infant. *Pediatr Infect Dis J*. 2017;36:e347-e348.
64. Jaton L, Pillonel T, Jaton K, et al. Common skin infection due to Panton–Valentine leucocidin-producing *Staphylococcus aureus* strains in asylum seekers from Eritrea: a genome-based investigation of a suspected outbreak. *Clin Microbiol Infect*. 2016;22:739.e5-739.e8.
65. Krieg A, Röhrborn A, Schulte Am Esch J, et al. Necrotizing fasciitis: microbiological characteristics and predictors of postoperative outcome. *Eur J Med Res*. 2009;14:30-36.
66. Svartman M, Finklea J, Potter E, et al. Epidemic scabies and acute glomerulonephritis in Trinidad. *Lancet*. 1972;1:249-251.
67. Hersch C. Acute glomerulonephritis due to skin disease, with special reference to scabies. *S Afr Med J*. 1967;41:29-34.
68. Streeton C, Hanna J, Messer R, et al. An epidemic of acute post-streptococcal glomerulonephritis among Aboriginal children. *J Paediatr Child Health*. 1995;31:245-248.
69. Hoy W, White A, Dowling A, et al. Post-streptococcal glomerulonephritis is a strong risk factor for chronic kidney disease in later life. *Kidney Int*. 2012;81:1026-1032.
70. Hoy W, Mathews J, McCreddie D, et al. The multidimensional nature of renal disease: rates and associations of albuminuria in an Australian Aboriginal Community. *Kidney Int*. 1998;54:1296-1304.
71. McDonald M, Currie BJ, Carapetis JR. Acute rheumatic fever: a chink in the chain that links the heart to the throat? *Lancet Infect Dis*. 2004;4:240-245.
72. Parks T, Smeesters PR, Steer AC. Streptococcal skin infection and rheumatic heart disease. *Curr Opin Infect Dis*. 2012;25:145-153.
73. Gemechu T, Mahmoud H, Parry EH, et al. Community-based prevalence study of rheumatic heart disease in rural Ethiopia. *Eur J Prev Cardiol*. 2017;24:717-723.
74. Thornley S, Marshall R, Jarrett P, et al. Scabies is strongly associated with acute rheumatic fever in a cohort study of Auckland children. *J Paediatr Child Health*. 2018;54:625-632.
75. Gear R, Carter J, Carapetis J, et al. Changes in the clinical and epidemiological features of group A streptococcal bacteraemia in Australia's Northern Territory. *Trop Med Int Health*. 2015;20:40-47.
76. Glover A, Young L, Goltz R. Norwegian scabies in acquired immunodeficiency syndrome: report of a case resulting in death from associated sepsis. *J Am Acad Dermatol*. 1987;16(2 pt 1):396-399.
77. Skinner S, DeVillez R. Sepsis associated with Norwegian scabies in patients with acquired immunodeficiency syndrome. *Cutis*. 1992;50:213-216.
78. Lin S, Farber J, Lado L. A case report of crusted scabies with methicillin-resistant *Staphylococcus aureus* bacteremia. *J Am Geriatr Soc*. 2009;57:1713-1714.
79. Lima F, Cerqueira A, Guimaraes M, et al. Crusted scabies due to indiscriminate use of glucocorticoid therapy in infant. *An Bras Dermatol*. 2017;92:383-385.
80. Anderson K, Strowd L. Epidemiology, diagnosis, and treatment of scabies in a dermatology office. *J Am Board Fam Med*. 2017;30:78-84.
81. Thompson M, Engelman D, Gholam K, et al. Systematic review of the diagnosis of scabies in therapeutic trials. *Clin Exp Dermatol*. 2017;42:481-487.
82. Engelman D, Fuller L, Steer A, et al. Consensus criteria for the diagnosis of scabies: a Delphi study of international experts. *PLoS Negl Trop Dis*. 2018;12:e0006549.
83. Walter B, Heukelbach J, Fengler G, et al. Comparison of dermoscopy, skin scraping, and the adhesive tape test for the diagnosis of scabies in a resource-poor setting. *Arch Dermatol*. 2011;147:468-473.
84. Dupuy A, Dehen L, Bourrat E, et al. Accuracy of standard dermoscopy for diagnosing scabies. *J Am Acad Dermatol*. 2007;56:53-62.
85. Cinotti E, Perrot J, Labeille B, et al. Diagnosis of scabies by high-magnification dermoscopy: the “delta-wing jet” appearance of *Sarcoptes scabiei*. *Ann Dermatol Venereol*. 2013;140:722-723.

86. Micali G, Lacarrubba F. Possible applications of videodermatoscopy beyond pigmented lesions. *Int J Dermatol.* 2003;42:430-433.
87. Lacarrubba F, Musumeci M, Caltabiano R, et al. High-magnification videodermatoscopy: a new noninvasive diagnostic tool for scabies in children. *Pediatr Dermatol.* 2001;18:439-441.
88. Micali G, Lacarrubba F, Lo Guzzo G. Scraping versus videodermatoscopy for the diagnosis of scabies: a comparative study. *Acta Derm Venereol.* 1999;79:396.
89. Longo C, Bassoli S, Monari P, et al. Reflectance-mode confocal microscopy for the *in vivo* detection of *Sarcoptes scabiei*. *Arch Dermatol.* 2005;141:1336.
90. Levi A, Mumcuoglu K, Ingber A, et al. Assessment of *Sarcoptes scabiei* viability *in vivo* by reflectance confocal microscopy. *Lasers Med Sci.* 2011;26:291-292.
91. Turan E, Erdemir A, Gurel M, et al. The detection of *Sarcoptes scabiei* in human skin by *in vivo* confocal microscopy. *Eur J Dermatol.* 2011;21:1004-1005.
92. Lacarrubba F, Verzi A, Micali G. Detailed analysis of *in vivo* reflectance confocal microscopy for *Sarcoptes scabiei hominis*. *Am J Med Sci.* 2015;350:414.
93. Levi A, Mumcuoglu K, Ingber A, et al. Detection of living *Sarcoptes scabiei* larvae by reflectance mode confocal microscopy in the skin of a patient with crusted scabies. *J Biomed Opt.* 2012;17:060503.
94. Gurel M, Turgut Erdemir A, Tekin B. A case report of real-time *in vivo* demonstration of *Sarcoptes scabiei*. *Turkiye Parazitol Derg.* 2017;41:229-232.
95. Cinotti E, Perrot J, Labeille B, et al. Reflectance confocal microscopy for quantification of *Sarcoptes scabiei* in Norwegian scabies. *J Eur Acad Dermatol Venereol.* 2013;27:e176-e178.
96. Uysal P, Gurel M, Erdemir A. Crusted scabies diagnosed by reflectance confocal microscopy. *Indian J Dermatol Venereol Leprol.* 2015;81:620-622.
97. Cinotti E, Labeille B, Cambazard F, et al. Videodermoscopy compared to reflectance confocal microscopy for the diagnosis of scabies. *J Eur Acad Dermatol Venereol.* 2016;30:1573-1577.
98. Micali G, Lacarrubba F, Verzi A, et al. Scabies: advances in noninvasive diagnosis. *PLoS Negl Trop Dis.* 2016;10: e0004691.
99. Olsen J, Themstrup L, Jemec G. Optical coherence tomography in dermatology. *G Ital Dermatol Venereol.* 2015;150:603-615.
100. Banzhaf C, Themstrup L, Ring H, et al. In vivo imaging of *Sarcoptes scabiei* infestation using optical coherence tomography. *Case Rep Dermatol.* 2013;5:156-162.
101. Strong M, Johnstone P. Interventions for treating scabies. *Cochrane Database Syst Rev.* 2007;(18):CD000320.
102. Rosomeck S, Nast A, Dressler C. Ivermectin and permethrin for treating scabies. *Cochrane Database Syst Rev.* 2018;(2): CD012994.
103. Le Cleach L, Chosidow O. Commentary on 'Interventions for treating scabies'. *Evidence-Based Child Health.* 2011;6:1865-1866.
104. World Health Organization. 20th edition WHO model list of essential medicines. Available at: <https://apps.who.int/iris/bitstream/handle/10665/273826/EML-20-eng.pdf?ua=1>. Accessed January 2, 2019.
105. Taplin D, Meinking T, Chen J, et al. Comparison of crotamiton 10% cream (Eurax) and permethrin 5% cream (Elimite) for the treatment of scabies in children. *Pediatr Dermatol.* 1990;7:67-73.
106. Commission for Environmental Cooperation. Northern American Regional Action Plan (NARAP) on lindane and other hexachlorocyclohexane (HCH) isomers. Available at: <http://www3.cec.org/islandora/en/item/11602-north-american-regional-action-plan-narap-lindane-and-other-en.pdf>. Accessed January 2, 2019.
107. Humphreys EH, Janssen S, Heil A, et al. Outcomes of the California ban on pharmaceutical lindane: clinical and ecologic impacts. *Environ Health Perspect.* 2008;116:297-302.
108. Wilkins AL, Steer AC, Cranswick N, et al. Question 1: is it safe to use ivermectin in children less than five years of age and weighing less than 15 kg? *Arch Dis Child.* 2018;103:514-519.
109. Chacour C, Hammann F, Rabinovich N. Ivermectin to reduce malaria transmission I. Pharmacokinetic and pharmacodynamic considerations regarding efficacy and safety. *Malar J.* 2017;16:161.
110. Salavastru C, Chosidow O, Boffa M, et al. European guideline for the management of scabies. *J Eur Acad Dermatol Venereol.* 2017;31:1248-1253.
111. Estrada-Chávez G, Estrada R, Engelman D, et al. Cushing syndrome due to inappropriate corticosteroid topical treatment of undiagnosed scabies. *Trop Med Infect Dis.* 2018;3:E82.
112. Purvis RS, Tyring SK. An outbreak of lindane-resistant scabies treated successfully with permethrin 5% cream. *J Am Acad Dermatol.* 1991;25(6 pt 1):1015-1016.
113. Roth W. Scabies resistant to lindane 1% lotion and crotamiton 10% cream. *J Am Acad Dermatol.* 1991;24:502-503.
114. van den Hoek J, van de Weerd J, Baayen T, et al. A persistent problem with scabies in and outside a nursing home in Amsterdam: indications for resistance to lindane and ivermectin. *Euro Surveill.* 2008;27:48.
115. Coskey R. Scabies - resistance to treatment with crotamiton. *Arch Dermatol.* 1979;115:109.
116. Currie B, Harumal P, McKinnon M, et al. First documentation of *in vivo* and *in vitro* ivermectin resistance in *Sarcoptes scabiei*. *Clin Infect Dis.* 2004;39:e8-e12.
117. Davis J, McGloughlin S, Tong S, et al. A novel clinical grading scale to guide the management of crusted scabies. *PLoS Negl Trop Dis.* 2013;7:e2387.
118. Sunderkötter C, Feldmeier H, Fölster-Holst R, et al. S1 guidelines on the diagnosis and treatment of scabies - short version. *J Dtsch Dermatol Ges.* 2016;14:1155-1167.
119. Executive Committee of Guideline for the Diagnosis and Treatment of Scabies. Guideline for the diagnosis and treatment of scabies in Japan (third edition): Executive Committee of Guideline for the Diagnosis and Treatment of Scabies. *J Dermatol.* 2017;44:991-1014.
120. Centers for Disease Control and Prevention. Medications. Available at: https://www.cdc.gov/parasites/scabies/health_professionals/meds.html. Accessed January 16, 2019.
121. Cotreau M, Warren S, Ryan J, et al. The antiparasitic moxidectin: safety, tolerability, and pharmacokinetics in humans. *J Clin Pharmacol.* 2003;43:1108-1115.
122. Bernigaud C, Fang F, Fischer K, et al. 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. *PLoS Negl Trop Dis.* 2016;10: e0005030.
123. US Food and Drug Administration. Moxidectin [package insert]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210867lbl.pdf. Accessed January 16, 2019.
124. Bernigaud C, Fang F, Fischer K, et al. Efficacy and pharmacokinetics evaluation of a single oral dose of afoxolaner against *Sarcoptes scabiei* in the porcine scabies model for

- human infestation. [e-pub ahead of print]. *Antimicrob Agents Chemother*; 2019. <https://doi.org/10.1128/AAC.02334-17>. Accessed December 30, 2018.
125. Taenzler J, Liebenberg J, Roepke R, et al. Efficacy of fluralaner administered either orally or topically for the treatment of naturally acquired *Sarcoptes scabiei* var. *canis* infestation in dogs. *Parasit Vectors*. 2016;9:392.
 126. US Food and Drug Administration. Fact sheet for pet owners and veterinarians about potential adverse events associated with isoxazoline flea and tick products. Available at: <https://www.fda.gov/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm620940.htm>. Accessed December 30, 2018.
 127. Carson C, Hammer K, Riley T. *Melaleuca alternifolia* (tea tree) oil: a review of antimicrobial and other medicinal properties. *Clin Microbiol Rev*. 2006;19:50-62.
 128. Castillo A, Osi M, Ramos J, et al. Efficacy and safety of *Tinospora cordifolia* lotion in *Sarcoptes scabiei* var *hominis*-infected pediatric patients: a single blind, randomized controlled trial. *J Pharmacol Pharmacother*. 2013;4:39-46.
 129. Luo B, Liao F, Hu Y, et al. Acaricidal activity of extracts from *Ligularia virgaurea* against the sarcoptes scabiei mite in vitro. *Exp Ther Med*. 2015;10:247-250.
 130. Pasay C, Mounsey K, Stevenson G, et al. Acaricidal activity of eugenol based compounds against scabies mites. *PLoS One*. 2010;5:e12079.
 131. Pasay C, Arlian L, Morgan M, et al. The effect of insecticide synergists on the response of scabies mites to pyrethroid acaricides. *PLoS Negl Trop Dis*. 2009;3:e354.
 132. Biele M, Campori G, Colombo R, et al. 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). *J Eur Acad Dermatol Venereol*. 2006; 20:717-720.
 133. Romani L, Marks M, Sokana O, et al. Efficacy of mass drug administration with ivermectin for control of scabies and impetigo, with coadministration of azithromycin: a single-arm community intervention trial. *Lancet Infect Dis*. 2019;19: 510-518.
 134. 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/>. Accessed June 16, 2018.
 135. Belvisi V, Orsi GB, Del Borgo C, et al. Large nosocomial outbreak associated with a Norwegian scabies index case undergoing TNF-alpha inhibitor treatment: management and control. *Infect Control Hosp Epidemiol*. 2015;36:1358-1360.
 136. Corbett E, Crossley I, Holton J, et al. Crusted ("Norwegian") scabies in a specialist HIV unit: successful use of ivermectin and failure to prevent nosocomial transmission. *Genitourin Med*. 1996;72:115-117.
 137. Andersen BM, Haugen H, Rasch M, et al. Outbreak of scabies in Norwegian nursing homes and home care patients: control and prevention. *J Hosp Infect*. 2000;45:160-164.
 138. Mounsey KE, Murray HC, King M, et al. Retrospective analysis of institutional scabies outbreaks from 1984 to 2013: lessons learned and moving forward. *Epidemiol Infect*. 2016;144:2462-2471.
 139. Hewitt KA, Nalabanda A, Cassell JA. Scabies outbreaks in residential care homes: factors associated with late recognition, burden and impact. A mixed methods study in England. *Epidemiol Infect*. 2015;143:1542-1551.
 140. Marotta M, Toni F, Dallocchio L, et al. Management of a family outbreak of scabies with high risk of spread to other community and hospital facilities. *Am J Infect Control*. 2018; 46:808-813.
 141. Capobussi M, Sabatino G, Donadini A, et al. Control of scabies outbreaks in an Italian hospital: an information-centered management strategy. *Am J Infect Control*. 2014;42:316-320.
 142. Lepard B, Naburi A. The use of ivermectin in controlling an outbreak of scabies in a prison. *Br J Dermatol*. 2000;143:520-523.
 143. Stoevesandt J, Carlé L, Leverkus M, et al. Control of large institutional scabies outbreaks. *J Dtsch Dermatol Ges*. 2012; 10:637-647.
 144. Agrawal S, Puthia A, Kotwal A, et al. Mass scabies management in an orphanage of rural community: an experience. *Med J Armed Forces India*. 2012;68:403-406.
 145. Centers for Disease Control and Prevention. Institutional settings. Available at: https://www.cdc.gov/parasites/scabies/health_professionals/institutions.html. Accessed February 3, 2019.
 146. Taplin D, Arrue C, Walker J, et al. Eradication of scabies with a single treatment schedule. *J Am Acad Dermatol*. 1983;9:546-550.
 147. Haar K, Romani L, Filimone R, et al. Scabies community prevalence and mass drug administration in two Fijian village. *Int J Dermatol*. 2014;53:739-745.
 148. Carapetis J, Connors C, Yarmirr D, et al. Success of a scabies control program in an Australian Aboriginal community. *Pediatr Infect Dis J*. 1997;16:494-499.
 149. Romani L, Marks M, Sokana O, et al. Feasibility and safety of mass drug coadministration with azithromycin and ivermectin for the control of neglected tropical diseases: a single-arm intervention trial. *Lancet Glob Health*. 2018;6:e1132-e1138.
 150. Engelman D, Steer A. Control strategies for scabies. *Trop Med Infect Dis*. 2018;3:98.
 151. Kearns TM, Speare R, Cheng AC, et al. Impact of an ivermectin mass drug administration on scabies prevalence in a remote Australian aboriginal community. *PLoS Negl Trop Dis*. 2015;9: e0004151.
 152. World Health Organization. Neglected tropical diseases. Available at: http://www.who.int/neglected_diseases/diseases/en/. Accessed June 10, 2018.
 153. Engelman D, Kiang K, Chosidow O, et al. Toward the global control of human scabies: introducing the International Alliance for the Control of Scabies. *PLoS Negl Trop Dis*. 2013;7:e2167.
 154. Permethrin cream 5% approval. Baltimore, MD: Alpharma. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/anda/98/074806ap.pdf. Accessed January 16, 2019.
 155. Schaefer C, Peters PWJ, Miller RK. *Drugs during pregnancy and lactation: treatment options and risk assessment*. 3rd ed. Oxford, United Kingdom: Elsevier Science & Technology; 2015.
 156. Ly F, Caumes E, Ndaw C, et al. Ivermectin versus benzyl benzoate applied once or twice to treat human scabies in Dakar, Senegal: a randomized controlled trial. *Bull World Health Organ*. 2009;87:424-430.
 157. Long SS, Prober CG, Fischer M. *Principles and practice of pediatric infectious disease*. 5th ed. New York: Elsevier; 2017.
 158. Singalavania S, Limpongsanurak W, Soponsakunkul S. 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. *J Med Assoc Thai*. 2003; 86(suppl 3):S531-S536.
 159. Burgess I, Robinson R, Robinson J, et al. Aqueous malathion 0.5% as a scabicide: clinical trial. *Br Med J (Clin Res Ed)*. 1986; 292:1172.

160. Ovide (malathion) lotion 0.5% [product insert]. Hawthorne, NY: Taro Pharmaceuticals. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/018613s017lbl.pdf. Accessed January 16, 2019.
161. Guyton KZ, Loomis D, Grosse Y, et al. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. *Lancet Oncol*. 2015;16:490-491.
162. Chouela E, Abeldaño A, Pellerano G, et al. Equivalent therapeutic efficacy and safety of ivermectin and lindane in the treatment of human scabies. *Arch Dermatol*. 1999;135:651-655.
163. Lindane lotion USP, 1% [product insert]. DeKalb, MS: Versa Pharm. Available at: <https://tapermd.com/bbw/Lindanae.pdf>. Accessed January 16, 2019.
164. Loomis D, Guyton K, Grosse Y, et al. Carcinogenicity of lindane, DDT, and 2,4-dichlorophenoxyacetic acid. *Lancet Oncol*. 2015;16:891-892.
165. Stromectol (ivermectin) [product insert]. Whitehouse Station, NJ: Merck & Co. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050742s026lbl.pdf. Accessed January 16, 2019.
166. Goa KL, McTavish D, Clissold SP. Ivermectin: a review of its antifilarial activity, pharmacokinetic properties and clinical efficacy in onchocerciasis. *Drugs*. 1991;42: 640-658.
167. Pai M, Kiser J, Gubbins P, et al. *Drug interactions in infectious diseases: antimicrobial drug interactions*. 4th ed. Cham, Switzerland: Humana Press; 2018.
168. Pourhasan A, Goldust M, Rezaee E. Treatment of scabies, permethrin 5% cream vs. crotamiton 10% cream. *Ann Parasitol*. 2013;59:143-147.
169. Amer M, El-Garib I. Permethrin versus crotamiton and lindane in the treatment of scabies. *Int J Dermatol*. 1992;31:357-358.



Ectoparasites

Pediculosis and tungiasis

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Learning objectives

After completing this learning objective participants should be able to discuss the clinical features and risk factors for body louse infestation, including rising homelessness in US coastal cities; describe the emerging evidence that head lice may act as a vector for severe infectious diseases; review geographic distribution, clinical signs, and risk factors for tungiasis; and identify promising new treatments for tungiasis.

Disclosures

Editors

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Authors

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Pediculosis is an infestation of lice on the body, head, or pubic region that occurs worldwide. Lice are ectoparasites of the order Phthiraptera that feed on the blood of infested hosts. Their morphotype dictates their clinical features. Body lice may transmit bacterial pathogens that cause trench fever, relapsing fever, and epidemic typhus, which are potentially life-threatening diseases that remain relevant in contemporary times. Recent data from some settings suggest that head lice may harbor pathogens. The epidemiology, clinical manifestations, and management of body, head, and pubic louse infestation are reviewed. New therapies for head lice and screening considerations for pubic lice are discussed. Tungiasis is an ectoparasitic disease caused by skin penetration by the female *Tunga penetrans* or, less commonly, *Tunga trimamillata* flea. It is endemic in Latin America, the Caribbean and sub-Saharan Africa and seen in travelers returning from these regions. Risk factors for acquiring tungiasis, associated morbidity, and potential strategies for prevention and treatment are discussed. (J Am Acad Dermatol 2020;82:551-69.)

Key words: body lice; ectoparasite; epidemic typhus; flea; head lice; homeless; homelessness; infestation; lice; pediculosis; *Pediculus capitis*; *Pediculus humanus*; *Phthirus pubis*; poverty; pubic lice; refugee; relapsing fever; returning traveler; trench fever; *Tunga penetrans*; *Tunga trimamillata*; tungiasis.

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HUMAN BODY LOUSE (*PEDICULUS HUMANUS HUMANUS*)

Key points

- Body lice infestation is associated with poor hygiene or neglect
- Given a homelessness epidemic, the diagnosis and management of body lice are essential dermatology skills
- Body lice are vectors for potentially life-threatening pathogens

Lice are obligate parasites, feeding exclusively on the blood of infested hosts.¹ Among thousands of lice species, only *Pediculus humanus* (*P. humanus*) and *Phthirus pubis* (pubic lice) require humans as hosts. *P. humanus* includes 2 morphotypes: *P. humanus corporis* (body) and *P. humanus capititis* (head) lice.²

Body lice are ovoid-shaped and measure 2.3 to 3.6 mm (Fig 1, A).³ They live on clothing and attach to nearby skin for blood meals. Females lay eggs ("nits") on clothing seams (Fig 1, B). In favorable environments, eggs hatch into nymphs after 6 to 10 days, which mature into adults that live 1 to 3 months.² Detached from hosts, lice die within 3 to 5 days.² Their ideal survival conditions are 29°C to 32°C and 70% to 90% humidity; they cannot survive above 50°C or below 40% humidity.⁴

Epidemiology

Lice infestations are not reportable diseases in most countries, limiting high-quality epidemiologic data collection.⁵ Known risk factors include close contact with infested persons, infrequent showering, an inability to wash and heat-dry clothing, and cold weather, which decreases the frequency of showering and changing clothes. These are especially prevalent among homeless persons,^{4,6,7} making body lice infestation more common in this population.⁷⁻¹⁰ In urban settings of high-income countries, ≤30% of homeless persons are infested with body lice.⁸ Unsheltered persons are more frequently affected.^{8,9} Additional risk factors include substance abuse, not showering, and previous pubic lice infestation.^{9,10} Untreated mental illness, which is more prevalent among homeless people in Western countries compared with the general population,^{11,12} may contribute to poor hygiene. Known prevalence and risk factors for infestation among homeless persons are shown in Table I.

The United States is currently experiencing a homelessness "epidemic," particularly on the West Coast, where several cities have declared states

of emergency.¹³⁻¹⁵ From 2016 to 2017, homelessness increased for the first time in 7 years, by 9%, mostly because of a rise in unsheltered homeless persons.¹⁴ Chronic (>1 year) homelessness also increased by 12%.¹⁴ During this period, homeless populations have risen in several European countries.¹⁶

Clinical manifestations

Patients with body lice infestation present with generalized pruritus and lesions distributed on the neck, shoulders, upper back, flanks, and waist—sites of close contact between clothing and the skin (Fig 2). Common lesions include excoriations and eczematous patches; papular urticaria and bullae may be seen. Prurigo nodules, lichenification, and hyperpigmentation are present in chronic infestation. Scratching predisposes to impetigo, ecthyma, and cellulitis. Diagnosis is achieved by carefully examining clothing seams ("clothing biopsy") for lice and nits. Severe iron deficiency anemia¹⁷⁻¹⁹ and eosinophilia^{17,19} have been associated with heavy/chronic body lice infestation.

Implications

Body lice transmit several potentially life-threatening infections (Table II). Despite being rare overall, these conditions remain major public health concerns in poor hygiene conditions.

Body lice transmit *Bartonella quintana*, which causes trench fever, named for its high prevalence among soldiers fighting together in unhygienic trenches during World War I.^{20,21} More recently, trench fever was seen in refugees after the civil war in Burundi,²² and since the 1990s, "urban trench fever" has been recognized in homeless and urban poor populations worldwide.²³⁻²⁵ *B. quintana* was identified in 21% of body lice in Marseilles, France,²⁶ 28.2% in Bogotá, Colombia,²⁷ 13.35% in northern Algeria,²⁸ 13.1% in Turkey,²⁹ and 15.9% in San Francisco, California.⁸ Trench fever classically manifests as headache, dizziness, conjunctival injection, severe shin pain, lymphadenopathy, a macular evanescent rash, and relapsing fevers lasting 4 to 8 days.^{2,21,30} Contemporary *B. quintana* infections present with variable manifestations: asymptomatic infections, relapsing fevers, headache, leg pain, "culture-negative" endocarditis, and, in immunocompromised persons with HIV or a previous transplant, bacillary angiomatosis.^{25,31,32} Diagnosis relies on culture, serology, immunohistochemical staining, or polymerase chain reaction assay. *B. quintana* grows slowly in culture, often requiring ≥14 days and up to 45 days.³³ The microbiology laboratory should be notified when

Abbreviations used:

FDA: US Food and Drug Administration
LBRF: louse-borne relapsing fever
RCT: randomized controlled trial

Bartonella is suspected because several techniques exist to optimize growth.³³ First-line treatment is gentamicin (3 mg/kg/day for 2 weeks) followed by doxycycline (200 mg/day for 4 weeks).³⁰ In bacillary angiomatosis, first-line treatment is erythromycin (500 mg 4 times daily) or doxycycline (100 mg 2 times daily) for ≤ 3 months in immunocompromised hosts.^{30,34}

The body louse also transmits *Borrelia recurrentis*, which causes louse-borne relapsing fever (LBRF). Most LBRF cases originate from the horn of Africa (Ethiopia, Eritrea, and Somalia), where *B recurrentis* is endemic and concentrated poverty contributes to sporadic epidemics.^{35,36} With the ongoing global refugee crisis, LBRF is an emerging infectious disease in Europe, seen in refugees and asylum seekers who acquired the infection in the horn of Africa, either during their journey through North Africa where migration routes into Europe join or in Europe through contact with new refugee arrivals.³⁷⁻⁴⁶ LBRF presents with an initial phase of high-grade fever, headache, dizziness, myalgias, and fatigue,³⁵ followed by shorter, less severe relapses every 7 to 19 days.² Complications include mucocutaneous hemorrhage, neurologic dysfunction, and liver or renal failure. Mortality is $\leq 40\%$ for untreated cases² and 2% to 5% when treated.⁴⁷ Serum polymerase chain reaction studies or observing organisms on blood smears confirms the diagnosis.⁴⁸ Treatment is with a single dose of intramuscular penicillin G (400,000-800,000 units) or doxycycline

200 mg once²; the optimal treatment remains unclear.⁴⁹ After antibiotic administration, observation for 4 to 6 hours is recommended⁵⁰ because a Jarisch-Herxheimer reaction is common. In LBRF, this typically occurs within 2 hours of antibiotic administration and manifests with chills/rigors, tachycardia, and hypotension that may require hospitalization for supportive care.^{51,52}

P humanus also transmits *Rickettsia prowazekii*, which causes epidemic typhus. While infected lice die within weeks, humans are the principle reservoir, remaining infected for life.²² The organism may reemerge years later during stressful periods.²² Outbreaks are associated with war, famine, crowding, refugee camps, and cold weather.^{22,53} Flying squirrels serve as a zoonotic reservoir in periods between outbreaks, when human-to-louse-to-human transmission is less common.⁵⁴ Widespread maculopapular exanthema that may become petechial are seen.²² Other features include fever, nausea, diarrhea, delirium, respiratory failure, and shock.^{2,22} Diagnosis is made via serology.⁵⁵ Mortality is $\leq 60\%$ if untreated but approximately 4% when treated.² First-line treatment is doxycycline 200 mg once.^{55,56}

Management

The management of body lice must address poor hygiene and clothing infestation. Regular showering/bathing is important. Clothes should be discarded appropriately or washed and dried using high heat ($>50^{\circ}\text{C}$).³ Associated bacterial infections should be treated with appropriate antibiotics and eczematous lesions with topical corticosteroids. Physicians should involve social services to address underlying factors driving infestation.

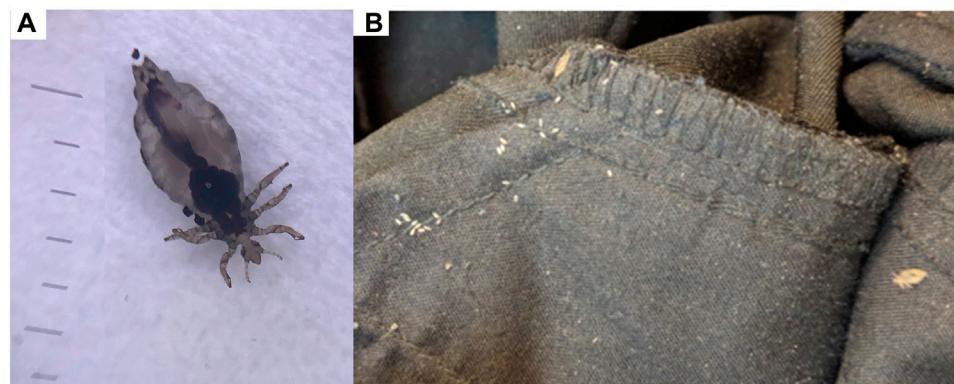


Fig 1. Body lice. **A**, Body louse morphology (courtesy of Charlotte Bernigaud, MD, Olivier Chosidow, MD, PhD, and Francoise Foulet, MD). **B**, Two lice and numerous nits (pinpoint white-yellow structures) in clothing seams (courtesy of Aileen Chang, MD).

Table I. Epidemiology of body lice infestation among homeless populations

Year	Location	Population	Prevalence of body lice	Risk factors for infestation
2014	San Francisco, California, United States ⁸	203 sheltered and unsheltered homeless persons	30% with body lice, 4.9% with head lice, and 3% with body and head lice	Male sex, African American race, and sleeping outdoors
2016	Paris, France ⁹	667 sheltered and 341 unsheltered homeless persons	5.4% of unsheltered persons with body lice and 0.15% of sheltered persons with body lice	Begging, history of pubic lice, and not taking showers in municipal baths
2017	Marseilles, France ¹⁰	2288 sheltered homeless persons	12.2% with body lice, 4.5% with head lice, and 3.2% with pubic lice	Older age, alcohol consumption, and tobacco smoking
2017	Bogotá, Colombia ²⁷	153 sheltered homeless persons	11.7% with body lice	Not reported



Fig 2. Clinical manifestations of body lice infestation. **A** and **B**, Bite marks along clothing seams that have evolved into prurigo nodules after chronic rubbing (courtesy of Sarah Coates, MD). **C**, Excoriations and prurigo nodules localized to upper back and shoulders in a patient with body lice infestation (courtesy of Kelly Fitzgerald, MD).

These measures can be effectively implemented during large outbreaks. In 1991, an Ethiopian refugee camp achieved large-scale delousing via shaving head and pubic hair, a 15-minute shower with soap, boiling clothing for 30 minutes, burning and replacing blankets, and spraying personal belongings with pesticide.⁵⁷ After a civil war in Burundi in the 1990s, a nationwide epidemic typhus outbreak was successfully managed with delousing interventions and doxycycline

administered to all confirmed and suspected cases of typhus.²²

In a randomized controlled trial (RCT) among sheltered homeless persons in France, persons who received permethrin-impregnated underwear were freer of lice (based on the absence of living lice in underwear) on day 14 compared with placebo, but these effects were not sustained 45 days later and thus this intervention was not recommended given the lack of sustained

Table II. Human pathogens associated with body lice infestation

Pathogen	Clinical manifestations	Microbiology	Diagnosis	Treatment
<i>Bartonella quintana</i>	Trench fever: headache, dizziness, severe shin pain, lymphadenopathy, macular evanescent rash, relapsing fevers lasting 4-8 days, recurring for weeks ^{2,21,30} , "culture-negative" endocarditis ¹⁷⁴ ; bacillary angiomatosis (in immunocompromised hosts) ^{31,32}	Facultative intracellular Gram-negative bacillus	Serology (anti- <i>Bartonella</i> antibodies); blood or tissue culture possible, but not sensitive. Slow growth in culture (≥ 14 days, ≤ 45 days) ³³	Gentamicin (3 mg/kg/day for 2 weeks), followed by doxycycline (200 mg/day for 4 weeks) ³⁰ ; erythromycin is the first-line treatment for bacillary angiomatosis
<i>Borrelia recurrentis</i>	Relapsing fever: high-grade fever, headache, dizziness, pain, anorexia, and fatigue; may progress to mucocutaneous hemorrhage, meningitis, encephalitis, liver and renal failure; relapses occur every 7-19 days ²	Spirochete	Thin and thick blood smears to identify organisms; PCR testing of serum if smear negative; CSF PCR if neurologic signs are present	Single dose IM penicillin G (400,000-800,000 units); oral doxycycline, once (200 mg for adults) monitor for Jarisch-Herxheimer reaction during first 24 hours
<i>Rickettsia prowazekii</i>	Epidemic typhus: fever, acute exanthem, diarrhea, neurologic dysfunction, respiratory failure, and shock; organism may emerge during stressful periods years later ²²	Obligate intracellular bacillus; infected lice die within 3 weeks; humans remain infected for life	Diagnose via serology; isolation in culture is impractical	Oral doxycycline 100 mg BID for 7-10 days ^{55,56} ; chloramphenicol 500 mg QID for 5 days (second-line); doxycycline 200 mg, once, in outbreaks ²

BID, Twice daily; CSF, cerebrospinal fluid; IM, intramuscular; PCR, polymerase chain reaction; QID, 4 times daily.



Fig 3. Head lice. **A**, Head louse morphology (courtesy of Arezki Izri, MD, PhD). **B**, Head louse nit attached to a hair shaft, visualized under microscopy (courtesy of Charlotte Bernigaud, MD, Olivier Chosidow, MD, PhD, and Francoise Foulet, MD). **C**, Head louse nit on a hair shaft, visualized under dermoscopy (courtesy of Aileen Chang, MD).

Table III. Treatment of head lice

Therapy	Mechanism of action	Instructions	Adverse events	Level of evidence*	Considerations
Over the counter					
Pyrethrin with piperonyl butoxide shampoo (A-200, Pronto, R&C, Rid, or Triple X)	Natural extract from the chrysanthemum flower. Blocks sodium transport, leading to depolarization of neuromembranes and respiratory paralysis	Apply to dry hair. Let sit for 10 min. Repeat in 7-10 days. Nit combing recommended (not ovicidal)	Contact dermatitis	Level 1B RCT: 50% ovicidal at day 14 ¹⁷⁵	Approved by the FDA for children >2 years of age; efficacy has waned because of resistance
Permethrin 1% lotion or cream rinse (Nix)	Synthetic pyrethrin. Blocks sodium transport, leading to depolarization of neuromembranes and respiratory paralysis	Apply after shampoo. Let sit for 10 min. Rinse. Repeat in 7 days. Nit combing recommended (not ovicidal)	Contact dermatitis	Cream rinse: level 1A RCT: 97% efficacy after 14 days ¹⁷⁶ Metaanalysis: >90% cure rates ¹⁷⁷	Approved by the FDA in 1986 for children >2 months of age; efficacy has waned because of resistance
Dimethicone 4% lotion (LiceMD)	Long-chain linear silicone dissolved in a volatile silicone base. Physical material (not an insecticide) that coats hair shafts	Apply to dry hair. Let sit for two 8-hour treatments, 7 days apart ¹⁷⁸ (reported to be ovicidal at higher concentration) ¹⁷⁹	Skin/eye irritation ¹⁷⁸	Level 1B RCT: Eradicated lice in 70% of patients ¹⁷⁸	Not approved by the FDA
Prescription					
Malathion 0.5% lotion (Ovide) or gel	Organophosphate cholinesterase inhibitor. Causes louse respiratory paralysis	Lotion: apply to dry hair. Let sit for 8-12 hours. Shampoo: repeat in 7-9 days if lice still present (partially ovicidal) Gel: Apply to dry hair. Let sit for 30 min. Repeat in 7-9 days if still present	Flammable; do not use a hair dryer/iron ⁵⁹ ; skin irritation ¹⁸⁰	Lotion: Level 1B RCT: 100% effective at 24 hours. 95.3% effective at 7 days ¹⁸⁰ Gel: Level 1B RCT: 98% response after 30 min ¹⁸¹	Withdrawn in 1995 because of flammability, then reinstated in 1999; approved for children >6 years of age ⁹⁶ Useful for permethrin-resistant lice ⁹³
Benzyl alcohol 5% lotion (Ulesfia)	Aromatic alcohol that kills lice via asphyxiation; not neurotoxic	Apply to dry hair. Let sit for 10 min. Rinse. Two applications needed (not ovicidal)	Skin irritation ¹⁸²	Level 1B Two RCTs: 75-76.2% elimination ¹⁸²	Approved by the FDA 2009 for children >6 months of age

Spinosad 0.9% suspension (Natroba)	Paralyzes lice by agonizing acetylcholine and antagonizing gamma-aminobutyric acid receptors	Apply to dry hair. Let sit for 10 min. Rinse. No nit combing required. ⁹⁷ Repeat in 7 days if lice are visualized (ovicidal) ^{97,98}	Skin/eye irritation ⁹⁷	Level 1B RCT: 84.6-86.7% effective (after 1 or 2 applications) ⁹⁷	Approved by the FDA 2011 for children >4 years of age; expensive ¹⁸³
Ivermectin 0.5% lotion (Sklice)	Binds glutamate-gated chloride channels in invertebrate nerve and muscle cells, leading to cellular hyperpolarization ⁹⁹	Apply to dry hair. Let sit for 10 min. Rinse. Two applications recommended (not ovicidal) ^{99,184}	Skin irritation ¹⁸⁴	Level 1B Two RCTs: 94.9% lice-free at day 2; 73.8% lice-free at day 15 ¹⁸⁴	Approved by the FDA in 2012 for children >6 months of age
Abametapir 0.74% lotion	Metalloproteinase inhibitor	Apply to dry hair. Let sit for 10 min. Rinse. No nit combing required (ovicidal)	Skin irritation ¹⁸⁵	Level 1B Two RCTs: 81.1-88.2% lice-free 14 days after 1 application ¹⁸⁵	Not approved by the FDA
Oral ivermectin (Stromectol)	Same as topical ivermectin above	200 µg/kg dosed once, or 400 µg/kg dosed twice at 7-day interval (not ovicidal) ¹⁰¹	Pruritus, headache	Level 1B RCT: 95.2% lice free by day 15 ¹⁰¹	Not approved by the FDA for the treatment of head lice; not for pregnant women or children weighing <15 kg ⁵⁹
Hot air delivered to the scalp	Causes louse death via overheating	30 min of heat applied to scalp (multiple delivery modalities studied)	None reported	Level 2B >88% effective in killing eggs at 14 days; variable efficacy in killing hatched lice ¹⁰⁹	Not approved by the FDA

Drug names are trademarks of their respective owners.

FDA, US Food and Drug Administration; RCT, randomized controlled trial.

*Level 1A, evidence from metaanalysis of randomized controlled trials; level 1B, evidence from ≥1 randomized controlled trial; level 2A, evidence from ≥1 controlled study without randomization; level 2B, evidence from ≥1 other type of experimental study; level 3, evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; level 4, evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

response and potential promotion of permethrin resistance.⁵⁸

HUMAN HEAD LOUSE (*PEDICULUS HUMANUS CAPITIS*)

Key points

- Head lice are a public health problem affecting all demographics
- Head lice can be infected with pathogens
- Novel US Food and Drug Administration (FDA) –approved topical therapies include benzyl alcohol 5% lotion, spinosad 0.9% suspension, and ivermectin 0.5% lotion

Head lice are ovoid-shaped, 2- to 3-mm arthropods (Fig 3, A).^{59,60} Head lice are obligate human parasites that spend their entire life cycle on the scalp, feeding off blood every few hours.⁶¹ Female lice live \leq 30 days and lay approximately 10 eggs daily.⁶¹ Nits are transparent, flask-shaped, 0.5-mm eggs found on hair shafts, typically 1 to 4 mm above the scalp, where warmth promotes survival (Fig 3, B).^{60,61}

Epidemiology

Head lice infest >100 million people worldwide and 6 to 12 million people in the United States annually.^{6,62} Transmission occurs via direct head-to-head contact, but lice can survive \leq 4 days on fomites, including hairbrushes or headgear.⁶¹ Most cases occur in children, particularly females, likely because of cultural hair length differences.^{6,63} Head lice affect people of all socioeconomic statuses.

Clinical manifestations

Pruritus, papular urticaria, excoriations, and cervical/occipital lymphadenopathy can occur.^{60,64} Diagnosis is achieved via direct observation of lice or nits on hair shafts. Dermoscopy distinguishes eggs containing nymphs (Fig 3, C) from empty, translucent “pseudonymphs” (hair casts, hair product debris, or seborrheic dermatitis).⁶⁵⁻⁶⁸ Pruritus and disturbed sleep may cause school and work absences.⁶⁹ Severe iron deficiency anemia^{17,70,71} has been associated with heavy/chronic head lice infestation.

Implications

Head lice can carry and transmit *Staphylococcus aureus* and *Streptococcus pyogenes*.⁶¹ Recent evidence suggest head lice may also harbor other pathogens. *B recurrentis* DNA was identified in 23% of head lice from patients with LBRF in Ethiopia⁷² and the Republic of the Congo.⁷³ *B quintana* was

detected in head lice from France⁷⁴ (although it was not detected in another French study⁷⁵), Senegal (3-5% of lice in 2 studies),^{76,77} Ethiopia (9.2%),⁷⁸ San Francisco (25%),⁷⁹ Nepal,⁸⁰ and various African countries (2%).⁸¹ Investigators in Mali identified *Coxiella burnetti* and *Rickettsia aeschlimannii* in 5.1% and 0.6% of head lice, respectively.⁸² Pathogenic Acinetobacter species were identified in head lice from Thailand,⁸³ Algeria,⁸⁴ and 2 locations in France.^{75,85} Whether the presence of these organisms yields an increased risk of clinical disease remains unclear.

Management

Management of head lice requires eradication of all living lice and eggs. Mechanical removal is possible but labor intensive and is more efficacious when combined with medications.⁵⁹

Topical therapies are summarized in Table III.⁶⁰ Over-the-counter treatments include pyrethrins (neurotoxins derived from chrysanthemums), permethrin 1% lotion/cream (synthetic pyrethrin), and dimethicone (often spelled “dimeticone” outside the United States).⁵⁹ Topical pyrethrin⁸⁶⁻⁸⁹ and 1% permethrin resistance is widespread.⁹⁰⁻⁹⁴ Prescription options include malathion 0.5% lotion/gel, benzyl alcohol 5% lotion, spinosad 0.9% suspension, and ivermectin 0.5% lotion. Lindane is no longer recommended because of potential neurotoxicity.⁹⁵ Malathion was temporarily withdrawn from the US market because of flammability.⁹⁶ Ovicidal agents, including malathion and spinosad, are advantageous because they may not require repeat treatments.⁹⁷⁻⁹⁹ Persistent infestations (live lice observed 24 hours after treatment) should be retreated with a new medication class because resistance is likely.^{69,100} Oral ivermectin is effective for refractory head lice but is not approved by the FDA.¹⁰¹

Essential oils have demonstrated efficacy in eradicating head lice in many studies (Table IV).¹⁰²⁻¹⁰⁸ Most studies were in vitro, although combination Melaleuca and lavender oil, and also combination eucalyptus oil and *Leptospermum petersonii* solution, were effective in in vivo RCTs.^{106,108} No essential oils have been approved by the FDA for treating head lice, and many carry a risk of allergic contact dermatitis.⁶⁹

Conditioner should not be applied before topical medications and hair should not be rewashed for 1 to 2 days after removing the medication.⁹⁶ For patients deferring medications, delivering hot air to the scalp for 30 minutes showed up to 88% efficacy in killing lice.¹⁰⁹ Nit combs can be used every 2 to 3 days

Table IV. Efficacy of essential oils in treating head lice

Year	Compound	Study type	Instructions	Results
2007	Combined eucalyptus and peppermint in total 10% concentration, dissolved in 50% ethanol plus isopropanol in water	In vitro	N/A	Showed the greatest (93%) knockdown (lice death) 10 min after application ¹⁸⁶
2010	<i>Cinnamomum porphyrium</i> oil	In vitro	N/A	Killed >50% of lice within 2 min ¹⁰⁵
2010	Melaleuca oil and lavender oil in combination	In vivo	Applied 3 times at 7-day intervals	97.6% efficacy (louse-free) and superiority to pyrethrins at 24 hours ¹⁰⁶
2011	Citronellol and geraniol (both active components of 2 essential oils)	In vitro	N/A	>60% mortality of adult and late-stage nymphs ¹⁸⁷
2012	Tea tree (Melaleuca) oil, 1% concentration	In vitro	N/A	100% lice mortality at 30 min, showing both pediculicidal and ovicidal effects ¹⁰²
2016	Fumigant bioassays of leaves/ fruits of <i>Schinus areira</i> (Anacardiaceae) and <i>Thymus vulgaris</i> (Lamiaceae)	In vitro	N/A	<i>S areira</i> derivatives were most toxic against adult lice (10 min to achieve 50% knockdown); <i>T vulgaris</i> was most ovicidal (0% hatching after 24 hours) ¹⁸⁸
2018	10% <i>Curcuma xanthorrhiza</i> and 10% <i>Eucalyptus globulus</i> oils	In vitro	N/A	5-min immersion halted egg hatching ¹⁰³
2018	Clove oil diluted in either coconut or sunflower oil	In vitro	N/A	90% lice mortality within 2 hours of a 30-min contact ¹⁰⁴
2018	Eucalyptus oil and <i>Leptospermum petersonii</i> solution	In vivo	Applied 3 times at 7-day intervals	More than twice as effective in curing lice than pyrethrin-containing mousse applied twice ¹⁰⁸
2018	Eucalyptus oil and <i>Leptospermum petersonii</i> solution	In vitro	N/A	Exposure in vitro killed 100% of lice and eggs ¹⁰⁸

after treatment to decrease the chance of reinfection.⁹⁶ Along with scalp treatment, decontaminating clothing/linens at temperatures >50°C is recommended.¹¹⁰ Children should not be sent home from school early to treat infestation and should be allowed to return immediately after beginning treatment.⁵⁹ The American Academy of Pediatrics recommends against strict no-nit policies in schools.⁵⁹ All household members should be screened.

HUMAN PUBIC LOUSE (*PHTHIRUS PUBIS*)

Key points

- Pubic lice infestation can involve multiple body regions
- A diagnosis warrants screening for other sexually transmitted infections and, in children, considering the possibility of abuse

Pubic lice measure 0.8 to 1.2 mm in diameter and are wider than they are long, unlike ovoid-shaped head and body lice.⁶⁰ This crab-like shape enables them to grasp widely spaced pubic hairs (Fig 4, A). Female lice lay roughly 30 eggs during their 3- to 4-week lifespan.¹¹¹

Epidemiology

Pubic lice are transmitted via close physical contact, including sexual contact and shared sleeping arrangements.¹¹² Infestation occurs worldwide and affects both genders. Pubic hair removal via shaving, waxing, or laser has been associated with a decreased incidence.¹¹³

Clinical manifestations

P pubis infestation occurs on hairs of the scalp, axilla, chest, thighs, pubic area, eyebrows, and

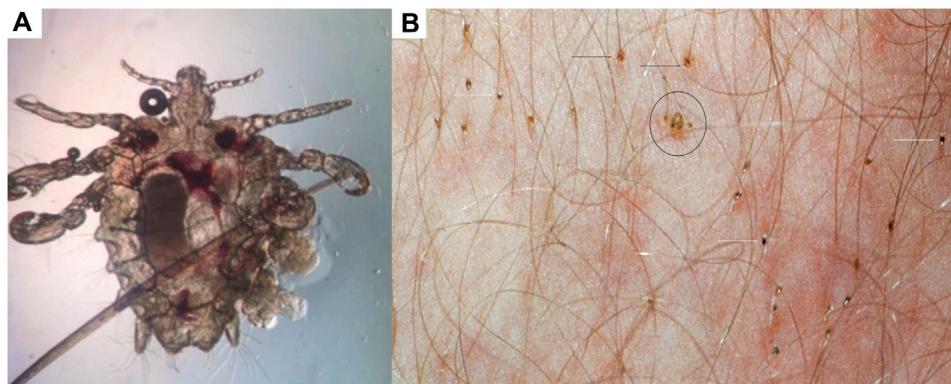


Fig 4. Pubic lice. **A**, Pubic louse morphology (courtesy of Charlotte Bernigaud, MD, Olivier Chosidow, MD, PhD, and Francoise Foulet, MD). **B**, Pubic louse (black circle) and numerous nits (several highlighted by white arrows) attached to hair shafts. Hemorrhagic macules (several highlighted by black arrows) at site of pubic lice bites (courtesy of Tim Berger, MD).

eyelashes. Symptomatic patients present with localized pruritus. Maculae ceruleae (blue-gray macules), red papules, and rust-colored feces can be seen at bite sites (Fig 4, B).^{60,114,115} In children, eyelashes are commonly involved^{112,116-118} and coinfection with head lice has been reported.¹¹⁸ Diagnosis is achieved by visualizing lice or nits on hair shafts (Fig 4, B). Bacterial superinfection of excoriations may occur. Pubic lice are not known to transmit other infections.

Management

A diagnosis of pubic lice warrants screening for other sexually transmitted infections.¹¹¹ While pediatric pubic lice infestation can occur through shared sleeping arrangements with infested individuals or contact with fomites,¹¹⁷ abuse should be considered.^{112,118}

The first-line treatment of pubic lice is topical 1% permethrin.^{111,114} Topical 0.5% ivermectin lotion is also approved by the FDA.¹¹¹ Petrolatum jelly is useful for treating eyelash infestation.¹¹⁹ Oral ivermectin is a second-line therapy but has not been approved by the FDA.^{114,120} Clean clothing should be worn when starting treatment.¹¹¹ Shaving is therapeutic and decreases the likelihood of recurrence. All clothing/linens used in the preceding 3 days should be washed and dried at temperatures >50°C.¹²¹

TUNGIASIS

Key points

- Tungiasis is an infestation, endemic to tropical world regions, caused by a flea burrowing into the skin

- Tungiasis is seen in travelers returning from endemic areas
- Tungiasis is associated with not wearing closed-toe footwear and dirt floors

Tungiasis is an ectoparasitic disease caused by skin penetration by the female *Tunga penetrans* or, less commonly, *Tunga trimamillata* flea.¹²² It is endemic in Latin America, the Caribbean, and sub-Saharan Africa¹²³ and occurs in travelers returning from endemic regions.¹²⁴⁻¹³³

Epidemiology

In travelers to endemic areas, tungiasis is usually acquired from walking barefoot or with open-toed shoes. In returning travelers between 2007 and 2011, 87 cases were reported in GeoSentinel, the largest global surveillance network for travel-related morbidity.¹³³ The top exposure countries were Brazil, Madagascar, Uganda, and Ethiopia. In returning travelers from Brazil who visited a GeoSentinel clinic between 1997 and 2013, 35 cases (2% of 1586) were diagnosed with tungiasis.¹³² At a German travel clinic, most returning travelers with tungiasis had been exposed in Africa or Latin America.¹³⁴

In endemic areas, the prevalence of tungiasis ranges from 19.1% to 58.7% (Table V).¹³⁵⁻¹⁴¹ In these settings, tungiasis is linked to inadequate health education,^{135,140} the lack of regular closed-toe footwear use,^{137,141,142} and poor housing conditions,^{135,140} including dirt floors or unclean floors,^{137,138,142} crowded living spaces,¹⁴⁰ and sleeping on the ground outside.¹⁴² Causative fleas may also exist in domestic or wild animal reservoirs, and therefore tungiasis is considered a zoonosis.¹⁴³⁻¹⁴⁵ Living on compounds with animals

Table V. Tungiasis prevalence and risk factors in endemic settings

Year	Location	Population	Prevalence of tungiasis	Risk factors for infestation
2006	Rural Northeast Brazil ¹³⁵	496 individuals in 132 households	51.0%	Poor housing conditions (OR = 4.7), lack of health education (OR = 4.1), and the presence of animals on the compound (OR = 1.9)
2006	Haiti (4 regions) ¹⁸⁹	383 patients	31.1%	Not studied
2007	Rural Western Nigeria ¹⁴²	643 individuals	42.5%	Presence of pigs (aOR = 17.98), sand or clay floor inside houses (aOR = 9.33), common resting place outside (aOR = 7.14), and no regular use of closed footwear (51% pop AR)
2012	Rural Western Tanzania ¹³⁶	586 individuals	42.5%	Age ≥45 years (OR = 3.71)
2015	Murang'a County, Kenya ¹³⁷	508 children	19.1%	Classrooms with dusty floors (aOR = 14.657), earthen mud walled houses (aOR = 13.78), and not regularly using closed footwear (aOR = 10.45)
2015	Maguye District, Eastern Uganda ¹³⁸	422 households in 12 villages	22.5%	Cracked house floor (aOR = 6.28), dirty feet (aOR = 3.86), dirty clothes (aOR = 3.46), dirty floor (aOR = 3.21), littered compounds (aOR = 2.95), and rearing cattle (aOR = 2.38)
2017	Southwest Nigeria ¹³⁹	545 children	24.4%	Not studied
2017	Kilifi County, Kenya ¹⁴⁰	1086 individuals from 233 households in 8 villages	25.0%	Only mud puddles as a washing source (OR = 25.48), washing the body without soap (OR = 7.36), mud walls (OR = 3.35), lack of water, permitting washing only once daily (OR = 2.23), number of people sleeping per room (OR = 1.77), and sleeping on the floor (OR = 1.68)
2017	Yirgacheffe, Southern Ethiopia ¹⁵⁶	343 children	34.7%	Closed footwear associated with increased lesion number
2018	Wensho District, Southern Ethiopia ¹⁴¹	366 children	58.7%	Never using footwear (aOR = 12.55), occasionally using footwear (aOR = 7.42), cat-owning household (aOR = 4.95), illiterate mothers (aOR = 3.62), and mothers who have attended only primary school education (aOR = 2.22)

aOR, Adjusted odds ratio; OR, odds ratio; pAR, population attributable risk.

confers a higher risk.^{135,138,141} Leading animal reservoirs differ by region, including stray cats/dogs in urban Brazil,¹⁴⁶ domestic cats in southern Ethiopia,¹⁴¹ and domesticated pigs in Uganda and Nigeria.^{142,147}

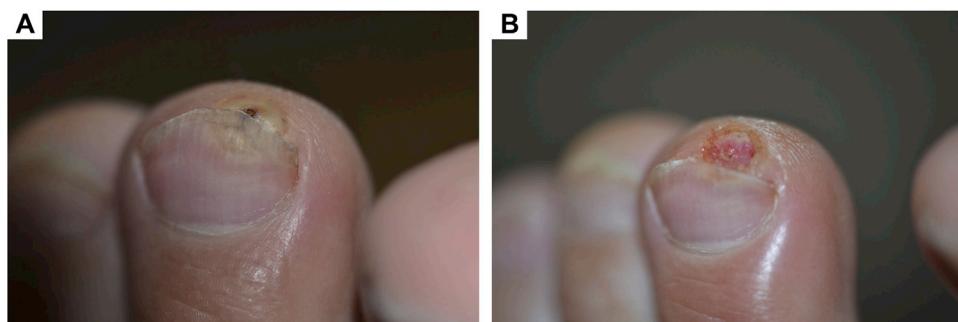
Clinical manifestations

Lesions predominantly affect the feet. Skin findings reflect the lesion's clinical stage, which is linked to the life cycle of the embedded flea and correlates with disease severity according to the Fortaleza classification (Table VI).¹⁴⁸ After painlessly burrowing into the

skin, typically on the feet, embedded fleas mature for several weeks.¹²³ An early-stage lesion is a 1-mm red-brown macule that evolves into a nodule with a central dark punctum (Fig 5, A). Subsequent flea engorgement from egg production leads to swelling, erythema, pruritus, and pain.¹²³ Eventually, egg release and parasite death trigger severe inflammation, leading to a black crusted papule that heals with a punched-out scar (Fig 5, B). Dermoscopy can be useful in diagnosing specific features, which in 1 series included dark central pores, whitish oval structures, silver dendritic fibers, and blue-black

Table VI. Fortaleza classification of the clinical stages of tungiasis

Stage	Duration	Parasite findings	Clinical findings	Histopathology findings
I	3-7 hours	Penetration at angle of 45°-90°; abdominal segments 2 and 3 begin separating	Itchy or painful red-brown 1-mm macule	Epidermis: hyperplasia, hyperkeratosis, parakeratosis Dermis: mild inflammatory infiltrate of neutrophils and eosinophils
II	1-2 days	Hypertrophic zone between abdominal segments 2 and 3	Pearly white nodule with surrounding erythema and a central dark punctum	Epidermis: hyperplasia, hyperkeratosis, parakeratosis, spongiosis, neutrophilic infiltrate, and intracorneal microabscesses Dermis: perivascular inflammatory infiltrate of neutrophils, lymphocytes, eosinophil, and plasma cells and mast cells
IIIa	2-3 days	Head of parasite at dermoepidermal interface	Growing, yellow-white halo around black dot. Fecal coils visible. Pain, foreign body sensation, severe itching	Epidermis: marked hyperplasia and hyperkeratosis, reactive pseudoepitheliomatous; marked mixed inflammatory infiltrate Dermis: mixed inflammatory infiltrate
IIIb	1-2 weeks	Thickening of chitin exoskeleton	Caldera formation; soft consistency; severe pain	Epidermis: same as above Dermis: dilated vessels and neutrophils
IV	3-5 weeks	Flea dying or dead	Crusted black lesion (containing dead parasite) with or without superinfection	Epidermis: same as above, plus vascularization of stratum corneum Dermis: moderate to severe mixed infiltrate
V	6 weeks to several months	No parasite	Residual scar, punched out depression; nail dystrophy or loss; lymphedema	Epidermis: hyperplasia, thickening and blunting of epidermal ridges, and thickened stratum spinosum Dermis: residual mild inflammation

Adapted from Eisele et al.¹⁴⁸**Fig 5.** Tungiasis. **A**, Early clinical stage of tungiasis with embedded flea (courtesy of Jorg Heukelbach, MD, PhD). **B**, Immediate aftermath of tungiasis infestation after death and expulsion of an embedded flea (courtesy of Jorg Heukelbach, MD, PhD).

blotches in most cases.¹⁴⁹ The penetration site measures $\leq 500 \mu\text{m}$ in diameter,¹⁵⁰ and therefore secondary bacterial infection occurs frequently, including cellulitis and necrotizing skin and soft tissue infection.^{150,151} In

returning travelers, the differential diagnosis depends on the clinical stage and includes arthropod bite, wart, pyogenic granuloma, abscess, leishmaniasis, myxoid cyst, myiasis, and foreign body.¹⁵²



Fig 6. Tungiasis. **A**, Multiple embedded fleas on the dorsal surfaces of the toes in a person living in an endemic area (courtesy of the Regional Dermatology Training Centre, Moshi, Tanzania). **B**, Multiple embedded fleas on the plantar surface of the foot in a person living in an endemic area (courtesy of Jean Marie Rukanikigitero, MD).

Quality of life

Tungiasis-associated morbidity in endemic settings is caused by severe foot pain, progressive foot mutilation, and nail dystrophy, complicating walking and contributing to stigmatization.^{153,154} Children may experience teasing and have higher school absenteeism and lower school performance than unaffected peers.¹⁵⁵ Tungiasis negatively impacts children's quality of life,^{156,157} with disturbed sleep and concentration reported most frequently in 1 Kenyan study.¹⁵⁷

Treatment

Tungiasis is self-limited because the organism typically dies within 6–8 weeks after penetration.¹⁴⁸ Treatment aims to reduce symptom severity and prevent secondary infection. Surgical removal of the organism is crucial. This can be achieved through shave or punch biopsy procedures. Early on, sterile needles can also be used before multiple embedded fleas or extensive inflammation occur.¹⁵⁸ Secondary bacterial infection requires appropriate antibiotics.

In endemic settings without access to appropriate equipment for surgical removal, commonplace sharp instruments, such as pins, needles, thorns, and sharpened wood pieces, are frequently reused by different people.¹⁵⁵ This can lead to bloodborne pathogen transmission,¹⁵⁵ tetanus,^{159,160} and life-threatening complications of secondary infection, including necrotizing fasciitis, gangrene, and sepsis.^{160–162} As such, nonsurgical alternatives have been investigated. Topical Zanzarin, derived from coconut oil, jojoba oil, and aloe vera, decreases tungiasis incidence and morbidity^{163,164} but is no longer commercially available. Topical dimethicone has been shown to reduce inflammation and hasten parasite death in 1 RCT,¹⁶⁵ with targeted application to areas of parasite protrusion being more effective

than to the entire foot.¹⁶⁶ Oral ivermectin showed no efficacy in a RCT.¹⁶⁷

Screening and prevention

For prospective travelers to endemic areas, the best preventive measure is wearing closed-toe shoes.¹⁶⁸ Only 54% of returning travelers diagnosed with tungiasis reported a pretravel medical visit,¹³³ and even when a visit occurs tungiasis may not be discussed.¹³³ Clinicians should therefore counsel patients with relevant planned travel.

In endemic areas, where nearly 95% of lesions are restricted to the feet,¹⁶⁹ targeted evaluation of periungual feet is useful for estimating prevalence, severity, and identifying persons needing treatment.¹⁷⁰ While improving education and health care access are important, clinical knowledge does not necessarily translate into effective prevention and treatment.¹⁷¹ Large-scale provision of closed-toe footwear is essential. In a metaanalysis, footwear use was associated with significantly lower odds of acquiring tungiasis.¹⁷² However, regular shoe replacement is costly¹⁴³ and may not reduce exposure inside houses, where shoes are not typically worn.¹⁴³ As such, modifications are important, including switching to sealed cement floors and cleaning floors daily.¹⁶² Unfortunately, human hosts living in endemic areas are frequently reinfested unless proper footwear and housing changes are widely implemented.¹⁶² Finally, increasing tetanus vaccination coverage in tungiasis-endemic regions will help prevent secondary tetanus.¹⁷³

In conclusion, in the context of a global refugee crisis and homelessness epidemic, diagnosing and managing lice infestations are important dermatologic skills. Dermatologists should know that careful clothing inspection is key to diagnosing body lice and that head lice have widespread

resistance to topical pyrethrin and permethrin. Tungiasis is an infestation affecting the feet that has substantial negative impact on communities in endemic regions. It is seen in returning travelers and can be prevented by wearing closed-toe shoes.

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REFERENCES

1. Rivet R, Mccoy KD, Brouqui P, Raoult D. Evidence that head and body lice on homeless persons have the same genotype. *PLoS One*. 2012;7:e45903.
2. Badiaga S, Brouqui P. Human louse-transmitted infectious diseases. *Clin Microbiol Infect*. 2012;18:332-337.
3. Centers for Disease Control and Prevention. Body lice. Available at: <https://www.cdc.gov/parasites/lice/body/index.html>. Accessed November 3, 2018.
4. Brouqui P. Arthropod-borne diseases associated with political and social disorder. *Annu Rev Entomol*. 2011;56: 357-374.
5. Sweileh WM. Global output of research on epidermal parasitic skin diseases from 1967 to 2017. *Infect Dis Poverty*. 2018;7:74.
6. Chosidow O. Scabies and Pediculosis. *Lancet*. 2000;355:819-826.
7. Gravatti M, Faccini-Martinez A, Ruys S, Timenetsky J, Biondo A. Preliminary report of body lice infesting homeless people in Brazil. *Rev Inst Med Trop Sao Paulo*. 2018;60:e9.
8. Bonilla DL, Cole-Porse C, Kjemtrup A, Osikowicz L, Kosoy M. Risk factors for human lice and bartonellosis among the homeless, San Francisco, CA, USA. *Emerg Infect Dis*. 2014;20: 1645-1651.
9. Arnaud A, Chosidow O, Detrez M, et al. Prevalences of scabies and pediculosis corporis among homeless people in the Paris region: results from two randomized cross-sectional surveys (HYTPEAC study). *Br J Dermatol*. 2016;174: 104-112.
10. Calloix C, Badiaga S, Raoult D, Tissot-dupont H, Brouqui P, Gautret P. Changing demographics and prevalence of body lice among homeless persons, Marseille, France. *Emerg Infect Dis*. 2017;23:1894-1897.
11. Fazel S, Khosla V, Doll H, Geddes J. The prevalence of mental disorders among the homeless in Western countries: systematic review and meta-regression analysis. *PLoS Med*. 2008; 5:e225.
12. Fazel S, Geddes J, Kushel M. The health of homeless people in high-income countries: descriptive epidemiology, health consequences, and clinical and policy recommendations. *Lancet*. 2014;384:1529-1540.
13. Gee A. "Human tragedy": LA homelessness jumps to record-breaking level. Available at: <https://www.theguardian.com/us-news/2017/may/31/homelessness-count-los-angeles-record-level>. Accessed February 21, 2019.
14. Henry M, Watt R, Rosenthal L, Shivji A. The 2017 Annual Homeless Assessment Report (AHAR) to Congress, part 1: point-in-time estimates of homelessness. Available at: <https://www.hudexchange.info/resources/documents/2017-AHAR-Part-1.pdf>. Accessed February 21, 2019.
15. Smith N. Homelessness is a tragedy the U.S. can afford to fix. Bloomberg. Available at: <https://www.bloomberg.com/view/articles/2018-05-21/ending-homelessness-is-a-job-for-the-federal-government>. Accessed June 1, 2018.
16. Feantsa and Abbe Pierre Foundation. Third overview of housing exclusion in Europe 2018. Available at: <https://www.feantsa.org/en/report/2018/03/21/the-second-overview-of-housing-exclusion-in-europe-2017>. Accessed February 21, 2019.
17. Guss DA, Koenig M, Castillo EM. Severe iron deficiency anemia and lice infestation. *J Emerg Med*. 2011;41:362-365.
18. Nara A, Nagai H, Yamaguchi R, et al. An unusual autopsy case of lethal hypothermia exacerbated by body lice-induced severe anemia. *Int J Leg Med*. 2016;130:765-769.
19. Woodruff C, Chang A. More than skin deep: severe iron deficiency anemia and eosinophilia associated with pediculosis capitis and corporis infestation. *JAAD Case Rep*. 2019;5: 444-447.
20. Ruiz J. *Bartonella quintana*, past, present, and future of the scourge of World War I. *APMIS*. 2018;126:831-837.
21. Anstead GM. The centenary of the discovery of trench fever, an emerging infectious disease of World War 1. *Lancet Infect Dis*. 2016;16:e164-e172.
22. Raoult D, Ndihokubwayo J, Tissot-Dupont H, et al. Outbreak of epidemic typhus associated with trench fever in Burundi. *Lancet*. 1998;352:353-358.
23. Spach D, Kanter A, Dougherty M, et al. *Bartonella (Rochalimae) quintana* bacteremia in inner-city patients with chronic alcoholism. *N Engl J Med*. 1995;332:424-428.
24. Seki N, Sasaki T, Sawabe K, et al. Epidemiological studies on *Bartonella quintana* infections among homeless people in Tokyo, Japan. *Jpn J Infect Dis*. 2006;59:31-35.
25. Ohl ME, Spach DH. *Bartonella quintana* and urban trench fever. *Clin Infect Dis*. 2000;31:131-135.
26. Drali R, Sangare A, Boutellis A, et al. *Bartonella quintana* in body lice from scalp hair of homeless persons, France. *Emerg Infect Dis*. 2014;20:907-908.
27. Faccini-Martinez ÁA, Márquez AC, Bravo-Estupiñan DM, et al. *Bartonella quintana* and typhus group Rickettsiae exposure among homeless persons, Bogota, Colombia. *Emerg Infect Dis*. 2017;23:1876-1879.
28. Louni M, Mana N, Bitam I, et al. Body lice of homeless people reveal the presence of several emerging bacterial pathogens in northern Algeria. *PLoS Negl Trop Dis*. 2018;12: e0006397.
29. Ulutasdemir N, Eroglu F, Tanrıverdi M, Dagli El, Koltas IS. The epidemic typhus and trench fever are risk for public health due to increased migration in southeast of Turkey. *Acta Trop*. 2018;178:115-118.
30. Angelakis E, Raoult D. Pathogenicity and treatment of *Bartonella* infections. *Int J Antimicrob Agents*. 2014;44:16-25.
31. Moulin C, Kanitakis J, Ranchin B, et al. Cutaneous bacillary angiomatosis in renal transplant recipients: report of three new cases and literature review. *Transpl Infect Dis*. 2012;14: 403-409.
32. Orsag J, Flodr P, Melter O, et al. Cutaneous bacillary angiomatosis due to *Bartonella quintana* in a renal transplant recipient. *Transpl Int*. 2015;28:626-631.
33. Scola BLA, Raoult D. Culture of *Bartonella quintana* and *Bartonella henselae* from human samples: a 5-year experience (1993 to 1998). *J Clin Microbiol*. 1999;37: 1899-1905.
34. Koehler J, Tappero J. Bacillary angiomatosis and bacillary peliosis in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1993;17:612.
35. Ramos JM, Malmierca E, Reyes F, Tesfamariam A. Louse-borne relapsing fever in Ethiopian children: experience of a rural hospital. *Trop Doct*. 2009;39:34-36.

36. Nordmann T, Feldt T, Bosselmann M, et al. Outbreak of louse-borne relapsing fever among urban dwellers in Arsi Zone, central Ethiopia, from July to November 2016. *Am J Trop Med Hyg.* 2018;98:1599-1602.
37. Osthoff M, Schibli A, Fadini D, Lardelli P, Goldenberger D. Louse-borne relapsing fever - report of four cases in Switzerland, June-December 2015. *BMC Infect Dis.* 2016;16:210.
38. Hoch M, Wieser A, Loscher T, et al. Louse-borne relapsing fever (*Borrelia recurrentis*) diagnosed in 15 refugees from northeast Africa: epidemiology and preventive control measures, Bavaria, Germany, July to October 2015. *Euro Surveill.* 2015;20:42.
39. Wilting K, Stienstra Y, Sinha B, Braks M, Cornish D, Grundmann H. Louse-borne relapsing fever (*Borrelia recurrentis*) in asylum seekers from Eritrea, the Netherlands, July 2015. *Euro Surveill.* 2015;20:21196.
40. Goldenberger D, Claas G, Bloch-Infanger C, et al. Louse-borne relapsing fever (*Borrelia recurrentis*) in an Eritrean refugee arriving in Switzerland, August 2015. *Euro Surveill.* 2015;20:2-5.
41. Antinori S, Mediannikov O, Corbellino M, Raoult D. Louse-borne relapsing fever among East African refugees in Europe. *Trav Med Infect Dis.* 2016;14:110-114.
42. Colombo C, Scarlata F, Di Carlo P, et al. Fourth case of louse-borne relapsing fever in Young Migrant, Sicily, Italy, December 2015. Mini Review Article. *Public Health.* 2016;139:22-26.
43. Darcis G, Hayette MP, Bontems S, et al. Louse-borne relapsing fever in a refugee from Somalia arriving in Belgium. *J Trav Med.* 2016;23. <https://doi.org/10.1093/jtm/taw009>.
44. Hytönen J, Khawaja T, Grönroos JO, Jalava A, Meri S, Oksi J. Louse-borne relapsing fever in Finland in two asylum seekers from Somalia. *APMIS.* 2017;125:59-62.
45. Antinori S, Tonello C, Edouard S, et al. Diagnosis of louse-borne relapsing fever despite negative microscopy in two asylum seekers from Eastern Africa. *Am J Trop Med Hyg.* 2017;97:1669-1672.
46. Isenring E, Fehr J, Gürtekin N, Schlagenhauf P. Infectious disease profiles of Syrian and Eritrean migrants presenting in Europe: a systematic review. *Trav Med Infect Dis.* 2018;25:65-76.
47. European Centre for Disease Prevention and Control. Facts about louse-born relapsing fever. Available at: <https://ecdc.europa.eu/en/louse-borne-relapsing-fever/facts>. Accessed February 21, 2019.
48. Halperin T, Orr N, Cohen R, et al. Detection of relapsing fever in human blood samples from Israel using PCR targeting the glycerophosphodiester phosphodiesterase (GlpQ) gene. *Acta Trop.* 2006;98:189-195.
49. Guerrier G, Doherty T. Comparison of antibiotic regimens for treating louse-borne relapsing fever: a meta-analysis. *Trans R Soc Trop Med Hyg.* 2011;105:483-490.
50. Barbour A. Clinical features, diagnosis, and management of relapsing fever. Up to Date. Available at: https://www.uptodate.com/contents/clinical-features-diagnosis-and-management-of-relapsing-fever?search=relapsing%20fever&source=search_result&selectedTitle=1~41&usage_type=default&display_rank=1. Accessed February 21, 2019.
51. Negussie Y, Remick D, DeForge L, Kunkel S, Eynon A, Griffin G. Detection of plasma tumor necrosis factor, interleukins 6, and 8 during the Jarisch-Herxheimer reaction of relapsing fever. *J Exp Med.* 1992;175:1207-1212.
52. Butler T. The Jarisch-Herxheimer reaction after antibiotic treatment of spirochetal infections: a review of recent cases and our understanding of pathogenesis. *Am J Trop Med Hyg.* 2017;96:46-52.
53. Tarasevich I, Rydkina E, Raoult D. Outbreak of epidemic typhus in Russia. *Lancet.* 1998;352:1151.
54. Centers for Disease Control and Prevention. Epidemic typhus. Available at: <https://www.cdc.gov/typhus/epidemic/index.html>. Accessed March 30, 2019.
55. Bechah Y, Capo C, Mege J, Raoult D. Epidemic typhus. *Lancet Infect Dis.* 2008;8:417-426.
56. Johns Hopkins Bloomberg School of Public Health. *Rickettsia prowazekii* (epidemic typhus). Johns Hopkins Center for Health Security. Available at: <http://www.centerforhealthsecurity.org/resources/fact-sheets/pdfs/typhus.pdf>. Accessed December 9, 2018.
57. Sundnes KO, Haimanot AT. Epidemic of louse-borne relapsing fever in Ethiopia. *Lancet.* 1993;342:1213-1215.
58. Benkouiten S, Drali R, Badiaga S, et al. Effect of permethrin-impregnated underwear on body lice in sheltered homeless persons: a randomized controlled trial. *JAMA Dermatol.* 2014;150:273-279.
59. Devore CD, Schutze GE. Head Lice. *Pediatrics.* 2015;135:e1355-e1365.
60. Ko CJ, Elston DM. Pediculosis. *J Am Acad Dermatol.* 2004;50:1-14.
61. Burkhardt CN, Burkhardt CG. Fomite transmission in head lice. *J Am Acad Dermatol.* 2007;56:1044-1047.
62. Do-Pham G, Monsel G, Chosidow O. Lice. *Semin Cutan Med Surg.* 2014;33:116-118.
63. Tagka A, Lambrou GI, Braoudaki M, Panagiotopoulos T, Papanikolaou E, Laggas D. Socioeconomical factors associated with pediculosis (Phthiraptera: Pediculidae) in Athens, Greece. *J Med Entomol.* 2016;53:919-922.
64. Dagrosa AT, Elston DM. What's eating you? Head lice (*Pediculus humanus capitis*). *Cutis.* 2017;100:389-392.
65. Stefanī A, Hofmann-Wellenhof R, Zalaudek I. Dermoscopy for diagnosis and treatment monitoring of pediculosis capitis. *J Am Acad Dermatol.* 2006;54:909-911.
66. Bakos R, Bakos L. Dermoscopy for diagnosis of pediculosis capitis. *J Am Acad Dermatol.* 2007;57:727-728.
67. Badri T, Hammami H, Benmously R, Mokhtar I, Fenniche S. Dermoscopic diagnosis of pediculosis capitis. *Acta Dermato-venereol Alp Pannonica Adriat.* 2010;19:45-46.
68. Haliasos EC, Kerner M, Jaimes-Lopez N, et al. Dermoscopy for the pediatric dermatologist part I: dermoscopy of pediatric infectious and inflammatory skin lesions and hair disorders. *Pediatr Dermatol.* 2013;30:163-171.
69. Koch E, Clark JM, Cohen B, et al. Management of head louse infestations in the United States—a literature review. *Pediatr Dermatol.* 2016;33:466-472.
70. Althomali S, Alzubaidi L, Alkhaldi D. Severe iron deficiency anaemia associated with heavy lice infestation in a young woman. *BMJ Case Rep.* 2015. bcr2015212207.
71. Burke S, Mir P. Pediculosis causing iron deficiency anaemia in school children. *Arch Dis Child.* 2011;96:989.
72. Boutellis A, Mediannikov O, Bilcha KD, et al. *Borrelia recurrentis* in Head Lice, Ethiopia. *Emerg Infect Dis.* 2013;19:796-798.
73. Amanzougaghene N, Akiana J, Mongo Ndombe G, et al. Head lice of Pygmies reveal the presence of relapsing fever Borreliae in the Republic of Congo. *PLoS Negl Trop Dis.* 2016;10:e0005142.
74. Angelakis E, Rolain JM, Raoult D, Brouqui P. *Bartonella quintana* in head louse nits. *FEMS Immunol Med Microbiol.* 2011;62:244-246.

75. Bouvresse S, Socolovshi C, Berdjane Z, et al. No evidence of *Bartonella quintana* but detection of *Acinetobacter baumannii* in head lice from elementary schoolchildren in Paris. *Comp Immunol Microbiol Infect Dis.* 2011;34:475-477.
76. Diatta G, Mediannikov O, Sokhna C, et al. Short report: Prevalence of *Bartonella quintana* in patients with fever and head lice from rural areas of Sine-Saloum, Senegal. *Am J Trop Med Hyg.* 2014;91:291-293.
77. Boutellis A, Veracx A, Angelakis E, et al. *Bartonella quintana* in Head Lice from Sénégal. *Vector Borne Zoonotic Dis.* 2012;12: 564-567.
78. Cutler S, Abdissa A, Adamu H, Tolosa T, Gashaw A. *Bartonella quintana* in Ethiopian lice. *Comp Immunol Microbiol Infect Dis.* 2012;35:17-21.
79. Bonilla DL, Kabeya H, Henn J, Kramer VL, Kosoy MY. *Bartonella quintana* in body lice and head lice from homeless persons, San Francisco, California, USA. *Emerg Infect Dis.* 2009;15:912-915.
80. Sesaki T, Poudel S, Iswaka H, et al. First molecular evidence of *Bartonella quintana* in *Pediculus humanus capitis* (Phthiraptera: Pediculidae), collected from Nepalese children. *J Med Entomol.* 2006;43:110-112.
81. Sangaré AK, Boutellis A, Drali R, et al. Detection of *Bartonella quintana* in African body and head lice. *Am J Trop Med Hyg.* 2014;91:294-301.
82. Amanzougaghene N, Fenollar F, Sangare AK, et al. Detection of bacterial pathogens including potential new species in human head lice from Mali. *PLoS One.* 2017;12: e0184621.
83. Sunantaraporn S, Sanprasert V, Pengsakul T, et al. Molecular survey of the head louse *Pediculus humanus capitis* in Thailand and its potential role for transmitting *Acinetobacter spp.* *Parasit Vectors.* 2015;8:127.
84. Mana N, Louni M, Parola P, Bitam I. Human head lice and pubic lice reveal the presence of several *Acinetobacter* species in Algiers, Algeria. *Comp Immunol Microbiol Infect Dis.* 2017;53:33-39.
85. Candy K, Amanzougaghene N, Izri A, et al. Molecular survey of head and body lice, *Pediculus humanus*, in France. *Vector Borne Zoonotic Dis.* 2018;18:243-251.
86. Downs AMR, Stafford KA, Hunt LP, Ravenscroft JC, Coles GC. Widespread insecticide resistance in head lice to the over-the-counter pediculocides in England, and the emergence of carbaryl resistance. *Br J Dermatol.* 2002;146: 88-93.
87. Cueto G, Zerba E, Picollo M. Evidence of pyrethroid resistance in eggs of *Pediculus humanus capitis* (Phthiraptera: Pediculidae) from Argentina. *J Med Entomol.* 2008;45:693-697.
88. Durand R, Bouvresse S, Andriantsoanirina V, Berdjane Z, Chosidow O, Izri A. High frequency of mutations associated with head lice pyrethroid resistance in schoolchildren from Bobigny, France. *J Med Entomol.* 2011;48:74-75.
89. Marcoux D, Palma KG, Kaul N, et al. Pyrethroid pediculicide resistance of head lice in Canada evaluated by serial invasive signal amplification reaction. *J Cutan Med Surg.* 2010;14:115-118.
90. Mumcuoglu K, Hemingway J, Miller J, et al. Permethrin resistance in the head louse *Pediculus capitis* from Israel. *Med Vet Entomol.* 1995;9:427-432.
91. Rupes V, Moravec J, Chmela J, Ledvinka J, Zelenkova J. A resistance of head lice (*Pediculus capitis*) to permethrin in Czech Republic. *Cent Eur J Public Health.* 1995;3:30-32.
92. Pollack R, Kiszevski A, Armstrong P, et al. Differential permethrin susceptibility of head lice sampled in the United States and Borneo. *Arch Pediatr Adolesc Med.* 1999;153:969-973.
93. Yoon KS, Gao J, Lee SH, Clark JM. Permethrin-resistant human head lice, *pediculus capitis*, and their treatment. *Arch Dermatol.* 2003;139:994-1000.
94. Bouvresse S, Berdjane Z, Durand R, Bouscaillou J, Izri A, Chosidow O. Permethrin and malathion resistance in head lice: results of ex vivo and molecular assays. *J Am Acad Dermatol.* 2012;67:1143-1150.
95. Centers for Disease Control and Prevention. Parasites: lice. Available at: <https://www.cdc.gov/parasites/lice/head/index.html>. Accessed June 17, 2018.
96. Centers for Disease Control and Prevention. Head lice: treatment. Available at: <https://www.cdc.gov/parasites/lice/head/treatment.html>. Accessed November 21, 2018.
97. Stough D, Shellabarger S, Quiring J, Gabrielsen AA. Efficacy and safety of spinosad and permethrin creme rinses for *Pediculosis capitis* (head lice). *Pediatrics.* 2009;124:e389-e395.
98. McCormick PL. Spinosad in pediculosis capitis. *Am J Clin Dermatol.* 2011;12:349-353.
99. Deeks LS, Naunton M, Currie MJ, Bowden FJ. Topical ivermectin 0.5% lotion for treatment of head lice. *Ann Pharmacother.* 2013;47:1161-1167.
100. Chosidow O, Giraudeau B. Topical ivermectin — a step toward making head lice dead lice? *N Engl J Med.* 2012;367: 1750-1752.
101. Chosidow O, Giraudeau B, Cottrell J, et al. Oral ivermectin versus malathion lotion for difficult-to-treat head lice. *N Engl J Med.* 2010;362:896-905.
102. Di Campli E, Di Bartolomeo S, Delli Pizzi P, et al. Activity of tea tree oil and nerolidol alone or in combination against *Pediculus capitis* (head lice) and its eggs. *Parasitol Res.* 2012; 111:1985-1992.
103. Soonwera M, Wongnet O, Sittichok S. Ovicidal effect of essential oils from Zingiberaceae plants and *Eucalyptus globulus* on eggs of head lice, *Pediculus humanus capitis* De Geer. *Phytomedicine.* 2018;47:93-104.
104. Candy K, Nicolas P, Andriantsanirina V, Izri A, Durand R. In vitro efficacy of five essential oils against *Pediculus humanus capitis*. *Parasitol Res.* 2018;117:603-609.
105. Tolosa AC, Zygaldo J, Biurrun F, Rotman A, Picollo MI. Bioactivity of Argentinean essential oils against permethrin-resistant head lice, *Pediculus humanus capitis*. *J Insect Sci.* 2010;10:185.
106. Barker SC, Altman PM. 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. *BMC Dermatol.* 2010;10:6.
107. Barker SC, Altman PM. An ex vivo, assessor blind, randomised, parallel group, comparative efficacy trial of the ovicidal activity of three pediculicides after a single application—melaleuca oil and lavender oil, eucalyptus oil and lemon tea tree oil, and a "suffocation" pediculicide. *BMC Dermatol.* 2011;11:14.
108. Greive KA, Barnes TM. The efficacy of Australian essential oils for the treatment of head lice infestation in children: a randomised controlled trial. *Australas J Dermatol.* 2018;59: e99-e105.
109. Goates BM, Atkin JS, Wilding KG, et al. An effective nonchemical treatment for head lice: a lot of hot air. *Pediatrics.* 2006;118:1962-1970.
110. Izri A, Chosidow O. Efficacy of machine laundering to eradicate head lice: recommendations to decontaminate

- washable clothes, linens, and fomites. *Clin Infect Dis.* 2006;42:e9-e10.
111. Centers for Disease Control and Prevention. Pubic "crab" lice. Available at: <https://www.cdc.gov/parasites/lice/pubic/index.html>. Accessed November 3, 2018.
112. Klaus S, Shvil Y, Mumcuoglu KY. Generalized infestation of a 3 1/2-year-old girl with the pubic louse. *Pediatr Dermatol.* 1994; 11:26-28.
113. Dholakia S, Buckler J, Jeans JP, Pillai A, Eagles N, Dholakia S. Pubic lice: an endangered species? *Sex Transm Dis.* 2014;41: 388-391.
114. Salavastru CM, Chosidow O, Janier M, Tiplica GS. European guideline for the management of pediculosis pubis. *J Eur Acad Dermatol Venereol.* 2017;31:1425-1428.
115. Brown TJ, Yen-Moore A, Tyring SK. An overview of sexually transmitted diseases. Part II. *J Am Acad Dermatol.* 1999;41: 661-677.
116. Michali G, Lacarrubba F. Phthiriasis palpebrarum in a child. *N Engl J Med.* 2015;373:e35.
117. Yi JW, Li L, Luo DW. Phthiriasis palpebrarum misdiagnosed as allergic blepharoconjunctivitis in a 6-year-old girl. *Niger J Clin Pr.* 2014;17:537-539.
118. Ryan MF. Phthiriasis palpebrarum infection: a concern for child abuse. *J Emerg Med.* 2014;46:e159-e162.
119. Ma DL, Vano-Galvan S. Infestation of the eyelashes with Phthirus pubis. *CMAJ.* 2010;182:E187.
120. Burkhardt C, Burkhardt C. Oral ivermectin therapy for phthiriasis palpebrum. *Arch Ophthalmol.* 2000;118:134-135.
121. Karabela Y, Yardimci G, Yildirim I, Atalay E, Karabela SN. Treatment of phthiriasis palpebrarum and crab louse: petrolatum jelly and 1% permethrin shampoo. *Case Rep Med.* 2015;2015:287906.
122. Fioravanti M, Pampiglione S, Trentini M. A second species of *Tunga* (Insecta, Siphonaptera) infecting man: *Tunga trimaillata*. *Parasite.* 2003;10:282-283.
123. Karunamoorthy K. Tungiasis: a neglected epidermal parasitic skin disease of marginalized populations — a call for global science and policy. *Parasitol Res.* 2013;112:3635-3643.
124. Sachse MM, Guldbakke KK, Khachemoune A. *Tunga penetrans*: a stowaway from around the world. *J Eur Acad Dermatol Venereol.* 2007;21:11-16.
125. Veraldi S, Valsecchi M. Imported tungiasis: a report of 19 cases and review of the literature. *Int J Dermatol.* 2007;46: 1061-1066.
126. Grupper M, Potasman I. Outbreak of tungiasis following a trip to Ethiopia. *Trav Med Infect Dis.* 2012;10:220-223.
127. Sood A, Raman DK, Joshi RK, Gupta D. Tungiasis: outbreak investigation of a zoonosis during overseas deployment. *Med J Armed Forces India.* 2017;73:375-379.
128. Belaz S, Gay E, Robert-Gangneux F, Beaucournu JC, Guiguen C. Tungiasis outbreak in travelers from Madagascar. *J Trav Med.* 2015;22:263-266.
129. Kulakov EL, Mann J, Bagla N, Cooper AJ. Painful nodule on the foot of a traveller returning from Africa. *Clin Exp Dermatol.* 2013;38:436-438.
130. Jackson A, Stevenson L, Coggleshall P, Whitman TJ. A patient returning from Africa finds a mass imbedded in the skin of her right foot. *Clin Infect Dis.* 2012;55:1227.
131. Peccerillo F, Zambito Spadaro F, Fabrizi G, Feliciani C, Pagliarello C, Stanganelli I. Not a simple plantar wart: a case of tungiasis. *J Eur Acad Dermatol Venereol.* 2018;32:e113-e114.
132. Wilson ME, Chen LH, Han PV, et al. Illness in travelers returned from Brazil: the geosentinel experience and implications for the 2014 FIFA World Cup and the 2016 Summer Olympics. *Clin Infect Dis.* 2014;58:1347-1356.
133. Leder K, Torresi J, Libman M, et al. GeoSentinel surveillance of illness in returned travelers, 2007-2011. *Ann Intern Med.* 2013; 158:456-468.
134. Herbinger K, Siess C, Nothdurft H, von Sonnenburg F, Loscher T. Skin disorders among travellers returning from tropical and non-tropical countries consulting a travel medicine clinic. *Trop Med Int Health.* 2011;16:1457-1464.
135. Muehlen M, Feldmeier H, Wilcke T, Winter B, Heukelbach J. Identifying risk factors for tungiasis and heavy infestation in a resource-poor community in northeast Brazil. *Trans R Soc Trop Med Hyg.* 2006;100:371-380.
136. Mazigo HD, Bahemana E, Konje ET, et al. Jigger flea infestation (tungiasis) in rural western Tanzania: high prevalence and severe morbidity. *Trans R Soc Trop Med Hyg.* 2012; 106:259-263.
137. Mwangi JN, Ozwara HS, Gicheru MM. Epidemiology of *Tunga penetrans* infestation in selected areas in Kiharu constituency, Murang'a County, Kenya. *Trop Dis Trav Med Vaccin.* 2015;1:13.
138. Wafula ST, Ssemugabo C, Namuhani N, Musoke D, Ssempebwa J, Halage AA. Prevalence and risk factors associated with tungiasis in Mayuge district, Eastern Uganda. *Pan Afr Med J.* 2016;24:77.
139. Ugbomoiko US, Ariza L, Babamale AO, Heukelbach J. Prevalence and clinical aspects of tungiasis in south-west Nigerian schoolchildren. *Trop Doct.* 2017;47:34-38.
140. Wiese S, Elson L, Reichert F, Mambo B, Feldmeier H. Prevalence, intensity and risk factors of tungiasis in Kilifi County, Kenya: I. Results from a community-based study. *PLoS Negl Trop Dis.* 2017;11:e0005925.
141. Girma M, Astatkie A, Asnake S. Prevalence and risk factors of tungiasis among children of Wensho district, southern Ethiopia. *BMC Infect Dis.* 2018;18:456.
142. Ugbomoiko US, Ariza L, Ofoezie IE, Heukelbach J. Risk factors for tungiasis in Nigeria: identification of targets for effective intervention. *PLoS Negl Trop Dis.* 2007; 1:1-7.
143. Feldmeier H, Heukelbach J, Ugbomoiko US, et al. Tungiasis—a neglected disease with many challenges for global public health. *PLoS Negl Trop Dis.* 2014;8:e3133.
144. Mutebi F, Krücke J, von Samson-Himmelstjerna G, et al. Animal and human tungiasis-related knowledge and treatment practices among animal keeping households in Bugiri District, South-Eastern Uganda. *Acta Trop.* 2018; 177:81-88.
145. Pilger D, Schwalenberg S. Investigations on the biology, epidemiology, pathology, and control of *Tunga penetrans* in Brazil: VII. The importance of animal reservoirs for human infestation. *Parasitol Res.* 2008;102:875-880.
146. Heukelbach J, Costa AML, Wilcke T, Mencke N, Feldmeier H. The animal reservoir of *Tunga penetrans* in severely affected communities of north-east Brazil. *Med Vet Entomol.* 2004;18: 329-335.
147. Mutebi F, Krücke J, Feldmeier H, et al. Animal reservoirs of zoonotic tungiasis in endemic rural villages of Uganda. *PLoS Negl Trop Dis.* 2015;9:e0004126.
148. Eisele M, Heukelbach J, Van Marck E, et al. Investigations on the biology, epidemiology, pathology and control of *Tunga penetrans* in Brazil: I. Natural history of tungiasis in man. *Parasitol Res.* 2003;90:87-99.
149. Kosumi H, Iwata H, Miyazawa H, et al. Dermoscopic features of tungiasis. *J Eur Acad Dermatol Venereol.* 2018;32:e313-e314.

150. Feldmeier H, Heukelbach J, Eisele M, Sousa AQ, Barbosa LMM. Bacterial superinfection in human tungiasis. *Trop Med Int Health.* 2002;7:559-564.
151. Nyangacha RM, Odongo D, Oyieke F, et al. Secondary bacterial infections and antibiotic resistance among tungiasis patients in Western, Kenya. *PLoS Negl Trop Dis.* 2017;11:e0005901.
152. Brane S, Adams B, Bazemore A. Tungiasis in the returning traveler. *J Am Acad Dermatol.* 2005;52:1105.
153. Heukelbach J, Ugbomoiko U. Tungiasis in the past and present: a dire need for intervention. *Nig J Parasitol.* 2007;28:1-5.
154. Feldmeier H, Eisele M, Sabóia-Moura RC, Heukelbach J. Severe tungiasis in underprivileged communities: case series from Brazil. *Emerg Infect Dis.* 2003;9:949-955.
155. Feldmeier H, Sentongo E, Krantz I. Tungiasis (sand flea disease): a parasitic disease with particular challenges for public health. *Eur J Clin Microbiol Infect Dis.* 2013;32:19-26.
156. Walker SL, Lebas E, De Sario V, et al. The prevalence and association with health-related quality of life of tungiasis and scabies in schoolchildren in southern Ethiopia. *PLoS Negl Trop Dis.* 2017;11:e0005808.
157. Wiese S, Elson L, Feldmeier H. Tungiasis-related life quality impairment in children living in rural Kenya. *PLoS Negl Trop Dis.* 2018;12:e0005939.
158. Vasievich MP, Villarreal JDM, Tomecki KJ. Got the travel bug? A review of common infections, infestations, bites, and stings among returning travelers. *Am J Clin Dermatol.* 2016;17:451-462.
159. Tonge B. Tetanus from chigger flea sores. *J Trop Pediatr.* 1989;35:94.
160. Pallangyo P, Nicholas P. Disseminated tungiasis in a 78-year-old woman from Tanzania: a case report. *J Med Case Rep.* 2016;10:354.
161. Veraldi S, Dassoni F, Çuka E, Nazzaro G. Two cases of imported tungiasis with severe *Staphylococcus aureus* super-infection. *Acta Derm Venereol.* 2014;94:463-464.
162. Elson L, Wright K, Swift J, Feldmeier H. Control of tungiasis in absence of a roadmap: grassroots and global approaches. *Trop Med Infect Dis.* 2017;2:1-13.
163. Thielecke M, Rahamimanga V, Rogier C, Stauss-Grabo M, Richard V, Feldmeier H. Prevention of tungiasis and tungiasis-associated morbidity using the plant-based repellent Zanzarin: a randomized, controlled field study in rural Madagascar. *PLoS Negl Trop Dis.* 2013;7:e2426.
164. Buckendahl J, Heukelbach J, Ariza L, Kehr JD, Seidenschwang M, Feldmeier H. Control of tungiasis through intermittent application of a plant-based repellent: an intervention study in a resource-poor community in Brazil. *PLoS Negl Trop Dis.* 2010;4:e879.
165. Thielecke M, Nordin P, Ngomi N, Feldmeier H. Treatment of tungiasis with dimeticone: a proof-of-principle study in rural Kenya. *PLoS Negl Trop Dis.* 2014;8:e3058.
166. Nordin P, Thielecke M, Ngomi N, Mudanga GM, Krantz I, Feldmeier H. Treatment of tungiasis with a two-component dimeticone: a comparison between moistening the whole foot and directly targeting the embedded sand fleas. *Trop Med Health.* 2017;45:1-7.
167. Heukelbach J, Franck S, Feldmeier H. Therapy of tungiasis: a double-blinded randomized controlled trial with oral ivermectin. *Mem Inst Oswaldo Cruz.* 2004;99:873-876.
168. Leung A, Woo T, Robson W, Trotter M. A tourist with tungiasis. *CMAJ.* 2007;177:343-344.
169. Heukelbach J, Wilcke T, Eisele M, Feldmeier H. Ectopic localization of tungiasis. *Am J Trop Med Hyg.* 2002;67:214-216.
170. Ariza L, Wilcke T, Jackson A, et al. A simple method for rapid community assessment of tungiasis. *Trop Med Int Health.* 2010;15:856-864.
171. Kimani B, Nyagero J, Ikamari L. Knowledge, attitude and practices on jigger infestation among household members aged 18 to 60 years: case study of a rural location in Kenya. *Pan Afr Med J.* 2012;13(suppl 1):1-5.
172. Tomczyk S, Deribe K, Brooker SJ, Clark H, Rafique K, Davey G. Association between footwear use and neglected tropical diseases: a systematic review and meta-analysis. *PLoS Negl Trop Dis.* 2014;8:e3285.
173. Joseph JK, Bazile J, Mutter J, et al. Tungiasis in rural Haiti: a community-based response. *Trans R Soc Trop Med Hyg.* 2006;100:970-974.
174. Jenkins N, Ferguson D, Alp N, Harrison T, Bowler I. Urban trench fever presenting as culture-negative endocarditis. *QJM.* 2009;102:63-65.
175. Pitman N, Hernandez A, Hernandez E. Comparison of pediculicidal and ovicidal effects of two pyrethrin-piperonyl-butoxide agents. *Clin Ther.* 1987;9:368-372.
176. Taplin D, Meinking T, Castillero P, Sanchez R. Permethrin 1% creme rinse for the treatment of *Pediculus humanus* var *capitis* infestation. *Pediatr Dermatol.* 1986;3:344-348.
177. Stichele RHV, Dezeure EM, Bogaert MG. Systematic review of clinical efficacy of topical treatments for head lice. *BMJ.* 1995;311:604-608.
178. Burgess IF, Brown CM, Lee PN. Treatment of head louse infestation with 4% dimeticone lotion: randomised controlled equivalence trial. *BMJ.* 2005;330:1423-1425.
179. Heukelbach J, Sonnberg S, Becher H, Melo I, Speare R, Oliveira FA. Ovicidal efficacy of high concentration dimeticone: a new era of head lice treatment. *J Am Acad Dermatol.* 2011;64(4):e61-e62.
180. Taplin D, Castillero PM, Spiegel J, Mercer S, Rivera AA, Schachner L. Malathion for treatment of *Pediculus humanus* var *capitis* infestation. *JAMA.* 1982;247:3103-3105.
181. Meinking TL, Vicaria M, Eyerdam DH, Villar ME, Reyna S, Suarez G. A randomized, investigator-blinded, time-ranging study of the comparative efficacy of 0.5% malathion gel versus Ovide Lotion (0.5% malathion) or Nix Creme Rinse (1% permethrin) used as labeled, for the treatment of head lice. *Pediatr Dermatol.* 2007;24:405-411.
182. Meinking TL, Villar ME, Vicaria M, et al. The clinical trials supporting benzyl alcohol lotion 5% (Ulesfia TM): a safe and effective topical treatment for head lice (*Pediculus humanus capitis*). *Pediatr Dermatol.* 2010;27:19-24.
183. Popescu C, Popescu R. Efficacy and safety of spinosad cream rinse for head lice. *Arch Dermatol.* 2012;148:1070.
184. Pariser D, Meinking T, Bell M, Ryan W. Topical 0.5% ivermectin lotion for treatment of head lice. *N Engl J Med.* 2012;367:1687-1693.
185. Bowles VM, VanLuvanee LJ, Alsop H, et al. Clinical studies evaluating abametapir lotion, 0.74%, for the treatment of head louse infestation. *Pediatr Dermatol.* 2018;35:616-621.
186. Gonzalez Audino P, Vassena C, Zerba E, Picollo M. Effectiveness of lotions based on essential oils from aromatic plants against permethrin resistant *Pediculus humanus capitis*. *Arch Dermatol Res.* 2007;299:389-392.
187. Gonzalez-Audino P, Picollo MI, Gallardo A, Toloza A, Vassena C, Mougabure-Cueto G. Comparative toxicity of oxygenated monoterpenoids in experimental hydroalcoholic

- lotions to permethrin-resistant adult head lice. *Arch Dermatol Res.* 2011;303:361-366.
188. Gutiérrez MM, Werdin-González JO, Stefanazzi N, Bras C, Ferrero AA. The potential application of plant essential oils to control *Pediculus humanus capitis* (Anoplura: Pediculidae). *Parasitol Res.* 2016;115:633-641.
189. Louis SJ, Bronsnick T, Louis FJ, Rao B. Tungiasis in haiti: a case series of 383 patients. *Int J Dermatol.* 2014;53:999-1004.

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| 2. d | 5. d |
| 3. d | 6. b |



Retiform purpura: A diagnostic approach

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Learning objectives

After completing this learning activity, participants should be able to categorize retiform purpura into distinct subgroups; delineate the differential diagnosis; and suggest appropriate workup.

Disclosures

Editors

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Retiform purpura is a specific morphology within the spectrum of reticulate eruptions of vascular origin. It develops when blood vessels serving the skin are compromised resulting in downstream cutaneous ischemia, purpura, and necrosis. Identifying retiform purpura is important particularly in the acutely ill patient. It may elucidate the underlying diagnosis, provide prognostic information, and suggest a treatment approach. The differential diagnosis of retiform purpura is vast, reflecting the myriad conditions that can lead to cutaneous vessel wall damage or lumen occlusion. In this article, we give an overview of the differential diagnosis of this cutaneous morphology, provide an approach to workup, and highlight updates in treatment of some of the more common conditions that manifest as retiform purpura.
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Key words: emboli; infection; purpura; retiform purpura; vasculitis; vasculopathy.

Retiform purpura is a specific morphology within the spectrum of reticulate eruptions of vascular origin. This morphology develops when blood vessels serving the skin are compromised, resulting in downstream cutaneous ischemia, purpura, and necrosis. Blood vessel compromise

Abbreviations used:

DIC: disseminated intravascular coagulation
 HUS: hemolytic uremic syndrome
 TTP: thrombotic thrombocytopenic purpura



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occurs by 1 of 2 mechanisms: vessel wall damage (vasculitis/depositional disease/angioinvasion by organism) or vessel lumen occlusion (thrombotic or embolic disease). Understanding the mechanisms that lead to retiform purpura helps inform the differential diagnosis.¹⁻³

Recognition of retiform purpura is paramount, especially in acute or severely ill patients, because it may elucidate the underlying diagnosis, provide prognostic information, and suggest a treatment approach. The differential diagnosis of retiform purpura is vast, reflecting the myriad conditions that can lead to cutaneous vessel wall damage or lumen occlusion. For example, a patient with bacterial sepsis may develop direct bacterial angioinvasion, reactive leukocytoclastic vasculitis, bacterial vaso-occlusive emboli, and/or disseminated intravascular coagulation, all of which can present with retiform purpura, although each through a distinct mechanism. Here, we provide an overview of the differential diagnosis of this cutaneous morphology, describe an approach to workup, and highlight updates in the treatment of some of the more common conditions that manifest as retiform purpura.

We suggest the following clinical approach to patients with retiform purpura:

1. What is the morphology of the lesion?
2. What is the status of the patient?
3. What is the location of the lesion?
4. What is the patient's past medical and family history?
5. Are there any pertinent positive signs on the review of systems?
6. Are there any additional relevant physical examination findings?

This 6-step approach is designed to guide the clinician toward a narrowed differential diagnosis based on patient history and physical examination. However, most (if not all) patients with new-onset retiform purpura warrant a skin biopsy and laboratory workup.

STEP 1: MORPHOLOGY OF THE LESION

Key points

- **Retiform purpura refers to a distinct clinical morphology.**
- **The differential diagnosis consists of pathophysiology centered on either the vessel lumen or the vessel wall.**

First, what does retiform purpura mean from a morphologic perspective? These lesions present with a branching (reticular), nonblanching (purpuric)

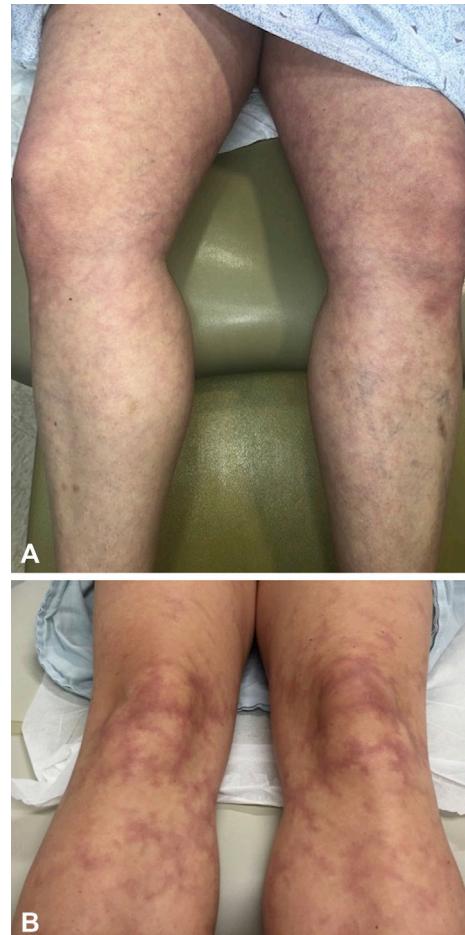


Fig 1. **A**, Livedo reticularis. Note the presence of complete rings, which are transient and often temperature related. **B**, Livedo racemosa. Note the presence of broken, irregular, fixed rings.

patch or plaque, which can occur anywhere on the body or mucous membranes.³ Lesions of retiform purpura are persistent and often accompanied by frank or impending central necrosis and/or ulceration. This contrasts with other reticulate eruptions of vascular etiology, including livedo reticularis and livedo racemosa. Livedo reticularis⁴ results from only partial or intermittent reduction of cutaneous blood flow leading to nonfixed, dusky patches forming complete rings that reflect the underlying cutaneous vasculature (Fig 1, A) Livedo racemosa, which is representative of a more irregular and significant reduction of blood flow, presents with broken rings that are persistent but rarely necrotic or ulcerative⁵ (Fig 1, B).

Unlike livedo, retiform purpura does not display the net-like pattern of rings but, instead, displays branching at the periphery and a purpuric or necrotic center. Some researchers have described it as



Fig 2. Retiform purpura in patients with (A) calciphylaxis, (B) septic vasculitis, (C) IgA vasculitis, and (D) disseminated intravascular coagulation.

river-like or *serpentine purpura*, and others note that the lesions may appear as puzzle pieces of livedo that fit together.³ Lesions may be extremely painful, reflecting the complete obstruction of blood flow to the skin with resultant ischemia and necrosis.² We have provided representative lesions of retiform purpura (Fig 2, A-D) to display the varied clinical presentation of these lesions. With experience and pattern recognition, clinicians will find that these lesions are often immediately obvious.

Fig 3 summarizes the differential diagnosis of retiform purpura. When considering this vast differential, we find that it is helpful to first consider (and then confirm with skin biopsy) whether the disease pathology is within the vessel wall or the vessel lumen. If the disease centers on the vessel wall, the differential diagnosis includes depositional diseases (such as calciphylaxis⁶), angioinvasive organisms, and vasculitides. Although palpable purpura is the classic manifestation of small-vessel vasculitis, concomitant retiform purpura indicates that a medium-vessel component is also present. Thus, purely medium-vessel vasculitides, such as polyarteritis nodosa,⁷ in addition to small and medium mixed-vessel vasculitides, such as IgA vasculitis⁸ and cryoglobulinemia,⁹ can occasionally present with retiform purpura, although this is not the most common presentation. On the other hand, if

cutaneous histology shows blockage of the vessel lumen, the differential diagnosis centers on thromboembolic processes. Occlusion of cutaneous blood vessels can occur through a wide variety of mechanisms, including hypercoagulable states (antiphospholipid syndrome,¹⁰ disseminated intravascular coagulation, genetic disorders), platelet plugging (thrombotic thrombocytopenic purpura [TTP], hemolytic uremic syndrome [HUS], heparin-induced thrombocytopenia), elevated or dysfunctional red and white blood cells (polycythemia vera, sickle cell anemia, intravascular lymphoma), temperature-related processes (cryoglobulinemia,¹¹ cryofibrinogenemia), and, finally, embolic processes (septic, cholesterol, marantic)^{3,5,12-17} (Fig 3).

In an effort to narrow this wide differential diagnosis, some researchers have recommended categorizing lesions as either inflammatory or noninflammatory retiform purpura.^{2,3} *Inflammatory retiform purpura* refers to the clinical presence of erythema around the lesion (accounting for a minimum of two thirds of the lesion) with up to one third of the lesion accounted for by central impending necrosis and suggests a vasculitic or infectious process. *Noninflammatory retiform purpura*^{2,3} refers to clinical lesions presenting with two thirds central frank or impending necrosis and up to one third surrounding erythema and

Depositional	
	Calciphylaxis Oxalosis
Infection	
	Ecthyma gangrenosum Meningococcemia Gram positive (staph/strep) Angioinvasive fungal Strongyloides "thumbprint" purpura Leprosy (Lucio phenomenon; erythema nodosum leprosum)
Vasculitis	
	IgA vasculitis ANCA vasculitides Polyarteritis nodosa Leukemic vasculitis Connective tissue disease Levamisole -induced vasculitis Cryoglobulinemia (type II/III) Septic vasculitis Drug induced vasculitis
Embolic	
	Septic emboli Fat Air Cholesterol Marantic
Thrombotic	
	Hypercoagulable state* Disseminated intravascular coagulation/purpura fulminans Warfarin necrosis Temperature related** Platelet Diathesis*** Red blood cell occlusion^ White blood cell occlusion^^

*Antiphospholipid antibody syndrome, antithrombin III deficiency, protein C/S deficiency, prothrombin III mutation, factor V Leiden, hyperhomocysteinemia
**Cryoglobulinemia (type I), cryofibrinogenemia, cold agglutinins
***Heparin induced thrombocytopenia, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, paroxysmal nocturnal hemoglobinuria, essential thrombocythemia
^Sickle cell disease, thalassemia, hereditary spherocytosis, severe malaria
^^Intravascular B-cell lymphoma

Fig 3. Differential diagnosis of retiform purpura based on pathophysiology. ANCA, Antineutrophil cytoplasmic autoantibody.

suggests an occlusive process. Although this clinical categorization can be helpful in many cases, significant overlap exists. In addition, a few select diseases, such as cryoglobulinemia, sepsis, and levamisole-associated retiform purpura, may have both vasculitic and thrombotic pathophysiologic components. Therefore, although the degree of inflammation may be suggestive, a strategized laboratory and pathologic evaluation (as detailed in subsequent sections) is necessary in all cases.

A final helpful clue when inspecting the morphology is the perceived acuity of the lesion. In a patient with multiple lesions of varying stages with atrophie blanche-like scarring of older lesions, one might surmise that the skin lesions result from a chronic, smoldering, intermittent process such as livedoid vasculopathy¹⁸ (Fig 4). In contrast, a patient with new onset of many lesions, all in a similar stage of development, may suggest a more acute, active process such as purpura fulminans (Fig 5) or a medication-induced process such as

warfarin-induced skin necrosis or heparin-induced thrombocytopenia^{2,5,19} (Fig 6).

STEP 2: PATIENT STATUS

Key points

- Acute retiform purpura in a sick patient should prompt a search for serious and reversible causes.
- It may be appropriate to send an initial battery of tests while awaiting skin biopsy results.

The next checkpoint is straightforward yet crucial. The clinician should briefly pause to consider the overall health of the patient. If, for example, the patient is severely ill, the clinician must first and foremost consider rapidly progressive, potentially fatal, and reversible causes. In many cases, this will mean proceeding with an initial battery of tests and urgent skin biopsy before moving any further in this diagnostic 6-step algorithm.



Fig 4. Livedoid vasculopathy in a 39-year-old woman with antiphospholipid syndrome.

In the emergent setting, when a patient presents with retiform purpura, fever, altered mental status, organ failure, and/or septic shock, we suggest a workup as outlined in Fig 7.²⁰⁻³⁰ Of course, the workup should be discussed and followed up with the intensivists, internists, and appropriate consultants. The dermatologist should pursue an immediate skin biopsy for H&E histology, and tissue culture and direct immunofluorescence when appropriate. In a patient with systemic infection, tissue culture from the skin may identify the offending organism and provide antimicrobial sensitivity data. Broad-spectrum antibacterial and antifungal coverage should be initiated in septic or immunocompromised patients while awaiting results. The clinician should review the patient's laboratory test results, including platelet count and coagulation studies, to evaluate evidence of disseminated intravascular coagulation (DIC). A review of medications should be rapidly undertaken to identify if the patient is taking any high-risk medications (newly started heparin or warfarin or drugs that can cause antineutrophil cytoplasmic antibody-positive vasculitis) that may need to be held or changed while the workup is underway.

STEP 3: LESION LOCATION

Key points

- Certain items on the differential diagnosis have characteristic anatomic locations.

- Disseminated retiform purpura can encompass both infectious and noninfectious causes.

The anatomic distribution of retiform purpura can guide the clinician (Fig 8). Some locations are classic, such as the free cartilage of the ear in levamisole-induced purpura^{31,32} (Fig 9) and perumbilical thumbprint purpura in disseminated strongyloides.³³

Acral retiform purpura, especially on the distal areas of the fingers and toes, should alert the clinician to a possible embolic cause or cold-associated disease. Acral lesions (retiform purpura or a purpuric digit) accompanied by a recent cardiac procedure and an elevated eosinophil count suggest cholesterol emboli³⁴ (Fig 10). Patients with acral lesions and sepsis should be examined for cutaneous findings of endocarditis, including splinter hemorrhages, Janeway lesions (nontender, small petechiae on the palms and soles), and Osler nodes (painful erythematous papules), and an echocardiogram should be considered.^{35,36} In a patient with a history of systemic lupus, noninfective (marantic) endocarditis should be ruled out.³⁷ Cryoglobulinemia (type I occlusive disease in the setting of myeloproliferative diseases and types II and III associated with cutaneous vasculitis) favors acral areas, including the ears and the nose, where body temperatures are lower.¹²

In lesions occurring predominantly on the lower extremities, vasculitides may be higher on the differential diagnosis (especially if seen in conjunction with palpable purpura). If patients present with small punched-out ulcerations and atrophie blanche (indicating chronicity) on the shins and dorsal feet, with a background of livedo, livedoid vasculopathy should be considered. In patients from Mexico and the Caribbean with lepromatous leprosy, an additional consideration would be the Lucio phenomenon.^{38,39}

Purpuric lesions occurring on fatty areas of the abdomen and thighs might suggest warfarin- or heparin-induced skin necrosis. Warfarin-induced skin necrosis classically starts within the first 10 days of warfarin initiation (most often on days 3-5), when protein C levels drop to the nadir, and it often occurs on the abdomen, thighs, buttocks, and breasts.⁵

Ecthyma gangrenosum⁴⁰ and meningococcemia^{5,41} may present with acute disseminated lesions. In the setting of acute widespread purpura without an infectious source, catastrophic anti-phospholipid syndrome, purpura fulminans, and calciphylaxis⁴² (uremic or nonuremic) should be considered.



Fig 5. A-D, Purpura fulminans presenting in patients admitted to the intensive care unit.



Fig 6. Heparin-induced thrombocytopenia-induced retiform purpura.

STEP 4: MEDICAL AND FAMILY HISTORY

Key points

- Next, collect relevant medical and family history.
- Use previous clues for guidance.

For all patients with retiform purpura, we suggest thinking through the following set of general medical and family history questions, which should be specifically tailored to the location and acuity of the lesions:

1. Does the patient have any relevant personal or family history?
 - a. End-stage renal disease is associated with calciphylaxis.⁹

- b. Connective tissue disease can be associated with antiphospholipid syndrome. Additionally, small and medium vasculitis can be seen in the setting of Sjögren syndrome and rheumatoid arthritis. Mixed cryoglobulinemia can be seen in the setting of rheumatoid arthritis and lupus.⁴³
 - c. Previous history of cerebrovascular accident or spontaneous abortion may be indicative of antiphospholipid syndrome.⁴⁴
 - d. History of severe asthma or nasal polyposis as can be seen in eosinophilic granulomatosis with polyangiitis.^{45,46} Ear, nose, and airway manifestations are also commonly presenting symptoms in polyangiitis with granulomatosis.⁴⁷
 - e. Hepatitis is associated with cryoglobulinemia type II and III^{5,43} and polyarteritis nodosa.⁵
 - f. If there is a history of malignancy, IgA (and/or leukemic vasculitis) should be considered.⁴⁸⁻⁵⁴
 - g. History of hereditary hemoglobinopathies such as sickle cell disease, thalassemia, and spherocytosis must be asked about.
 - h. A family history of myeloproliferative disorders would highlight a tendency toward a hematologic disease that may present with cryoglobulinemia.⁵⁵
2. Does the patient have any recent or active infections?
 - a. Disseminated intravascular coagulation and purpura fulminans can occur in the setting

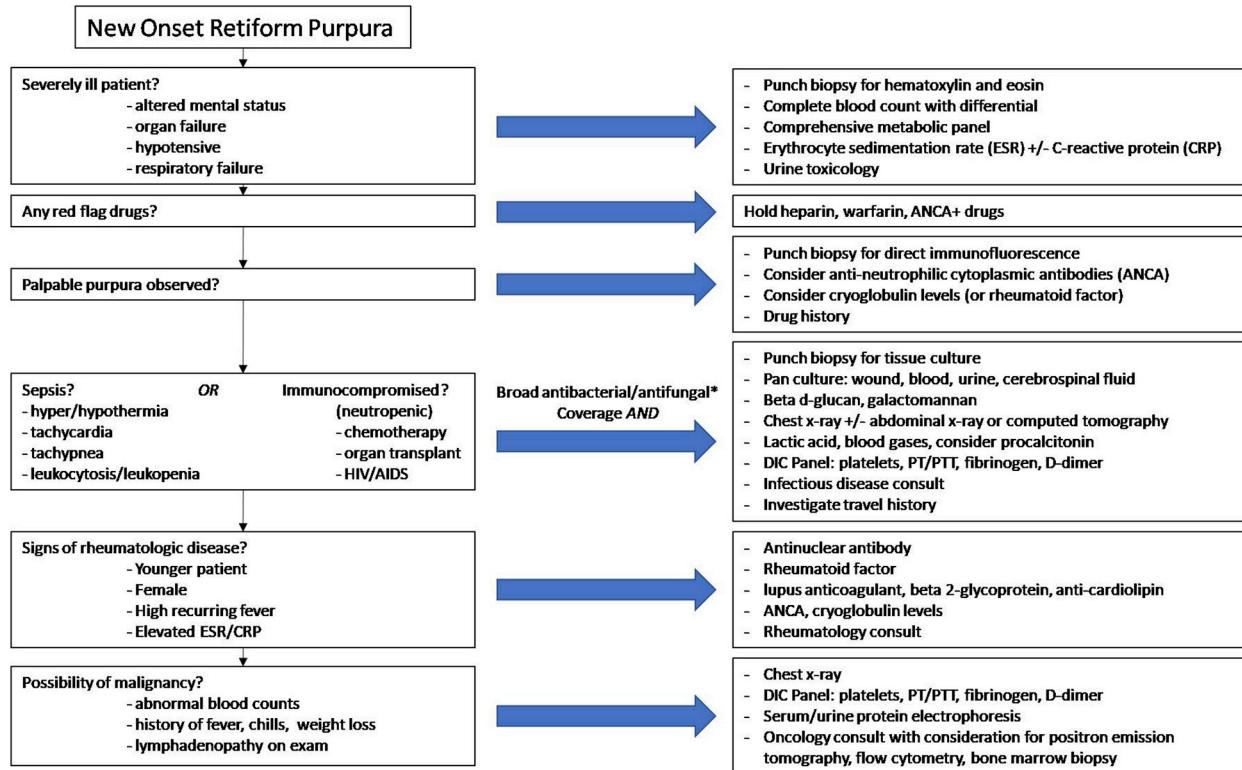


Fig 7. Workup for retiform purpura in the acutely ill patient. DIC, Disseminated intravascular coagulation; PT, prothrombin time; PTT, partial thromboplastin time.

- of various infections, especially encapsulated Gram-positive bacteria.^{25,56}
- Ecthyma gangrenosum is associated with Gram-negative sepsis.
 - Hemolytic uremic syndrome has been associated with Shiga toxin-producing *Escherichia coli*, pneumococcus, and influenza, among others.⁵⁷
 - Cold agglutinins are associated with infections, most commonly *Mycoplasma pneumoniae*.⁵⁸
 - Cutaneous polyarteritis nodosa is commonly associated with streptococcal infection.^{5,10}
 - Streptococcal and upper respiratory viral infections are associated with IgA vasculitis (Henoch-Schönlein purpura).⁵⁹
 - Angioinvasive fungal infections typically present in severely immunocompromised patients with signs of infection but who are not responding to broad antibiotic coverage.
3. Has the patient started any new medications or had exposure to illicit drugs?
- Warfarin-induced necrosis and heparin-induced thrombocytopenia most often occur within the first 3 to 5 and 7 to 10 days of initiation, respectively.⁵

- Certain medications, most commonly tumor necrosis factor inhibitors, propylthiouracil, hydralazine, minocycline, rituximab, and statins, among many others, have been implicated in drug-induced vasculitis.⁶⁰
 - Levamisole-contaminated cocaine is classically associated with retiform purpura of the ears and acral areas.^{31,32}
4. Has the patient undergone recent instrumentation?
- Embolization, most notably cholesterol emboli, is commonly associated with cardiac procedures.³⁴

STEP 5: REVIEW OF SYSTEMS

Key points

- The review of systems should be tailored toward the patient.
- Cutaneous vasculitis necessitates a search for systemic involvement.

A comprehensive review of systems for the patient presenting with retiform purpura can be found in Table I.^{2,3,5,15-17,19,43,61-66} However, it must be emphasized that the review of systems can

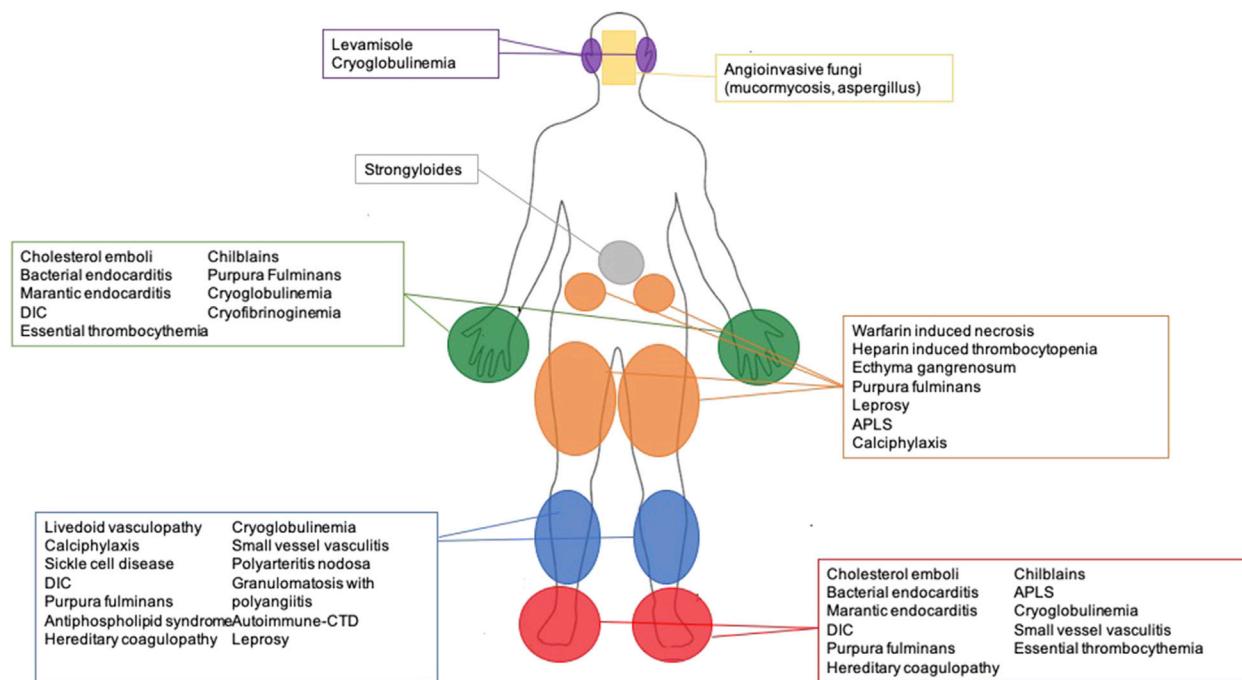


Fig 8. Anatomic distribution of common causes of retiform purpura. *APLS*, Antiphospholipid antibody syndrome; *CTD*, connective tissue disease; *DIC*, disseminated intravascular coagulation.



Fig 9. Levamisole-induced retiform purpura. (Photograph courtesy of Christine Ahn, MD).

(and should) be focused on entities highest on the differential diagnosis. For example, for patients with retiform purpura and deep vein thrombosis, clinicians should ask about pulmonary symptoms, given concern for pulmonary embolism. In patients from endemic areas, clinicians should consider

Strongyloides and ask about malaise, fatigue, and pulmonary or gastrointestinal symptoms. In the patient with streptococcal infection, clinicians should ask about abdominal pain, joint pain, and change in urine color.

Finally, whenever vasculitis is suspected, systemic involvement must be ruled out with the review of systems, in addition to the physical examination and laboratory workup. Systems affected by the various vasculitides include: neurologic (cerebrovascular accident, mononeuritis multiplex), ocular, head and neck (epistaxis, sinusitis), pulmonary (hemoptysis or chest pain), cardiac (chest pain), abdominal (pain, diarrhea, melena), musculoskeletal (arthralgia), and renal (change in urine color).^{2,7,17,43,62}

STEP 6: ASSOCIATED PHYSICAL EXAMINATION FINDINGS

Key points

- Thorough physical examination is requisite in patients with retiform purpura.
- Full skin examination is important because obscured areas can have diagnostic clues.

As outlined, previous steps in this diagnostic algorithm involve assessing lesion morphology, degree of inflammation, and location. A full physical examination is also essential to fully evaluate

Table I. Complete retiform purpura review of systems

System	Symptom	Associations
General	Fatigue	Connective tissue disease, leukemia/lymphoma, chronic infections (hepatitis, malaria, parasitic), endocarditis, anemia (sickle cell, paroxysmal nocturnal hemoglobinuria)
	Weight changes	Malignancy, chronic infections
	Fever	Connective tissue disease, leukemia/lymphoma, acute infection (bacterial, fungal), chronic infections (hepatitis, malaria, parasitic), endocarditis, ANCA vasculitis
Ocular	Conjunctival hemorrhage (red eye)	Hemoglobinopathies, TTP, HUS, DIC, connective tissue disease
	Vision change	Vasculitis (ANCA, leukemic, septic, cryoglobulinemia), infection (mucormycosis)
Ear	Hearing change, tinnitus	Vasculitis (ANCA, leukemic, septic, cryoglobulinemia)
Nose	Epistaxis	Vasculitis (polyangiitis with granulomatosis), thrombocytopenia (TTP, HUS, DIC)
Mouth	Sinusitis	Eosinophilic granulomatosis with polyangiitis
	Xerostomia	Sjögren syndrome, connective tissue disease
	Recurrent ulcers	Connective tissue disease
Neurologic	Headache	Connective tissue disease (lupus), infection (meningococcemia, angioinvasive fungi), vasculitis, cryoglobulinemia
	Altered mental status	Infection (sepsis), TTP
	Numbness, loss of sensation	Vasculitis (ANCA, polyarteritis nodosa), leprosy, cerebrovascular accident (antiphospholipid syndrome)
	Loss of motor function	Vasculitis (ANCA, polyarteritis nodosa), leprosy, cerebrovascular accident (antiphospholipid syndrome)
	Seizure	Connective tissue disease (lupus)
Respiratory	Chest pain	Connective tissue disease (pleuritis), hypercoagulative state (embolus)
	Shortness of breath	Connective tissue disease (pulmonary hypertension, interstitial lung disease), hypercoagulative state (embolus), infection (endocarditis, pneumonia)
Cardiovascular	Hemoptysis	Infection (pneumonia), vasculitis (granulomatosis with polyangiitis)
	Chest pain	Connective tissue disease (carditis), cardiomyopathy (eosinophilic granulomatosis with polyangiitis)
	Edema	Renal disease (calciphylaxis), liver disease (cryoglobulinemia, IgA vasculitis), deep venous thrombosis (hypercoagulative state, antiphospholipid syndrome)
Gastrointestinal	Calf pain	Deep venous thrombosis (hypercoagulative state, antiphospholipid syndrome)
	Pain	Vasculitis (IgA, cryoglobulinemia, leukemic), bowel infarction (hypercoagulable state, embolus, DIC), malignant atrophic papulosis
	Melena	Vasculitis (IgA, cryoglobulinemia, leukemic)
	Appetite change	Lymphoma (leukemic vasculitis, cryoglobulinemia, intravascular lymphoma), malignancy (IgA vasculitis), parasite (<i>Strongyloides</i>)
Genitourinary	Jaundice/kernicterus	Liver disease (cryoglobulinemia, IgA vasculitis)
	Change in color	Vasculitis (IgA, ANCA, cryoglobulinemia), connective tissue disease (lupus, systemic sclerosis), paroxysmal nocturnal hemoglobinuria
Musculoskeletal	Dysuria	Infection (urosepsis)
	Proximal weakness	Connective tissue disease (dermatomyositis)
	Arthralgia	Connective tissue disease (lupus, mixed connective tissue disease), cryoglobulinemia
Hematologic	Ease of bruising	Lymphoma (leukemic vasculitis, cryoglobulinemia, intravascular lymphoma), liver disease (cryoglobulinemia, IgA vasculitis), thrombocytopenia (TTP, HUS, DIC, HIT)
	Ease of bleeding	Thrombocytopenia (TTP, HUS, DIC, HIT)

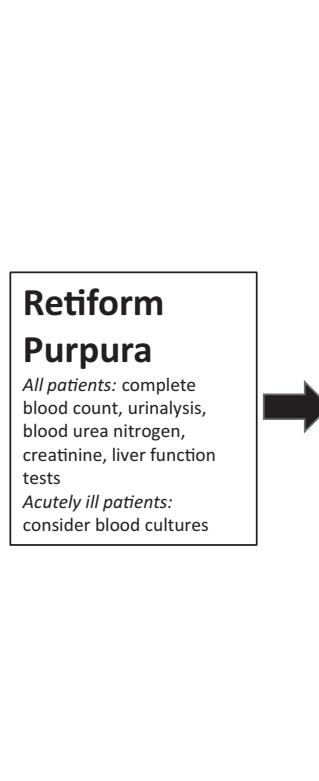
ANCA, Antineutrophil cytoplasmic autoantibody; DIC, disseminated intravascular coagulation; HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura.



Fig 10. Retiform purpura in the setting of cholesterol emboli following cardiac catheterization.



Fig 11. The bullseye infarct purpuric lesions of mucormycosis. **A** and **B**, A 6-year-old with acute lymphoblastic leukemia presented with retiform purpura next to an intravenous puncture site that evolved into a non-retiform purpuric plaque. **C** and **D**, A 52-year-old in septic shock presents with a purpuric patch under a chest lead. Although not retiform in this photograph, systemic fungal infections can sometimes present with retiform lesions that quickly evolve into different morphologies.



Depositional		Labs to Consider
	Calciophylaxis Oxalosis	Calcium, phosphate, parathyroid hormone, serum/urine oxalates
Infection		
	Ecthyma gangrenosum Meningococcemia Gram positive (staph/strep) Angioinvasive fungal Strongyloides "thumbprint" purpura Leprosy (Lucio phenomenon; erythema nodosum leprosum)	Anti-treptolysin, DNase B, procalcitonin, beta-d glucan, galactomannan, stool ova and parasite, strongyloides IgM and IgG, blood culture For patients with strongyloides antibodies: consider immunosuppression (untreated HIV, etc.)
Vasculitis		
	IgA vasculitis ANCA vasculidites Polyarteritis nodosa Leukemic vasculitis Connective tissue disease Levamisole-induced vasculitis Cryoglobulinemia (type II/III) Septic vasculitis Drug induced vasculitis	Antinuclear antibody (+/- double stranded DNA, complement 3/4, total complement (CH50), anti-Ro, anti-La, anti-Smith, erythrocyte sedimentation rate, complement related protein anti-topoisomerase I, anti-histone antibody), anti-neutrophil cytoplasmic antibody, cryoglobulins, cryofibrinogens, cold agglutinins, Anti-streptolysin, DNase B, tuberculosis testing (quantiferon gold), hepatitis B and C panel, urine toxicology, stool guaiac if abdominal involvement suspected, serum/urine protein electrophoresis (or immunofixation electrophoresis)
Embolic		
	Septic emboli Fat Air Cholesterol Marantic	Complete blood counts with eosinophil differential (+/- urine eosinophils) for suspected cholesterol emboli
Thrombotic		
	Hypercoagulable state* Disseminated intravascular coagulation Warfarin necrosis Temperature related** Platelet Diathesis*** Red blood cell occlusion^	Complete blood counts with differential, lactic acid, prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, D-dimer, protein C, protein S, lupus anticoagulant, anticardiolipin, antiphosphatidylserine, apolipoprotein, lipoprotein(a), factor V Leiden, plasminogen activator/inhibitor, antithrombin III level, prothrombin G20210A mutation, homocysteine levels, Factor VIII, ADAMTS13, HIT PF4 antibody, cryoglobulin levels, hemolytic anemia workup^^*, CD55/59 flow cytometry for paroxysmal nocturnal hemoglobinuria,

*Antiphospholipid antibody syndrome, antithrombin III deficiency, protein C/S deficiency, prothrombin III mutation, factor V Leiden, hyperhomocysteinemia

**Cryoglobulinemia (type I), cryofibrinogenemia, cold agglutinins

***Heparin induced thrombocytopenia, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, paroxysmal nocturnal hemoglobinuria, essential thrombocythemia

^Sickle cell disease, thalassemia, hereditary spherocytosis, severe malaria

^^Intravascular B-cell lymphoma

^^^Hemoglobin, lactate dehydrogenase, bilirubin, haptoglobin, and reticulocyte counts

Fig 12. Retiform purpura laboratory evaluation. ANCA, Antineutrophil cytoplasmic autoantibody.

patients who present with retiform purpura. The heart and lung examination, as performed by the intensivist, should be reviewed for associated findings (the murmur of bacterial endocarditis, friction rub of pericarditis, rales of interstitial lung disease, etc). A musculoskeletal examination should be performed. Muscle strength should be assessed with an emphasis on the pelvic and shoulder girdles. Careful palpation for lymphadenopathy should be performed.⁶⁷⁻⁶⁹

The final step in the diagnostic algorithm is a complete and thorough skin examination. A myriad of cutaneous examination findings can give support to the suspected diagnosis.

Going (anatomically) from top to bottom, the physician should start with the scalp, looking for any sign of scarring alopecia, which may be associated with connective tissue disease. The conchal bowls can be examined for signs of chronic cutaneous lupus. All mucous membranes should be inspected. Conjunctival hemorrhage can be suggestive of a platelet diathesis or disseminated intravascular coagulation.⁷⁰ The nares deserve inspection because nasal polyps and angioinvasive fungi (mucormycosis) can be obvious without endoscopy. The oral mucosa should be carefully examined for signs of ulceration, purpura, or xerostomia.

Additionally, the clinician can look for the strawberry gingivitis of polyangiitis with granulomatosis.⁷¹⁻⁷⁴

The dermatologist should perform a full skin examination of the trunk, extremities, and genitals. The patient should be repositioned when necessary to observe obscured areas. No area should be neglected; areas under chest leads, adhesives, and surrounding intravenous line sites must be examined because diagnostic lesions may otherwise remain concealed (Fig 11). These are also potential sites of inoculation of invasive fungal organisms in immunosuppressed hospitalized patients.

Finally, the nails deserve close inspection. Koilonychia, or spoon nails, can be observed in anemia that is associated with malignancy, autoimmune disorders, or other chronic disease.⁷⁵ Lindsay's nails, or half and half nails, may be associated with chronic renal disease.⁷⁶ Terry's nails are associated with cirrhosis, as can be seen in hepatitis C.⁷⁷ Muehrcke's nails, which present as parallel lines of blanchable leukonychia (pathology of the nail bed), are associated with low protein states, such as nephrotic syndrome or liver disease.⁷⁸ The proximal nailfold should be inspected for the presence of vascular dropout, meandering and dilated vessels, or frayed cuticles (Samitz sign⁷⁹), which can signify the presence of autoimmune

connective tissue disease.⁸⁰⁻⁸² Finally, in immunocompromised patients, nails should be inspected for inflammation and subungual discoloration because fusarium and other angioinvasive organisms can disseminate from a primary cutaneous paronychia or onychomycosis.^{83,84}

COMPLETING THE WORKUP

Key points

- **Biopsy location should be selected to maximize the probability of capturing representative pathology.**
- **Laboratory evaluation will vary and is dependent on previous steps detailed in the diagnostic algorithm.**

Now the clinician is prepared to complete the diagnostic workup by performing a biopsy for H&E histology (plus tissue culture and/or direct immunofluorescence as deemed appropriate) and collecting laboratory data.

The biopsy specimen should be collected at the peripheral purpuric rim of the lesion. When hemorrhagic bullae are present, as is often the case in bacterial and fungal sepsis, fluid can be obtained for bacterial culture, and the blister roof should be scraped for potassium hydroxide examination. In other cases, biopsy specimens can be smeared on a glass slide for touch preparation, as described by other researchers.⁸⁵ Finally, in patients with suspected infection, the clinician should consider obtaining a second biopsy specimen from the necrotic center for tissue culture.⁸⁶

The differential diagnosis of retiform purpura informs the laboratory evaluation. The extent and timing of the laboratory workup will vary depending on the acuity of the skin manifestations, the overall health of the patient, and any relevant history and physical examination findings that may narrow the differential diagnosis. If the patient is severely or acutely ill, it may be reasonable to send many tests immediately to try to narrow the differential diagnosis while biopsy results are pending. If skin lesions are more chronic and/or stable, it may be preferable to wait for biopsy results, confirm if the pathology is in the vessel wall or lumen, and then work through the evaluation based on a narrowed differential diagnosis. Retiform purpura laboratory evaluation is detailed in Fig 12.^{3,5,15-17,19,22,27,34,43,62,63,87}

Prompt treatment should follow. Part II of this Continuing Medical Education series will detail these steps in relation to 4 of the most common causes of retiform purpura.

REFERENCES

1. Parsi K, Partsch H, Rabe E, Ramelet AA. Reticulate eruptions: part 2. Historical perspectives, morphology, terminology and classification. *Australas J Dermatol.* 2011;52(4):237-244.
2. Piette WW. The differential diagnosis of purpura from a morphologic perspective. *Adv Dermatol.* 1994;9:3-23.
3. Li JY, Ivan D, Patel AB. Acral retiform purpura. *Lancet.* 2017; 390:2382.
4. Sajjan VV, Lunge S, Swamy MB, Pandit AM. Livedo reticularis: a review of the literature. *Indian Dermatol Online J.* 2015;6(5): 315-321.
5. Wysong A, Venkatesan P. An approach to the patient with retiform purpura. *Dermatol Ther.* 2011;24(2):151-172.
6. García-Lozano JA, Ocampo-Candiani J, Martínez-Cabriales SA, Garza-Rodríguez V. An update on calciphylaxis. *Am J Clin Dermatol.* 2018;19(4):599-608.
7. Díaz-Pérez JL, De Lagrán ZM, Díaz-Ramón JL, Winkelmann RK. Cutaneous polyarteritis nodosa. *Semin Cutan Med Surg.* 2007; 26(2):77-86.
8. Piette WW, Stone MS. A cutaneous sign of IgA-associated small dermal vessel leukocytoclastic vasculitis in adults (Henoch-Schönlein purpura). *Arch Dermatol.* 1989;125(1):53-56.
9. Roccatello D, Saadoun D, Ramos-Casals M, et al. Cryoglobulinemia. *Nat Rev Dis Primers.* 2018;4(1):11.
10. Cervera R, Tektonidou MG, Espinosa G, et al. Task Force on Catastrophic Antiphospholipid Syndrome (APS) and Non-criteria APS Manifestations (II): thrombocytopenia and skin manifestations. *Lupus.* 2011;20(2):174-181.
11. Payet J, Livartowski J, Kavian N, et al. Type I cryoglobulinemia in multiple myeloma, a rare entity: analysis of clinical and biological characteristics of seven cases and review of the literature. *Leuk Lymphoma.* 2013;54(4):767-777.
12. Martinez-Mera C, Fraga J, Capusan TM, et al. Vasculopathies, cutaneous necrosis and emergency in dermatology. *G Ital Dermatol Venereol.* 2017;152(6):615-637.
13. Gru AA, Salavaggione AL. Vasculopathic and vasculitic dermatoses. *Semin Diagn Pathol.* 2017;34(3):285-300.
14. Pickett A. An approach to vasculitis and vasculopathy. *Cutis.* 2012;89(5):E1-E3.
15. Prendecki M, Pusey CD. Recent advances in understanding of the pathogenesis of ANCA-associated vasculitis. *F1000Res.* 2018;19:7.
16. Frumholtz L, Laurent-Roussel S, Aumaître O, et al. French Vasculitis Study Group. Clinical and pathological significance of cutaneous manifestations in ANCA-associated vasculitides. *Autoimmun Rev.* 2017;16(11):1138-1146.
17. Chen KR. Skin involvement in ANCA-associated vasculitis. *Clin Exp Nephrol.* 2013;17(5):676-682.
18. Alavi A, Hafner J, Dutz JP, et al. Livedoid vasculopathy: an in-depth analysis using a modified Delphi approach. *J Am Acad Dermatol.* 2013;69(6):1033-1042.e1.
19. Chen KR, Carlson JA. Clinical approach to cutaneous vasculitis. *Am J Clin Dermatol.* 2008;9(2):71-92.
20. Fan SL, Miller NS, Lee J, Remick DG. Diagnosing sepsis—the role of laboratory medicine. *Clin Chim Acta.* 2016;460:203-210.
21. Coelho FR, Martins JO. Diagnostic methods in sepsis: the need of speed. *Rev Assoc Med Bras (1992).* 2012;58(4):498-504.
22. Cunha BA, Lortholary O, Cunha CB. Fever of unknown origin: a clinical approach. *Am J Med.* 2015;128(10):1138.e1-1138.e15.
23. Bland CM, Sutton SS, Dunn BL. What are the latest recommendations for managing severe sepsis and septic shock? *JAAPA.* 2014;27(10):15-19.
24. Efthathiou SP, Pefanis AV, Tsakou AG, et al. Fever of unknown origin: discrimination between infectious and non-infectious causes. *Eur J Intern Med.* 2010;21:137-143.

25. Cunha BA. Fever of unknown origin: clinical overview of classic and current concepts. *Infect Dis Clin North Am.* 2007;21:867-915.
26. Cunha BA. Fever of unknown origin: focused diagnostic approach based on clinical clues from the history, physical examination and laboratory tests. *Infect Dis Clin North Am.* 2007;21:1137-1188.
27. Zenone T. Fever of unknown origin in rheumatic diseases. *Infect Dis Clin North Am.* 2007;21:1115-1136.
28. White L, Ybarra M. Neutropenic fever. *Emerg Med Clin North Am.* 2014;32(3):549-561.
29. Mulders-Manders CM, Simon A, Bleeker-Rovers CP. Rheumatologic diseases as the cause of fever of unknown origin. *Best Pract Res Clin Rheumatol.* 2016;30(5):789-801.
30. Dibble EH, Yoo DC, Noto RB. Role of PET/CT in workup of fever without a source. *Radiographics.* 2016;36(4):1166-1177.
31. Dartevet A, Chaigne B, Moachon L, et al. Levamisole-induced vasculopathy: a systematic review. *Semin Arthritis Rheum.* 2019;48(5):921-926.
32. Roberts JA, Chévez-Barrios P. Levamisole-induced vasculitis: a characteristic cutaneous vasculitis associated with levamisole-adulterated cocaine. *Arch Pathol Lab Med.* 2015;139(8):1058-1061.
33. Weiser JA, Scully BE, Bulman WA, Husain S, Grossman ME. Periumbilical parasitic thumbprint purpura: *Strongyloides* hyperinfection syndrome acquired from a cadaveric renal transplant. *Transpl Infect Dis.* 2011;13(1):58-62.
34. Saric M, Kronzon I. Cholesterol embolization syndrome. *Curr Opin Cardiol.* 2011;26(6):472-479.
35. Servy A, Valeyrue-Allanore L, Alla F, et al. Prognostic value of skin manifestations of infective endocarditis. *JAMA Dermatol.* 2014;150(5):494-500.
36. Long B, Koyfman A. Infectious endocarditis: an update for emergency clinicians. *Am J Emerg Med.* 2018;36(9):1686-1692.
37. Liu J, Frishman WH. Nonbacterial thrombotic endocarditis: pathogenesis, diagnosis, and management. *Cardiol Rev.* 2016;24(5):244-247.
38. Kamath S, Vaccaro SA, Rea TH, Ochoa MT. Recognizing and managing the immunologic reactions in leprosy. *J Am Acad Dermatol.* 2014;71(4):795-803.
39. Pai VV, Athanikar S, Naveen KN, Sori T, Rao R. Lucio phenomenon. *Cutis.* 2014;93(2):E12-E14.
40. Vaiman M, Lazarovitch T, Heller L, Lotan G. Ecthyma gangrenosum and ecthyma-like lesions: review article. *Eur J Clin Microbiol Infect Dis.* 2015;34(4):633-639.
41. Ramos-e-Silva M, Pereira AL. Life-threatening eruptions due to infectious agents. *Clin Dermatol.* 2005;23(2):148-156.
42. Nigwekar SU, Kroshinsky D, Nazarian RM, et al. Calciphylaxis: risk factors, diagnosis, and treatment. *Am J Kidney Dis.* 2015;66(1):133-146.
43. Carlson JA, Cavaliere LF, Grant-Kels JM. Cutaneous vasculitis: diagnosis and management. *Clin Dermatol.* 2006;24(5):414-429.
44. Gómez-Puerta JA, Cervera R. Diagnosis and classification of the antiphospholipid syndrome. *J Autoimmun.* 2014;48-49:20-25.
45. Mounthor L, Dunogue B, Guillemin L. Diagnosis and classification of eosinophilic granulomatosis with polyangiitis (formerly named Churg-Strauss syndrome). *J Autoimmun.* 2014;48-49:99-103.
46. Bacciu A, Buzio C, Giordano D, et al. Nasal polyposis in Churg-Strauss syndrome. *Laryngoscope.* 2008;118(2):325-329.
47. Lutalo PM, D'Cruz DP. Diagnosis and classification of granulomatosis with polyangiitis (aka Wegener's granulomatosis). *J Autoimmun.* 2014;48-49:94-98.
48. Akpunonu B, Sabgir D, Panchal K, Kahaleh B. An elderly man with vasculitis and IgA myeloma. *J Eur Acad Dermatol Venereol.* 1998;10(2):186-187.
49. Sugaya M, Nakamura K, Asahina A, Tamaki K. Leukocytoclastic vasculitis with IgA deposits in angioimmunoblastic T cell lymphoma. *J Dermatol.* 2001;28(1):32-37.
50. Fox MC, Carter S, Khouri IF, et al. Adult Henoch-Schönlein purpura in a patient with myelodysplastic syndrome and a history of follicular lymphoma. *Cutis.* 2008;81(2):131-137.
51. Schena FP, Soerjadi N, Zwi J, de Zoysa JR. Lymphoma presenting as Henoch-Schönlein purpura. *Clin Kidney J.* 2012;5(6):600-602.
52. Podjasek JO, Wetter DA, Pittelkow MR, Wada DA. Henoch-Schönlein purpura associated with solid-organ malignancies: three case reports and a literature review. *Acta Derm Venereol.* 2012;92(4):388-392.
53. Mifune D, Watanabe S, Kondo R, et al. Henoch Schönlein purpura associated with pulmonary adenocarcinoma. *J Med Case Rep.* 2011;5:226.
54. Akizue N, Suzuki E, Yokoyama M, et al. Henoch-Schönlein purpura complicated by hepatocellular carcinoma. *Intern Med.* 2017;56(22):3041-3045.
55. Platto J, Alexander CE, Kurtzman DJB. A violaceous, photo-distributed cutaneous eruption and leg ulcer in a woman with essential thrombocytosis. *JAMA Dermatol.* 2018;154(1):95-96.
56. Chalmers E, Cooper P, Forman K, et al. Purpura fulminans: recognition, diagnosis and management. *Arch Dis Child.* 2011;96(11):1066-1071.
57. Fakhouri F, Zuber J, Frémeaux-Bacchi V, Loirat C. Haemolytic uraemic syndrome. *Lancet.* 2017;390(10095):681-696.
58. de Groot RCA, Meyer Sauteur PM, Unger WWJ, van Rossum AMC. Things that could be *Mycoplasma pneumoniae*. *J Infect.* 2017;74(Suppl 1):S95-S100.
59. Farhadian JA, Castilla C, Shvartsbeyn M, Meehan SA, Neimann A, Pomeranz MK. IgA vasculitis (Henoch-Schönlein purpura). *Dermatol Online J.* 2015;21(12).
60. Grau RG. Drug-induced vasculitis: new insights and a changing lineup of suspects. *Curr Rheumatol Rep.* 2015;17(12):71.
61. Micheletti RG, Werth VP. Small vessel vasculitis of the skin. *Rheum Dis Clin North Am.* 2015;41(1):21-32.
62. Goeser MR, Laniosz V, Wetter DA. A practical approach to the diagnosis, evaluation, and management of cutaneous small-vessel vasculitis. *Am J Clin Dermatol.* 2014;15(4):299-306.
63. Batu ED, Ozen S. Vasculitis: do we know more to classify better? *Pediatr Nephrol.* 2015;30(9):1425-1432.
64. Reyhan I, Goldberg BR, Gottlieb BS. Common presentations of pediatric rheumatologic diseases: a generalist's guide. *Curr Opin Pediatr.* 2013;25(3):388-396.
65. Lisnevskaya L, Murphy G, Isenberg D. Systemic lupus erythematosus. *Lancet.* 2014;384(9957):1878-1888.
66. Yu C, Gershwin ME, Chang C. Diagnostic criteria for systemic lupus erythematosus: a critical review. *J Autoimmun.* 2014;48-49:10-13.
67. Woolf AD, Akesson K. Primer: history and examination in the assessment of musculoskeletal problems. *Nat Clin Pract Rheumatol.* 2008;4(1):26-33.
68. Kunzler E, Hynan LS, Chong BF. Autoimmune diseases in patients with cutaneous lupus erythematosus. *JAMA Dermatol.* 2018;154(6):712-716.
69. Weetman AP, Walport MJ. The association of autoimmune thyroiditis with systemic lupus erythematosus. *Br J Rheumatol.* 1987;26(5):359-361.
70. Azar P, Smith RS, Greenberg MH. Ocular findings in disseminated intravascular coagulation. *Am J Ophthalmol.* 1974;78(3):493-496.

71. Wawrzycka K, Szczeklik K, Darczuk D, Lipska W, Szczeklik W, Musial J. Strawberry gingivitis as the first manifestation of granulomatosis with polyangiitis. *Pol Arch Med Wewn.* 2014; 124(10):551-552.
72. Ghiasi M. Strawberry gingivitis in granulomatosis with polyangiitis. *N Engl J Med.* 2017;377(21):2073.
73. van der Leeuw J, Flinsenberg TWH, Siezen MA. Strawberry gingivitis as a manifestation of granulomatosis with polyangiitis. *Rheumatology (Oxford).* 2018;57(2):226.
74. Kumar RR, Jha S, Sharma A. Strawberry gingivitis: a rare manifestation of granulomatosis with polyangiitis. *QJM.* 2019; 112(1):53.
75. Walker J, Baran R, Vélez N, Jellinek N. Koilonychia: an update on pathophysiology, differential diagnosis and clinical relevance. *J Eur Acad Dermatol Venereol.* 2016;30(11):1985-1991.
76. Gagnon AL, Desai T. Dermatological diseases in patients with chronic kidney disease. *J Nephropathol.* 2013;2(2):104-109.
77. Witkowska AB, Jasterbski TJ, Schwartz RA. Terry's nails: a sign of systemic disease. *Indian J Dermatol.* 2017;62(3):309-311.
78. Muerhrcke RC. The finger-nails in chronic hypoalbuminaemia; a new physical sign. *Br Med J.* 1956;1(4979):1327-1328.
79. Samitz MH. Cuticular changes in dermatomyositis. A clinical sign. *Arch Dermatol.* 1974;110(6):866-867.
80. Cortes S, Cutolo M. Capillaroscopic patterns in rheumatic diseases. *Acta Reumatol Port.* 2007;32(1):29-36.
81. Redisch W, Messina EJ, Hughes G, McEwen C. Capillaroscopic observations in rheumatic diseases. *Ann Rheum Dis.* 1970; 29(3):244-253.
82. Hasegawa M. Dermoscopy findings of nail fold capillaries in connective tissue diseases. *J Dermatol.* 2011;38(1):66-70.
83. Bourgeois GP, Cafardi JA, Sellheyer K, Andea AA. Disseminated *Fusarium* infection originating from paronychia in a neutropenic patient: a case report and review of the literature. *Cutis.* 2010;85(4):191-194.
84. Girmenia C, Arcese W, Micozzi A, Martino P, Bianco P, Morace G. Onychomycosis as a possible origin of disseminated *Fusarium solani* infection in a patient with severe aplastic anemia. *Clin Infect Dis.* 1992;14(5):1167.
85. Elston DM, Stratman EJ, Miller SJ. Skin biopsy: biopsy issues in specific diseases. *J Am Acad Dermatol.* 2016;74(1):1-16.
86. Singer HM, Reddy BY, Grossman ME. Touch preparation for the rapid diagnosis of disseminated aspergillosis. *JAAD Case Rep.* 2017;3(3):202-204.
87. Galimberti R, Torre AC, Baztán MC, Rodriguez-Chiappetta F. Emerging systemic fungal infections. *Clin Dermatol.* 2012; 30(6):633-650.



Retiform purpura: Workup and therapeutic considerations in select conditions

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Learning objectives

After completing this learning activity, participants should be able to outline treatment strategies and considerations and describe a treatment algorithm.

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In this article we focus on updates in select etiologies of retiform purpura. These causes of retiform purpura, in addition to bacterial or fungal sepsis, disseminated intravascular coagulation, purpura fulminans, and catastrophic antiphospholipid syndrome, are important diagnoses with potential for morbidity and mortality. Important aspects in the pathophysiology, patient demographics and risk factors, updates in the diagnostic workup, histopathology, and treatment of these specific conditions are discussed. (J Am Acad Dermatol 2020;82:799-816.)

Key words: ANCA; calciphylaxis; cryoglobulinemia; livedoid vasculopathy; purpura; retiform purpura; vasculitis; vasculopathy.

For part II of this continuing medical education article, we focus on updates in select etiologies of retiform purpura. These causes of retiform purpura, in addition to bacterial or fungal

sepsis, disseminated intravascular coagulation, purpura fulminans, and catastrophic antiphospholipid syndrome, are “not to miss” diagnoses with potential for significant morbidity and mortality.

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Abbreviations used:

ANCA:	antineutrophil cytoplasmic antibody
EGPA:	eosinophilic granulomatosis with polyangiitis
GPA:	granulomatosis with polyangiitis
HCV:	hepatitis C virus
Ig:	immunoglobulin
MPA:	microscopic polyangiitis
MPO:	myeloperoxidase
PR3:	proteinase 3
STS:	sodium thiosulfate

We discuss important aspects of the pathophysiology, patient demographics and risk factors, updates in the diagnostic workup, histopathology, and treatment of these specific conditions. The 4 conditions reviewed in part II have been the subject of many recent articles, and therefore updates in their respective workups and treatments are timely and relevant.

CALCIPHYLAXIS

Key points

- Calciphylaxis is a complex and multifactorial process that results in calcium deposition and microthrombi in dermal and subcutaneous vessels.
- Prognosis is poor.
- Treatment consists of multidisciplinary care and a multifaceted approach with consideration for patient risk factors, pharmacotherapy, wound care, and pain management.

Despite novel treatment strategies, calciphylaxis has a poor prognosis, with a 1-year survival rate of 40% to 45%.¹⁻³ Calciphylaxis presents in patients with end-stage renal disease, acute kidney injury, kidney transplant, and even those without kidney disease.^{1,4-6} Nonuremic calciphylaxis carries an overall better prognosis.^{1,7} Women are affected more frequently than men, with most patients being older than 50 years.⁷ Calciphylaxis is a complex disease, with significant morbidity, and requires

interdisciplinary care (dermatology, nephrology, pain management, nutrition, and wound care).⁸ The most frequent cause of death for all types of calciphylaxis is sepsis.^{8,9}

Clinical characteristics

Calciphylaxis may present with pain before skin changes¹⁰; lesions begin as indurated subcutaneous plaques or nodules that progress to retiform purpura with bullae and central ulceration⁸ (Fig 1). Lesions predominate in proximal areas with abundant adipose tissue (thighs, abdomen, and buttocks). Distal lesions are less common but may present as digital¹¹ and penile necrosis¹² (Fig 2). Distal calciphylaxis may portend better prognosis; however, penile calciphylaxis is notable for a mortality rate of 69% in 6 months. Those with both distal and proximal lesions have increased mortality, likely due to increased disease burden.¹³

Pathophysiology

Calciphylaxis is the clinical presentation of cutaneous vessel blockade that is thought to occur via a 2-hit model. The first hit is medial calcification, which results in vessel lumen narrowing and endothelial cell damage.¹ Researchers have proposed models whereby endothelial damage from reactive oxygen species and uremic toxins, mineral imbalances in the context of hyperphosphatemia, increased inducers of calcification (bone morphogenic protein-4), and decreased calcification inhibitory factors (matrix Gla protein and α -2 Heremans-Schmid glycoprotein) induce calcium deposition in vessel walls.^{1,8,13-16}

The second hit is thrombotic occlusion, which leads to downstream cutaneous necrosis. Thrombotic clotting results from slower blood flow through narrowed vessels, endothelial cell damage, a localized prothrombotic state, and sometimes underlying hypercoagulability. Interestingly, combined thrombophilia (2 or more inherited thrombophilia polymorphisms) has been identified



Fig 1. Calciphylaxis in (A) a patient with end-stage renal disease and (B) a patient with pulmonary embolus receiving warfarin.



Fig 2. Penile calciphylaxis in a patient with renal disease. (Photograph courtesy of Andrew Avarbock, MD.)

in 60% of patients with calciphylaxis.¹⁷ In addition, in 1 study, 38 of 44 (86%) patients with calciphylaxis showed evidence of thrombosis on biopsy.⁷

Risk factors

We illustrate common risk factors in Table I.^{1,2,7,8} The major risk factor for the development of calciphylaxis is end-stage renal disease; however, risk factors for nonuremic calciphylaxis are numerous. Chronic steroid use, liver disease, and diabetes are most common. Patients taking warfarin have a significantly increased risk secondary to the direct and downstream effects of vitamin K inhibition.²

Histopathology

Biopsy specimens of calciphylaxis display intimal fibroplasia with calcification and thrombosis in the dermis and subcutaneous tissue (Fig 3). Additional features include epidermal ulceration, dermal necrosis, perieccrine calcification, panniculitis, and proliferation of dermal endothelial cells.^{18,19} If necessary, the calcifications can be highlighted by von Kossa stain²⁰ or Alizarin red stain¹⁸ (Fig 3).

Workup

Elevations in serum calcium and phosphate may be found, but they are not specific and are rarely helpful in clinical practice. We recommend evaluation for hypercoagulability (notably protein C/S deficiency)²¹; renal dysfunction; and evidence of infection, autoimmune disease, or malignancy when appropriate.^{4,8} Parathyroid hormone levels should be assessed.^{1,8,22} Although not always required, biopsy remains the criterion standard.

Table I. Risk factors for calciphylaxis

Risk factors	Comments
Sex	Female
Obesity	Body mass index > 30 kg/m ²
Diabetes mellitus	—
End-stage renal disease	Glomerular filtration rate < 15 mL/min
Hypercalcemia	—
Hyperphosphatemia	—
Hyperparathyroidism	Primary or secondary
Elevated alkaline phosphatase level	—
Liver disease	Alcoholic cirrhosis, chronic hepatitis, nonalcoholic steatohepatitis
Thrombophilia	Antithrombin deficiency, protein C/S deficiency, lupus anticoagulant
Vitamin K deficiency	May be induced by warfarin
Autoimmune connective tissue disease	—
Hypoalbuminemia	May be secondary to malnutrition
Malignancy	Metastatic colon, lung, breast cancer
Rapid weight loss	—
Skin trauma	Subcutaneous injection, intravenous, etc
Exposure to aluminum	Found in some phosphate binders
POEMS syndrome	Polyneuropathy, organomegaly, endocrinopathy, M component, skin changes
Medications (iatrogenic)	Warfarin, calcium, vitamin D, parathyroid hormone, chronic steroid use

The presence of micro-occlusion and microcalcification in subcutaneous vessels is diagnostic²⁰; therefore, we recommend an incisional wedge biopsy or a punch within a punch to collect adequate subcutaneous tissue.¹ Should the diagnosis remain in question, plain radiographs or nuclear bone scans can aid in detecting net-like soft tissue microcalcifications.^{8,23}

Treatment

No randomized controlled trials for calciphylaxis treatment are available; however, case reports, case series, and retrospective studies can guide management. Treatment addresses optimization of the calcium dysregulation and reversing micro-occlusive processes that potentiate calciphylaxis (Fig 4^{1,8,12,15}).

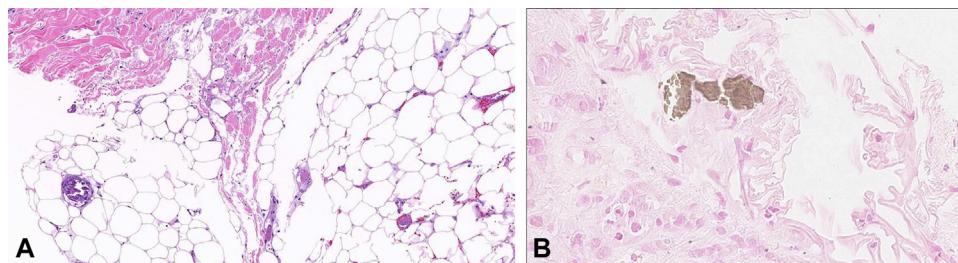


Fig 3. **A**, Subcutaneous calcium deposition and intraluminal microthrombi are apparent on H&# staining. **B**, von Kossa stain highlights calcium.

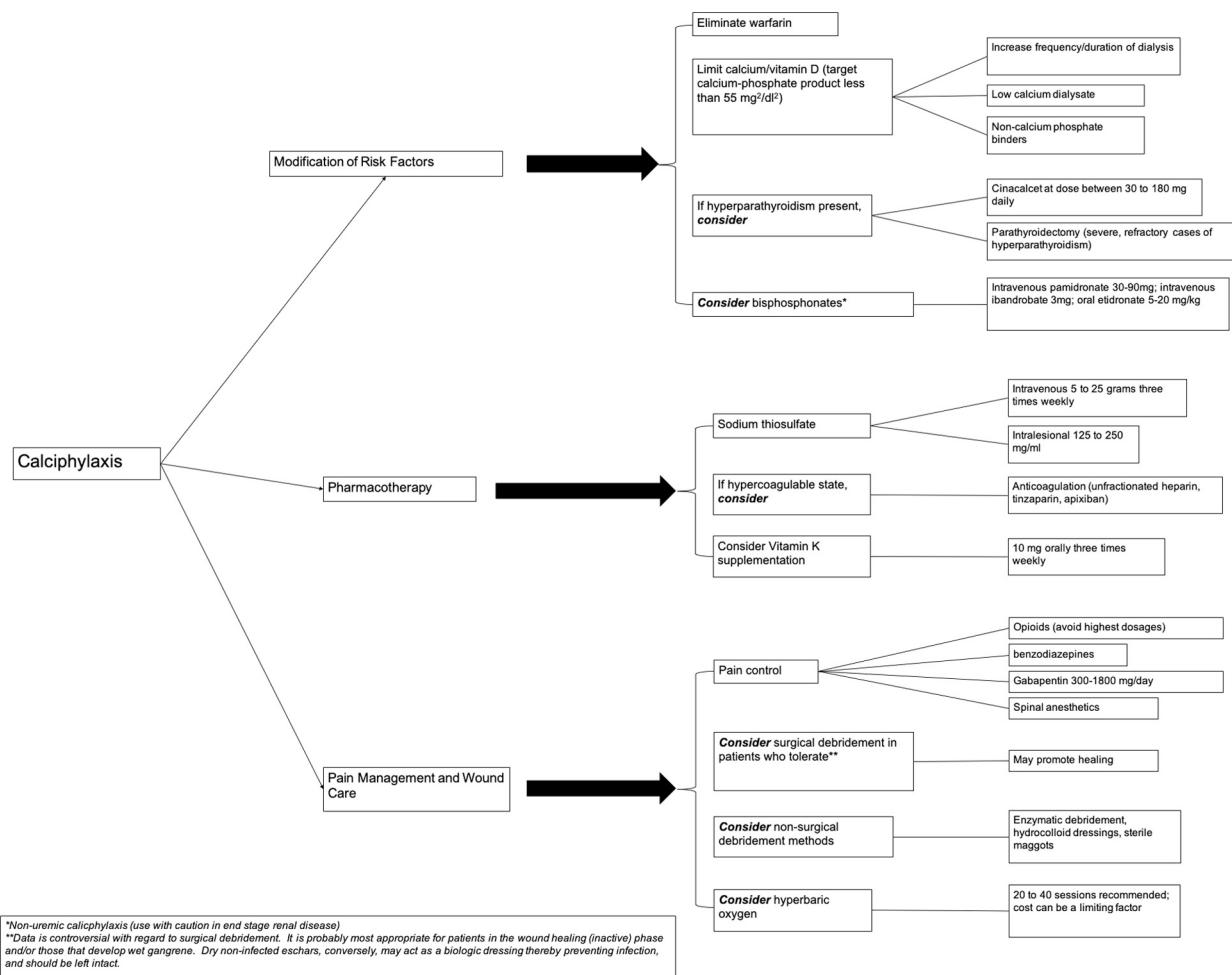


Fig 4. Treatment strategies in calciphylaxis.

Calcium imbalance and deposition

For patients receiving dialysis, mineral imbalance should be corrected by increased frequency and duration of dialysis,²⁴ elimination of high-calcium dialysate, and noncalcium phosphate binders including sevelamer or lanthanum.^{8,12,15}

Optimal parathyroid levels are unknown, but calcimimetic agents can be considered.²⁵ In a randomized trial,²⁶ administration of cinacalcet to

hemodialysis patients resulted in a lower rate of calciphylaxis, although the role of cinacalcet after calciphylaxis diagnosis has not been investigated. Parathyroidectomy, along with kidney transplantation, can be considered in refractory cases.^{8,21,27,28}

Sodium thiosulfate (STS) is increasingly being used in the treatment of calciphylaxis (uremic and nonuremic). The exact mechanism is unknown, but STS is thought to work by increasing calcium



Fig 5. **A**, Ulcer; **(B)** retiform purpura; and **(C)** necrotic eschar in patients with cryoglobulinemia.

solubility. STS may have additional vasodilatory and antioxidant properties.^{1,27} Retrospective studies have shown remission in 26% to 52% of patients treated with STS.^{29,30} STS may be used intravenously (with dialysis sessions at doses between 5 and 25 g) or intralesionally (at dilutions between 125 and 250 mg/mL) if disease is localized.²⁷ Electrocardiograms should be obtained to monitor for QT elongation. Adverse effects include nausea and vomiting and, rarely, severe metabolic acidosis.³¹ Metabolic acidosis presents with drowsiness, confusion, headache, hyperventilation, and tachycardia, along with an elevated anion gap. Acidosis should be managed with intravenous fluids, supplemental oxygen, and for those patients with obtundation, possible ICU admission for intubation when indicated.²⁷⁻³¹

Finally, bisphosphonates may be considered and can be particularly effective in nonuremic calciphylaxis.^{8,15} Bisphosphonates should be used with care in end-stage renal disease to avoid adynamic bone disease; therefore, some researchers recommend their use only in severe, refractory cases.

Thrombotic occlusion

Given the increased risk of hypercoagulability and the evidence of thrombosis on biopsy, the use of antiplatelet and anticoagulation therapies is

increasingly being considered. However, further studies are needed, and full anticoagulation is not currently standard practice in patients without a clear or preceding indication (eg, deep vein thrombosis, atrial fibrillation).

Warfarin may worsen calciphylaxis.^{6,23,31,32} Thus, for patients with calciphylaxis who require anticoagulation, nonwarfarin options, which have less safety data, especially in patients with end-stage renal disease, must be considered. Acute anticoagulation options include a heparin drip in hospitalized patients. Subcutaneous unfractionated heparin and tinzaparin may be acceptable maintenance options.^{8,33,34} In addition, a recent case series of 18 patients showed good efficacy and safety data for oral apixaban in patients with end-stage renal disease and calciphylaxis.³⁵

Other options to consider (especially when full anticoagulation is contraindicated) include aspirin, dipyridamole, and pentoxifylline (which is thought to mitigate clotting by decreasing blood viscosity and platelet aggregation³⁶). Benefits of these agents should be weighed against bleeding risk. Clinicians typically consider full or partial anticoagulation when calciphylaxis is extensive or rapidly progressive, extensive clotting is noted during skin biopsy, and/or the patient has not responded to other therapies.

Table II. Risk factors for cryoglobulinemia

Type	Risk factors	Risk factors
Type I cryoglobulinemia	Lymphoproliferative disorders	Plasma cell dyscrasias
Monoclonal (IgM)	Multiple myeloma	Waldenstrom macroglobulinemia
	MGUS	Chronic lymphocytic leukemia
	Non-Hodgkin lymphoma	Hairy cell leukemia
Type II cryoglobulinemia	Hepatitis C	Hepatitis B
Monoclonal (IgM kappa) and polyclonal (IgG kappa and IgG lambda)	HIV	Other infections*
Type III cryoglobulinemia	Hepatitis C	Hepatitis B
Polyclonal IgM and IgG	HIV	Other infections*
	Lymphoproliferative disorders	Autoimmune connective tissue diseases†

IG, Immunoglobulin; MGUS, monoclonal gammopathy of undetermined significance.

*Epstein-Barr virus, cytomegalovirus, adenovirus, parvovirus, STREPTOCOCCUS, Brucella, Coxiella, leprosy, Lyme disease, syphilis, malaria, leishmaniasis, toxoplasmosis, schistosomiasis, echinococcus, candidiasis, coccidioidomycosis.

†Systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome.

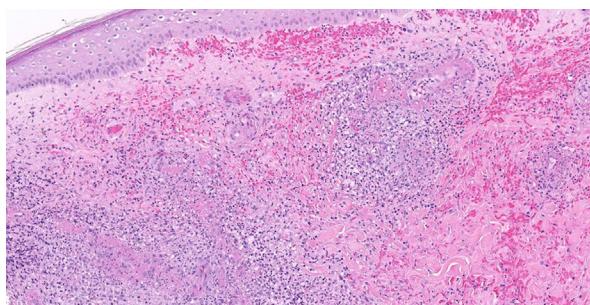


Fig 6. Leukocytoclastic vasculitis in a patient with hepatitis C and mixed cryoglobulinemia. H&E staining shows perivascular neutrophilic karyorrhexis and intraluminal fibrin.

Vitamin K is an emerging therapy thought to work by activating a protein that has an inhibitory effect on calcification.¹⁵ Several studies have shown vitamin K's role in reducing intra-arterial calcification and stiffness,³⁷⁻³⁹ and a proof-of-concept study in calciphylaxis is currently being conducted.¹ Supraphysiologic doses have not been reported to increase clotting risk, but controlled studies are needed.

Finally, pain management and wound care are vital components of the overall therapeutic strategy. Adequate pain relief may require opioids, gabapentin, ketamine, and benzodiazepines, among other agents. Wound care should focus on debridement of wet necrotic tissue and prevention of infection. Hyperbaric oxygen may facilitate wound healing in patients who are candidates.^{1,8}

CRYOGLOBULINEMIA

Key points

- Cryoglobulinemia can be seen in several disease states, most notably hepatitis and

myeloproliferative disorders, and can affect many organ systems.

- Proper collection for laboratory testing is difficult.
- Treatment is focused on the underlying disease state.

Cryoglobulinemia is defined by the presence of immunoglobulins that precipitate to form a gel at 37°C. Three subtypes are defined: monoclonal immunoglobulins (type I), polyclonal immunoglobulins (type III), or a combination of both (type II).⁴⁰ Together, types II and III are called *mixed cryoglobulinemia*.

Clinical findings

Classic skin manifestations of type I cryoglobulinemia include retiform purpura (Fig 5), acrocyanosis, livedo reticularis, and cold urticaria. Type II and III cryoglobulinemias present with palpable purpura and retiform purpura, reflecting a mixed small- and medium-vessel vasculitis.^{41,42} There may be an overlap in the clinical presentations of type I and mixed cryoglobulinemia.

Systemic manifestations are numerous, and there is significant potential for end organ damage. Arthralgia without frank arthritis,⁴³ renal disease (hematuria, proteinuria, and glomerulonephritis),^{41,44} distal symmetric sensorimotor polyneuropathy,⁴⁵ or interstitial lung disease⁴⁶ may be present. Patients with type I cryoglobulinemia may develop hyperviscosity symptoms, including headache, blurry vision, confusion, or chest pain.⁴⁷

Pathophysiology

The underlying mechanism of type I cryoglobulinemia is aberrant antibody production and B-cell proliferation. Mixed cryoglobulinemia is associated

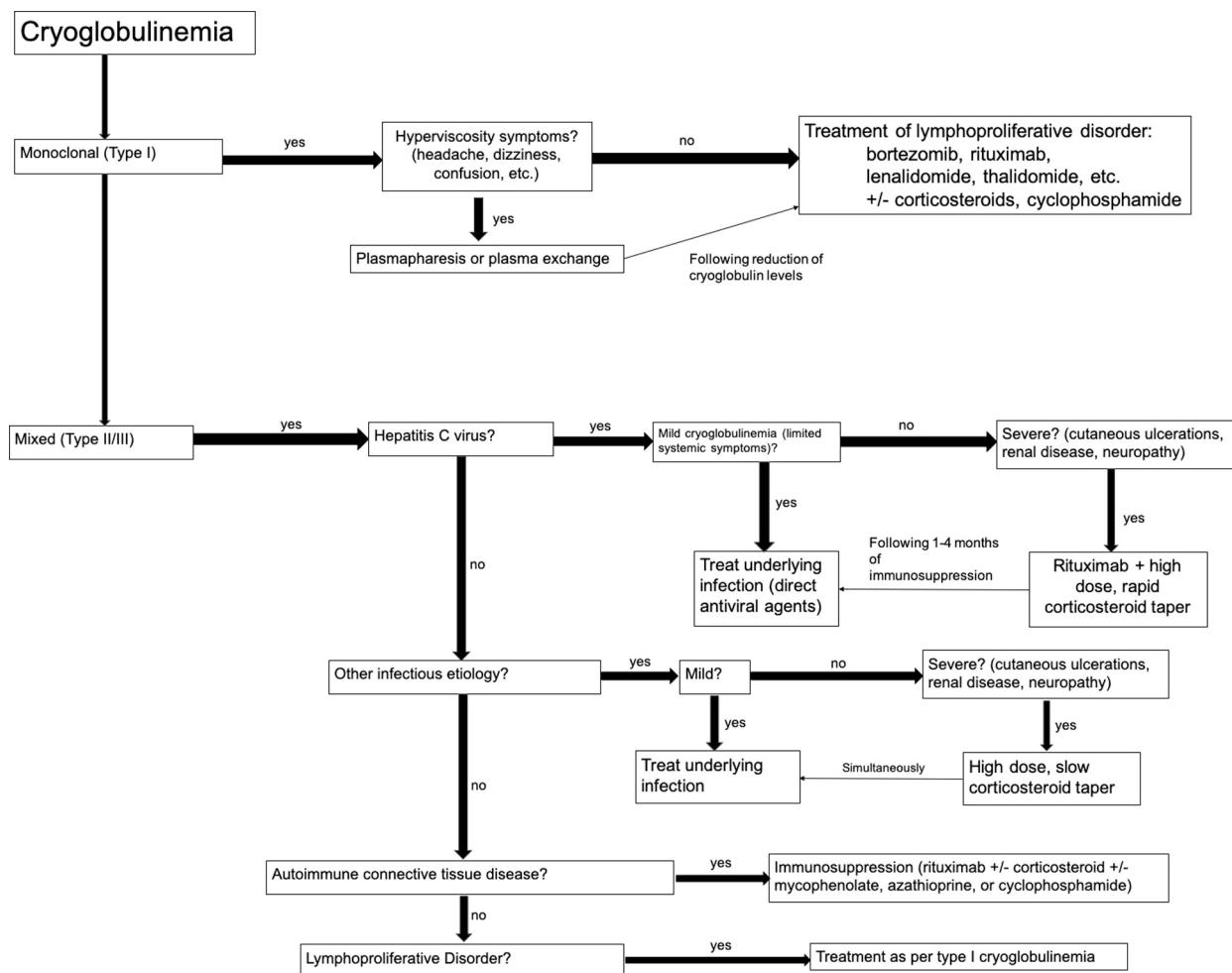


Fig 7. Treatment strategies in cryoglobulinemia.

with chronic immune and/or autoimmune stimulation, leading to production of monoclonal and polyclonal cryoglobulins with concomitant immune complex formation and ineffective clearance, which in turn leads to accumulation and deposition throughout the body.⁴⁰

Risk factors

Type I cryoglobulinemia is indicative of a B-cell lymphoproliferative disorder. Furthermore, the risk of subsequent hematologic malignancy is significantly increased (up to 35-fold).⁴¹ The main etiology of mixed cryoglobulinemia is chronic hepatitis C virus (HCV) infection, which accounts for 80% to 90% of cases.^{40,48-50} In the remainder of cases, B-cell malignancy, autoimmune disease, and other infectious diseases may be implicated⁵¹ (Table II^{40,41}).

Histopathology

A biopsy of type I cryoglobulinemia shows thromboses in dermal vessels, often indistinguishable from

other causes of coagulopathy.⁵² Types II and III, conversely, are represented by leukocytoclastic vasculitis with the presence of neutrophilic karyorrhexis, fibrinoid necrosis of vessel walls, and extravasation of red blood cells⁵² (Fig 6).

Workup

Characteristic symptoms, representative cutaneous lesions (especially on acral surfaces), and histopathology in the context of associated disorders warrant laboratory evaluation. A comprehensive metabolic panel, complete blood count, and urinalysis must be collected. Low complement levels (C4) are often present in mixed cryoglobulinemia, and rheumatoid factor level is elevated in two thirds of patients. Serum protein electrophoresis, immunofixation, serum and urine free light chains, urine toxicology, hepatitis B and C, and HIV can be assessed. Additional nonspecific findings include elevated erythrocyte sedimentation rate, C-reactive protein, and mild normochromic normocytic anemia.⁴¹



Fig 8. **A-C,** Retiform purpura and atrophie blanche on the medial and lateral malleoli in a patient with factor V Leiden deficiency and livedoid vasculopathy.

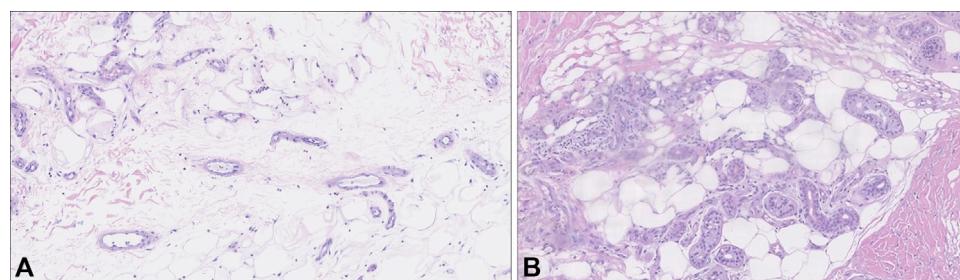


Fig 9. **A and B,** H&E specimens show vascular proliferative changes with endothelial edema and intraluminal hyaline thrombi.

Demonstration of serum cryoglobulins confirms the diagnosis (in those patients with clinical manifestations), but meticulous collection and laboratory techniques are necessary and difficult. Inexperience or improper collection and storage may result in false negative results. Blood samples must be collected and centrifuged at 37°C. Although type II and III cryoglobulins typically yield concentrations of 1 to 5 mg/dL, type I cryoglobulins yield higher concentrations of 5 to 10 mg/dL. Thereafter, samples are refrigerated at 4°C for 72 to 168 hours to allow for cryoprecipitation. Cryoglobulins are then identified by electrophoresis and immunofixation.^{41,53}

Treatment

Management of cryoglobulinemia should focus on treatment of the underlying disorder with or without the addition of immunosuppression, depending on the severity of symptoms (Fig 7^{40,41,47,52}).

Type I cryoglobulinemia is always treated by targeting the underlying hematologic disease. In those cases of hyperviscosity, plasmapheresis should be considered.⁴⁰

In patients with HCV and mixed cryoglobulinemia, the severity of clinical manifestations dictates treatment. A variety of novel direct antiviral agents are currently used and are beyond the scope of this

review, although we provide references.^{40,54-61} Severe vasculitis precipitating cutaneous ulceration, kidney disease, and neuropathy warrants immunosuppression, as outlined in Fig 7.^{40,41,47,52}

Finally, for those patients with non-HCV-associated mixed cryoglobulinemia, treatment should focus on the underlying infection or autoimmune disease (Fig 7^{40,41,47,52}).

LIVEDOID VASCULOPATHY

- Livedoid vasculopathy is shown histologically by intraluminal thrombi, endothelial damage, and proliferation.
- Patients present with painful ulcers, atrophie blanche, and retiform purpura.
- Underlying hypercoagulable states and anti-coagulation should always be considered.

Livedoid vasculopathy presents as retiform purpura accompanied by chronic, painful ulcerations.⁶² It should be distinguished from atrophie blanche, which is the accompanying white, scar-like component that can be seen in a number of different entities.^{62,63}

Livedoid vasculopathy is a thrombo-occlusive disease potentiated by fibrin thrombi.⁶⁴ The disease is chronic, painful, and associated with considerable quality of life impairment. Female patients are more

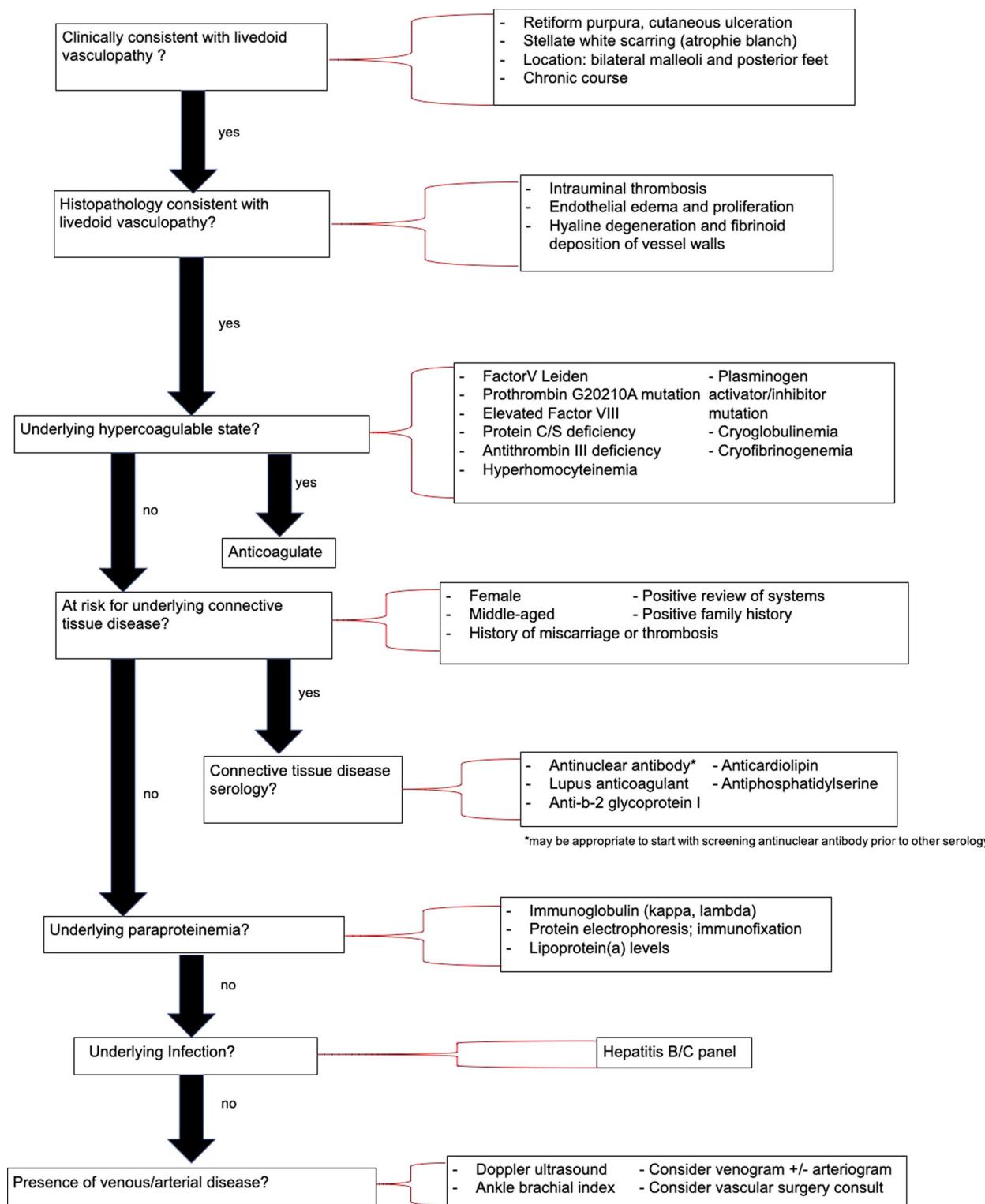


Fig 10. Diagnostic approach to livedoid vasculopathy.

commonly affected than male patients,⁶⁴ and the median age of onset is 32 years.⁶³ Although no standard treatment has been established, case series and small prospective trials exist.

Clinical findings

Painful or pruritic, stellate, retiform, purpuric papules and plaques are typically located around the bilateral ankles. These lesions subsequently

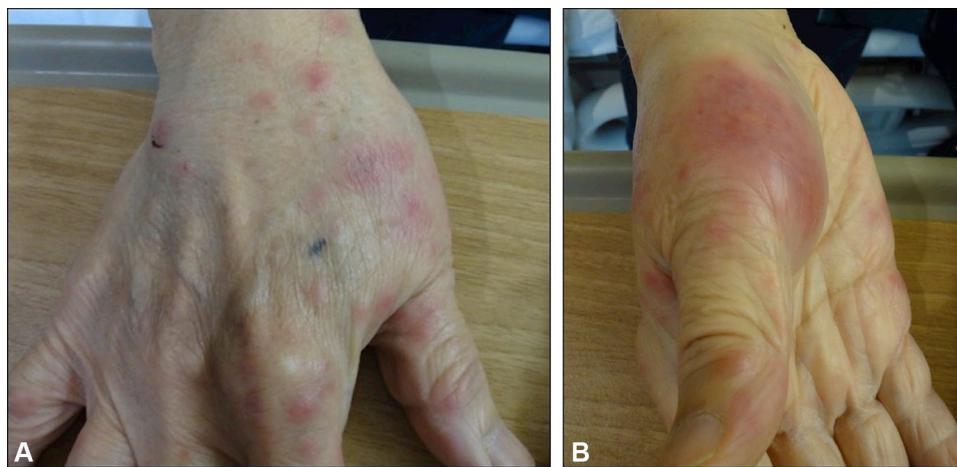


Fig 11. **A** and **B**, Erythematous and edematous acral papules and plaques in a patient with eosinophilic granulomatosis with polyangiitis.

ulcerate and then heal over the ensuing 3 or 4 months, leaving atrophic stellate white scarring⁶³ (Fig 8). Atrophie blanche can be seen as an end-stage manifestation of a variety of conditions, including venous stasis; however, when involving the bilateral malleoli and dorsal feet, it is more likely associated with livedoid vasculopathy.⁶²

Pathophysiology

Increased propensity for coagulation and/or impaired fibrinolysis (both as result of numerous factors precipitating a final common pathway) with endothelial cell damage are key components in the development of livedoid vasculopathy.⁶² Improvement in patients who begin receiving anticoagulation, fibrinolytic, and antiplatelet therapies supports this pathogenic model.^{65,66}

Risk factors

The strongest risk factor for the development of livedoid vasculopathy is hypercoagulability. Retrospective^{65,67} cohort studies have indicated that more than 50% of patients have an identifiable hypercoagulable state on laboratory evaluation. The most common associations include factor V Leiden mutation, antiphospholipid antibody syndrome, protein C deficiency, and hyperhomocysteinemia.⁶⁵

The next most common association is connective tissue disease, specifically systemic lupus erythematosus in association with antiphospholipid syndrome. Patients with paraproteinemia are also at risk. Finally, the clinician must consider associated infections, including hepatitis B virus or HCV.⁶²

Histopathology

Early lesions of livedoid vasculopathy display intraluminal hyaline thrombi, eventuating in infarction of the papillary dermis and epidermal ulceration.^{62,68} Direct immunofluorescence may show fibrin only.⁶⁹ Developed lesions show thickening and hyalinization of vessel walls with endothelial edema and proliferation, along with intraluminal fibrin thrombi^{62,68} (Fig 9). In mature lesions, immunoglobulin (Ig) M, IgG, and complement (C3) can be shown by immunofluorescence.⁶⁹

Workup

We suggest a diagnostic workup as outlined in Fig 10.^{62-65,68} Thrombophilia evaluation can provide diagnostic relevance and genetic counseling information. Screening for connective tissue disease should be guided by family history and review of systems. A skin biopsy for H&E staining should be taken from at the periphery of the ulcer⁶² or in a purpuric area if present. A second biopsy for immunofluorescence can be considered because vasculitis is in the differential diagnosis. Finally, before initiating compression in patients with venous insufficiency, significant peripheral arterial disease should be excluded.

Treatment

Micieli and Alavi⁶³ reviewed treatments for livedoid vasculopathy. Anticoagulants (most frequently rivaroxaban 10-20 mg once or twice daily) are the most frequently reported monotherapy, achieving a favorable response in 98% of patients, with adverse events in 14%.^{63,65,70-74} Anticoagulation should be

Table III. Systemic manifestations of ANCA-associated vasculitis

System affected	% of patients	Symptoms	Comments
Granulomatosis with polyangiitis			
Nasal	90	Sinusitis, rhinorrhea, epistaxis	Common presenting symptoms
Pulmonary	90	Cough, hemoptysis	Sequelae of pulmonary vasculitis
Renal	80-90	Hematuria, red blood cell casts	Sequelae of glomerulonephritis
Neurologic	50-60	Neuropathy, cerebrovascular accident	Peripheral more common than central neuropathy
Cardiac	0		
Gastrointestinal	0		
Microscopic polyangiitis			
Nasal	0		
Pulmonary	35	Cough, hemoptysis	Sequelae of alveolar hemorrhage
Renal	80-90	Hematuria, red blood cell casts	Focal segmental necrotizing glomerulonephritis
Neurologic	35	Neuropathy	Frequently mononeuritis multiplex
Cardiac	0		
Gastrointestinal	0		
Eosinophilic granulomatosis with polyangiitis			
Nasal	50	Polyposis, rhinitis	
Pulmonary	60	Asthma	Typically adult onset
Renal	35	Hematuria	Late complication
Neurologic	70	Neuropathy	Mononeuritis multiplex, symmetric polyneuropathy
Cardiac	60-70	Cardiomyopathy, valve and pericardial disease	Eosinophilic cardiomyopathy, Loeffler endocarditis
Gastrointestinal	40-50	Nausea, vomiting, abdominal pain	Can masquerade as Henoch-Schönlein purpura

ANCA, Antineutrophil cytoplasmic antibody.

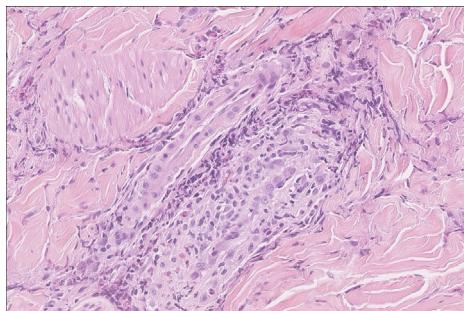


Fig 12. Extravascular granuloma with a collection of histiocytes surrounded by an admixture of lymphocytes, neutrophils, and a marked number of eosinophils.

strongly considered, especially in those with associated hypercoagulability.

Anabolic steroids, including danazol (200 mg daily), methylprednisolone, and betamethasone, can be effective in patients with connective tissue disease.^{63,75-80} Danazol might also be effective in patients with elevated lipoprotein(a) levels.⁷⁵ Antiplatelet medications, including aspirin, pentoxifylline, and dipyridamole, can be used as monotherapy or in combination with other agents. Intravenous immunoglobulin, hyperbaric oxygen,

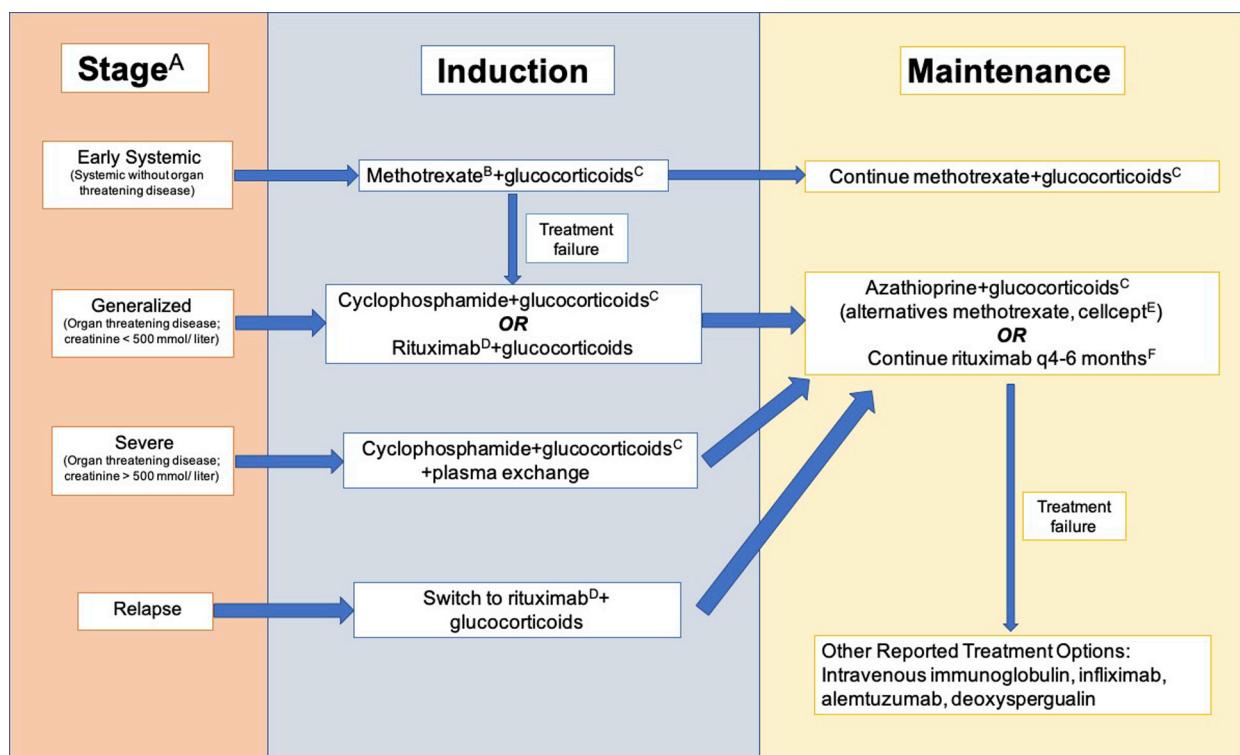
and psoralen plus ultraviolet A light therapy have shown good clinical response, but because of cost and compliance, Micieli and Alavi⁶³ recommend limiting use to refractory cases. Finally, Klein and Pittelkow⁸¹ reported favorable response to tissue plasminogen activator (10 mg intravenously for 14 days) in 6 patients; however, safety and efficacy need to be confirmed.

ANTINEUTROPHIL CYTOPLASMIC ANTIBODY-ASSOCIATED VASCULITIS

Key points

- **Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis can be rapidly progressive and fatal, although modern treatment strategies have improved outcomes.**
- **Clinical and histologic presentation can be varied.**
- **Rituximab has emerged as a promising therapy for many patients with ANCA-associated vasculitis.**

ANCA-associated vasculitis, nomenclature that encompasses granulomatosis with polyangiitis (GPA; formerly *Wegener granulomatosis*), microscopic



- A. Disease Stage as defined by EUVAS/EULAR¹⁰⁸
- B. Not inferior to cyclophosphamide in achieving remission (and therefore reasonable for early systemic disease), but quicker time to relapse¹⁰⁹
- C. Authors¹⁰⁵⁻¹⁰⁷ have suggested 1 gram methylprednisolone x 3 days, followed by 1 mg/kg prednisone taper, though this glucocorticoid regimen hasn't been validated in controlled trials.
- D. The RAVE¹¹⁰ and RITUXVAS¹¹¹ trials demonstrated superiority to cyclophosphamide in patients with relapsing disease. Patients should be on *Pneumocystis jirovecii* prophylaxis.
- E. Less effective than azathioprine at preventing relapse¹¹²
- F. Recent trials suggest superiority to azathioprine in preventing relapse following cyclophosphamide/glucocorticoid induction.^{113,114} Patients should be on *Pneumocystis jirovecii* prophylaxis.

Fig 13. Treatment algorithm for antineutrophil cytoplasmic antibody–associated vasculitis.
q, Every.

polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA; formerly *Churg-Strauss syndrome*), falls under the designation of small- and medium-vessel vasculitis. Because numerous organ systems are affected, prompt diagnosis is essential so that appropriate therapy can be initiated.^{82,83}

Clinical findings

Cutaneous lesions occur in approximately 60% of patients with EGPA,⁸⁴⁻⁸⁷ 40% of patients with MPA,^{84,86,88} and 20% of patients with GPA.^{84,89} Skin findings reflect the involvement of both small and medium vessels and include palpable purpura, retiform purpura, nodules, livedo, and ulceration. Additional reported lesions include bullae, urticaria-like lesions, erythematous papules or plaques (Fig 11), erythema multiforme–like lesions, angioedema-like lesions in EGPA, and pyoderma gangrenosum–like ulcers in GPA.⁸⁴ Systemic manifestations are numerous and summarized in Table III.^{82,83,90-92}

Pathophysiology

ANCA^s are IgG antibodies directed against neutrophilic (1) cytoplasmic (c-ANCA) antigen proteinase 3 (PR3) and (2) perinuclear (p-ANCA) antigen myeloperoxidase (MPO). These are intracellular proteins that, when activated, can translocate to the cell surface, thereby promoting neutrophil adhesion, release of inflammatory cytokines, and resultant vessel damage. *Cytoplasmic* and *neutrophilic* refer to the pattern of staining on indirect immunofluorescence, and PR3 and MPO are the antibodies most commonly associated with that pattern of staining on indirect immunofluorescence. GPA is most commonly associated with PR3. MPA and EGPA (MPA more often than EGPA) are frequently MPO mediated.⁹³

Risk factors

The median age of onset is between 40 and 60 years. Women and children are more frequently

Table IV. Treatment dosing schedules for ANCA-associated vasculitis

Treatment	Dose	Trial
Induction therapy		
Methotrexate + glucocorticoids + folic acid	Methotrexate 15 mg/wk increasing to 20-25 mg/wk	NORAM ¹⁰²
Cyclophosphamide + glucocorticoids	Cyclophosphamide <ul style="list-style-type: none"> - Intravenous: 3 pulses of 15 mg/kg every 2-3 weeks, total 6-9 pulses - Oral: 2 mg/kg daily 	CYCLOPS ¹⁰⁸
Rituximab	4 infusions of 375 mg/m ² weekly	RAVE ¹⁰³ RITUXVAS ¹⁰⁴ MEPEX ¹⁰⁹
Plasma exchange	7 rounds of 60 mL/kg body weight	
Maintenance therapy		
Methotrexate + folic acid	Methotrexate 20-25 mg/wk	NORAM ¹⁰² WEGENT ¹¹⁰
Azathioprine	2 mg/kg for 12 months, then 1.5 mg/kg	CYCAZAREM ¹¹¹
Mycophenolate	2 g daily	Joy et al ¹¹²
Rituximab	375 mg/m ² or 0.5- to 1.0-g infusions every 4-6 mo	MAINRITSAN ¹⁰⁶ MAINRITSAN ¹⁰⁷ Ongoing trials (RITZAREM) ¹¹³
Intravenous immunoglobulin	2 g/kg over 4 d	Jayne et al ¹¹⁴
Infliximab	3-5 mg/kg infusion, every 1-2 mo	Lamprecht et al ¹¹⁵
15-deoxyspergualin	0.5 mg/kg for 6 cycles	Birck et al ¹¹⁶

ANCA, Antineutrophil cytoplasmic antibody.

afflicted with GPA and men with MPA; no sex predilection is apparent for EGPA.⁹³ Researchers have suggested various medication and infectious triggers; however, the etiology is currently unknown.⁹²

Histopathology

Leukocytoclastic vasculitis is a common feature of GPA and MPA and is occasionally present in EGPA. Vasculitis in GPA may be surrounded by perivascular granulomatous inflammation, sometimes with extravascular fibrinoid necrosis; lesions of EGPA can be eosinophil or neutrophil predominant, and necrotizing vasculitis with extravascular eosinophilic granulomas with degenerated collagen may be present (Fig 12).⁸⁴

Workup

The clinician must first rule out medication- (or cocaine-^{94,95}) induced vasculitis in any patient with a positive ANCA result. Common drug culprits include propylthiouracil, hydralazine, anti-tumor necrosis factor α agents, sulfasalazine, D-penicillamine, and minocycline.⁹⁶

There are no standardized diagnostic criteria for ANCA-associated vasculitis; we provide the American College of Rheumatology 1990 criteria⁹⁷

and 2012 Chapel Hill Consensus Conference⁹⁸ for guidance in diagnosis and classification. Upcoming conclusions from the Diagnostic and Classification Criteria for Vasculitis (DCVAS) study⁹⁸ will provide further clarification.

All patients should have complete blood count, metabolic panel, and urinalysis. Patients with EGPA often have peripheral eosinophilia and elevated IgE level.⁸² Additional diagnostic tests directed by patient history and examination include chest radiography or computed tomography, nerve conduction studies, lung or kidney biopsy, echocardiography, computed tomography of sinuses (GPA and EGPA), and ophthalmologic examination (GPA and EGPA).⁹³

Treatment

Randomized trials have revolutionized management of ANCA-associated vasculitis. Diseases that were once considered fatal now have 75% survival at 10 years.⁸³ Management focuses on rapid induction with immunosuppression (3-6 months) followed by maintenance therapy (18-24 months), as presented in Fig 13⁹⁹⁻¹¹⁶ and Table IV.^{99-104,106-116}

Induction therapy with cyclophosphamide and glucocorticoids¹⁰⁸ has long been considered the standard of care. More recently, alternate therapies

Table V. Levels of evidence for treatment recommendations of selected conditions

Condition	Treatment	Evidence level*	Notes	References
Calciphylaxis	Noncalcium phosphate binders	IV	—	8,12,15
	Cinacalcet	IB, IV	Level I evidence exists for prevention, but not treatment, of calciphylaxis	25,26
	Parathyroidectomy	III, IV	—	8,21,27
	Sodium thiosulfate	III, IV	—	27,29-31
	Bisphosphonates	IV	—	8,15
Cryoglobulinemia	Anticoagulation	III, IV	—	33-35
	Plasmapheresis	IV	Reserved for those cases with hyperviscosity symptoms	40
	Rituximab	IB	Initiated before antiviral therapy	120
	Immunosuppression (corticosteroids, azathioprine, mycophenolate, cyclophosphamide)	III, IV	Initiated simultaneously with or before antiviral therapy	40,41,47,52
Livedoid vasculopathy	Anticoagulation	III, IV	—	63,65,70-74
	Anabolic steroids	III, IV	—	63,75-80
	Tissue plasminogen activator	III	—	81
ANCA vasculitis	Corticosteroids	IV	—	82,83,100
	Cyclophosphamide	IB, III, IV	—	82,101-104,108
	Mycophenolate	IB, III	Inferior to azathioprine at preventing relapse	105,112
	Azathioprine	IB, IV	Inferior to rituximab in preventing relapse after cyclophosphamide/ glucocorticoid induction	105-107,110
	Rituximab	IB, III, IV	Becoming the favored treatment modality in recent trials	103,104,106,107

ANCA, Antineutrophil cytoplasmic antibody.

*Level IB: evidence from at least 1 randomized controlled trial. Level III: evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies. Level IV: evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

are being investigated to avoid cyclophosphamide toxicities (Table IV^{83,102-104,108-116}). The complement (C5a) inhibitor CCX168 has recently shown promise as a glucocorticoid-sparing agent during induction therapy.¹¹⁷ Plasma exchange may be considered during induction for patients with severe disease (impending renal insufficiency, alveolar hemorrhage).¹⁰⁸

Maintenance therapy with azathioprine for 18 months is the criterion standard.¹¹¹ Methotrexate^{102,110} and mycophenolate¹¹² can be considered for patients who cannot tolerate azathioprine.

Rituximab, however, is likely to emerge as the first-line therapy for both induction and

maintenance. The RAVE¹⁰³ and RITUXVAS¹⁰⁴ trials showed that rituximab (375 mg/m² weekly for 4 weeks combined with glucocorticoids) is as effective as cyclophosphamide (oral or intravenous) at inducing remission in GPA patients. Moreover, rituximab was superior to cyclophosphamide in patients with relapsing disease and is the current preferred treatment for this subgroup. The MAINRITSAN¹⁰⁶ trial showed that rituximab (500 mg every 6 months) is superior to azathioprine in preventing relapse after cyclophosphamide/ glucocorticoid induction. MAINRITSAN 2¹⁰⁷ showed that tailoring the rituximab dosing schedule based on CD19⁺ B-lymphocyte or ANCA levels is effective.

Unlike MPA and GPA, EGPA has been the subject of few controlled trials. Long-term glucocorticoids with or without additional immunosuppression are often required to control asthma, rhinosinusitis, and polyposis.¹¹³ Mepolizumab (a humanized monoclonal antibody targeting interleukin 5) has shown efficacy in refractory EGPA^{118,119} and is currently under further investigation (Table V†).

REFERENCES

1. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. *N Engl J Med.* 2018;378(18):1704-1714.
2. Nigwekar SU, Zhao S, Wenger J, et al. A nationally representative study of calcific uremic arteriolopathy risk factors. *J Am Soc Nephrol.* 2016;27:3421-3429.
3. McCarthy JT, El-Azhary RA, Patzelt MT, et al. Survival, risk factors, and effect of treatment in 101 patients with calciphylaxis. *Mayo Clin Proc.* 2016;91:1384-1394.
4. Nigwekar SU, Wolf M, Sterns RH, Hix JK. Calciphylaxis from nonuremic causes: a systematic review. *Clin J Am Soc Nephrol.* 2008;3:1139-1143.
5. Kalajian AH, Malhotra PS, Callen JP, Parker LP. Calciphylaxis with normal renal and parathyroid function: not as rare as previously believed. *Arch Dermatol.* 2009;145:451-458.
6. Yu WY, Bhutani T, Kornik R, et al. Warfarin-associated nonuremic calciphylaxis. *JAMA Dermatol.* 2017;153(3):309-314.
7. Weenig RH, Sewell LD, Davis MD, McCarthy JT, Pittelkow MR. Calciphylaxis: natural history, risk factor analysis, and outcome. *J Am Acad Dermatol.* 2007;56:569-579.
8. García-Lozano JA, Ocampo-Candiani J, Martínez-Cabriales SA, Garza-Rodríguez V. An update on calciphylaxis. *Am J Clin Dermatol.* 2018;19(4):599-608.
9. Wollina U. Update on cutaneous calciphylaxis. *Indian J Dermatol.* 2013;58(2):87-92.
10. Polizzotto MN, Bryan T, Ashby MA, Martin P. Symptomatic management of calciphylaxis: a case series and review of the literature. *J Pain Symptom Manage.* 2006;32:186-190.
11. Kazanji N, Falatko J, Neupane S, Reddy G. Calciphylaxis presenting as digital ischemia. *Intern Emerg Med.* 2015;10(4):529-530.
12. Barbera V, Di Lullo L, Gorini A, et al. Penile calciphylaxis in end stage renal disease. *Case Rep Urol.* 2013;2013:968916.
13. Jeong HS, Dominguez AR. Calciphylaxis: controversies in pathogenesis, diagnosis and treatment. *Am J Med Sci.* 2016;351(2):217-227.
14. Yerram P, Chaudhary K. Calcific uremic arteriolopathy in end stage renal disease: pathophysiology and management. *Ochsner J.* 2014;14(3):380-385.
15. Griethe W, Schmitt R, Jurgensen JS, Bachmann S, Eckardt KU, Schindler R. Bone morphogenic protein-4 expression in vascular lesions of calciphylaxis. *J Nephrol.* 2003;16(5):728-732.
16. Kramann R, Brandenburg VM, Schurges LJ, et al. Novel insights into osteogenesis and matrix remodelling associated with calcific uremic arteriolopathy. *Nephrol Dial Transplant.* 2013;28:856-868.
17. Dobry AS, Ko LN, St John J, Sloan JM, Nigwekar S, Kroshinsky D. Association between hypercoagulable conditions and calciphylaxis in patients with renal disease: a case-control study. *JAMA Dermatol.* 2018;154(2):182-187.
18. Mochel MC, Arakaki RY, Wang G, Kroshinsky D, Hoang MP. Cutaneous calciphylaxis: a retrospective histopathologic evaluation. *Am J Dermatopathol.* 2013;35(5):582-586.
19. Chen TY, Lehman JS, Gibson LE, Lohse CM, El-Azhary RA. Histopathology of calciphylaxis: cohort study with clinical correlations. *Am J Dermatopathol.* 2017;39:795-802.
20. Magro CM, Simman R, Jackson S. Calciphylaxis: a review. *J Am Col Certif Wound Spec.* 2010;2(4):66-72.
21. Harris RJ, Cropley TG. Possible role of hypercoagulability in calciphylaxis: review of the literature. *J Am Acad Dermatol.* 2011;64(2):405-412.
22. Nigwekar SU, Sprague SM. We do too many parathyroidectomies for calciphylaxis. *Semin Dial.* 2016;29(4):312-314.
23. Shmidt E, Murthy NS, Knudsen JM, et al. Net-like pattern of calcification on plain soft-tissue radiographs in patients with calciphylaxis. *J Am Acad Dermatol.* 2012;67(6):1296-1301.
24. Nigwekar SU, Kroshinsky D, Nazarian RM, et al. Calciphylaxis: risk factors, diagnosis, and treatment. *Am J Kidney Dis.* 2015;66(1):133-146.
25. Floege J, Kubo Y, Floege A, Chertow GM, Parfrey PS. The effect of cinacalcet on calcific uremic arteriolopathy events in patients receiving hemodialysis: the EVOLVE trial. *Clin J Am Soc Nephrol.* 2015;10(5):800-807.
26. The EVOLVE Trial Investigators. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med.* 2012;367:2482-2494.
27. Vedvyas C, Winterfield LS, Vleugels RA. Calciphylaxis: a systematic review of existing and emerging therapies. *J Am Acad Dermatol.* 2012;67(6):e253-e260.
28. Nordheim E, Dahle DO, Syse IM, Åsberg A, Reisæter AV, Hartmann A. Resolution of calciphylaxis after urgent kidney transplantation in 3 patients with end-stage kidney failure. *Transplant Direct.* 2016;2(11):e113.
29. Nigwekar SU, Brunelli SM, Meade D, Wang W, Hymes J, Lacson E Jr. Sodium thiosulfate therapy for calcific uremic arteriolopathy. *Clin J Am Soc Nephrol.* 2013;8:1162-1170.
30. Zitt E, König M, Vychtil A, et al. Use of sodium thiosulphate in a multi-interventional setting for the treatment of calciphylaxis in dialysis patients. *Nephrol Dial Transplant.* 2013;28:1232-1240.
31. Selk N, Rodby RA. Unexpectedly severe metabolic acidosis associated with sodium thiosulfate therapy in a patient with calcific uremic arteriolopathy. *Semin Dial.* 2011;24(1):85-88.
32. Al-ani M, Parperis K. Warfarin-induced calciphylaxis. *BMJ Case Rep.* 2016;2016:bcr2015214142.
33. Hull R, Delmore T, Carter C, et al. Adjusted subcutaneous heparin versus warfarin sodium in the long-term treatment of venous thrombosis. *N Engl J Med.* 1982;306(4):189-194.
34. Pautas E, Gouin I, Bellot O, Andreux JP, Sigaret V. Safety profile of tinzaparin administered once daily at a standard curative dose in two hundred very elderly patients. *Drug Saf.* 2002;25(10):725-733.
35. Garza-Mayers AC, Shah R, Sykes DB, Nigwekar SU, Kroshinsky D. The successful use of apixaban in dialysis patients with calciphylaxis who require anticoagulation: a retrospective analysis. *Am J Nephrol.* 2018;48(3):168-171.
36. Samlaska CP, Winfield EA. Pentoxifylline. *J Am Acad Dermatol.* 1994;30(4):603-621.

†8,12,15,21,25-27,29,31,33,35,40,41,47,52,63,65,70-81,82,83,100-108,110,112,120

37. Shea MK, O'Donnell CJ, Hoffmann U, et al. Vitamin K supplementation and progression of coronary artery calcium in older men and women. *Am J Clin Nutr.* 2009;89:1799-1807.
38. Knapen MH, Braam LA, Drummen NE, Bekers O, Hoeks AP, Vermeer C. Menaquinone-7 supplementation improves arterial stiffness in healthy postmenopausal women: a double-blind randomised clinical trial. *Thromb Haemost.* 2015;113:1135-1144.
39. Brandenburg VM, Reinartz S, Kaesler N, et al. Slower progress of aortic valve calcification with vitamin K supplementation: results from a prospective interventional proof-of-concept study. *Circulation.* 2017;135:2081-2083.
40. Roccatello D, Saadoun D, Ramos-Casals M, et al. Cryoglobulinaemia. *Nat Rev Dis Primers.* 2018;4(1):11.
41. Ghetie D, Mehraban N, Sibley CH. Cold hard facts of cryoglobulinemia: updates on clinical features and treatment advances. *Rheum Dis Clin North Am.* 2015;41(1):93-108.
42. Terrier B, Karras A, Kahn JE, et al. The spectrum of type I cryoglobulinemia vasculitis: new insights based on 64 cases. *Medicine (Baltimore).* 2013;92:61-68.
43. Frankel AH, Singer DR, Winearls CG, et al. Type II essential mixed cryoglobulinaemia: presentation, treatment and outcome in 13 patients. *Q J Med.* 1992;82:101-124.
44. D'Amico G. Renal involvement in hepatitis C infection: cryoglobulinemic glomerulonephritis. *Kidney Int.* 1998;54:650-671.
45. Garcia-Bragado F, Fernandez JM, Navarro C, et al. Peripheral neuropathy in essential mixed cryoglobulinemia. *Arch Neurol.* 1988;45:1210-1214.
46. Bombardieri S, Paoletti P, Ferri C, et al. Lung involvement in essential mixed cryoglobulinemia. *Am J Med.* 1979;66:748-756.
47. Ramos-Casals M, Stone JH, Cid MC, et al. The cryoglobulinaemias. *Lancet.* 2012;379:348-360.
48. Monti G, Pioltelli P, Saccardo F, et al. Incidence and characteristics of non-Hodgkin lymphomas in a multicenter case file of patients with hepatitis C virus-related symptomatic mixed cryoglobulinemias. *Arch Intern Med.* 2005;165:101-105.
49. Ferri C, Greco F, Longombardo G, et al. Association between hepatitis C virus and mixed cryoglobulinemia. *Clin Exp Rheumatol.* 1991;9:621-624.
50. Ferri C, Greco F, Longombardo C, et al. Antibodies to hepatitis C virus in patients with mixed cryoglobulinemia. *Arthritis Rheum.* 1991;34:1606-1610.
51. Terrier B, Marie I, Lacraz A, et al. Non HCV-related infectious cryoglobulinemia vasculitis: results from the French nationwide CryoVas survey and systematic review of the literature. *J Autoimmun.* 2015;65:74-81.
52. Cacoub P, Comarmond C, Domont F, Savey L, Saadoun D. Cryoglobulinemia Vasculitis. *Am J Med.* 2015;128(9):950-955.
53. Vermeersch P, Gijbels K, Marien G, et al. A critical appraisal of current practice in the detection, analysis, and reporting of cryoglobulins. *Clin Chem.* 2008;54:39-43.
54. Banerjee D, Reddy KR. Review article: safety and tolerability of direct-acting anti-viral agents in the new era of hepatitis C therapy. *Aliment Pharmacol Ther.* 2016;43:674-696.
55. Saadoun D, Thibault V, Si Ahmed SN, et al. Sofosbuvir plus ribavirin for hepatitis C virus-associated cryoglobulinaemia vasculitis: VASCUVALDIC study. *Ann Rheum Dis.* 2016;75:1777-1782.
56. Gragnani L, Visentini M, Fognani E, et al. Prospective study of guideline-tailored therapy with direct-acting antivirals for hepatitis C virus-associated mixed cryoglobulinemia. *Hepatology.* 2016;64:1473-1482.
57. Bonacci M, Lens S, Londoño MC, et al. Virologic, clinical, and immune response outcomes of patients with hepatitis C virus-associated cryoglobulinemia treated with direct-acting antivirals. *Clin Gastroenterol Hepatol.* 2017;15:575-583.e1.
58. Lauletta G, Russi S, Pavone F, Vacca A, Dammacco F. Direct-acting antiviral agents in the therapy of hepatitis C virus-related mixed cryoglobulinaemia: a single-centre experience. *Arthritis Res Ther.* 2017;19:74.
59. Emery JS, Kuczynski M, La D, et al. Efficacy and safety of direct acting antivirals for the treatment of mixed cryoglobulinemia. *Am J Gastroenterol.* 2017;112:1298-1308.
60. Kondili LA, Vella S, PITER Collaborating Group. PITER: an ongoing nationwide study on the real-life impact of direct acting antiviral based treatment for chronic hepatitis C in Italy. *Dig Liver Dis.* 2015;47:741-743.
61. Sise ME, Bloom AK, Wisocky J, et al. Treatment of hepatitis C virus-associated mixed cryoglobulinemia with direct acting antiviral agents. *Hepatology.* 2016;63:408-417.
62. Alavi A, Hafner J, Dutz JP, et al. Livedoid vasculopathy: an in-depth analysis using a modified Delphi approach. *J Am Acad Dermatol.* 2013;69(6):1033-1042.
63. Micieli R, Alavi A. Treatment for livedoid vasculopathy: a systematic review. *JAMA Dermatol.* 2018;154(2):193-202.
64. Criado PR, Rivitti EA, Sotto MN, de Carvalho JF. Livedoid vasculopathy as a coagulation disorder. *Autoimmun Rev.* 2011;10(6):353-360.
65. Di Giacomo TB, Hussein TP, Souza DG, Criado PR. Frequency of thrombophilia determinant factors in patients with livedoid vasculopathy and treatment with anticoagulant drugs—a prospective study. *J Eur Acad Dermatol Venereol.* 2010;24:1340-1346.
66. Yang CH, Shen SC, Hui RC, Huang YH, Chu PH, Ho WJ. Association between peripheral vascular endothelial dysfunction and livedoid vasculopathy. *J Am Acad Dermatol.* 2012;67:107-112.
67. Hairston BR, Davis MD, Pittelkow MR, Ahmed I. Livedoid vasculopathy: further evidence for procoagulant pathogenesis. *Arch Dermatol.* 2006;142:1413-1418.
68. Criado PR, Rivitti EA, Sotto MN, et al. Livedoid vasculopathy: an intriguing cutaneous disease. *An Bras Dermatol.* 2011;86:961-977.
69. Shornick JK, Nicholes BK, Bergstresser PR, Gilliam JN. Idiopathic atrophie blanche. *J Am Acad Dermatol.* 1983;8:792-798.
70. Francès C, Barete S. Difficult management of livedoid vasculopathy. *Arch Dermatol.* 2004;140(8):1011.
71. Weishaupt C, Strölin A, Kahle B, et al. Anticoagulation with Rivaroxaban for Livedoid Vasculopathy (RILIVA): a multi-centre, single-arm, open-label, phase 2a, proof-of-concept trial. *Lancet Haematol.* 2016;3(2):e72-e79.
72. Kerk N, Drabik A, Luger TA, Schneider SW, Goerge T. Rivaroxaban prevents painful cutaneous infarctions in livedoid vasculopathy. *Br J Dermatol.* 2013;168(4):898-899.
73. Chen W, Fan L, Wang Y, Deng X. Treatment application of rivaroxaban in Chinese patients with livedoid vasculopathy. *J Pain Res.* 2017;10:621-624.
74. Lee JM, Kim IH. Case series of recalcitrant livedoid vasculopathy treated with rivaroxaban. *Clin Exp Dermatol.* 2016;41(5):559-561.
75. Criado PR, de Souza Espinell DP, Valentef NS, Alavi A, Kirsner RS. Livedoid vasculopathy and high levels of

- lipoprotein: response to danazol. *Dermatol Ther.* 2015;28(4):248-253.
76. Acland KM, Darvay A, Wakelin SH, Russell-Jones R. Livedoid vasculitis: a manifestation of the antiphospholipid syndrome? *Br J Dermatol.* 1999;140(1):131-135.
 77. Hsiao GH, Chiu HC. Low-dose danazol in the treatment of livedoid vasculitis. *Dermatology.* 1997;194(3):251-255.
 78. Yasue T. Livedoid vasculitis and central nervous system involvement in systemic lupus erythematosus. *Arch Dermatol.* 1986;122(1):66-70.
 79. Winkelmann RK. Livedoid vasculitis (segmental hyalinizing vasculitis). *Jpn J Dermatol B.* 1972;82(3):84-89.
 80. Gray HR, Graham JH, Johnson W, Burgoon CF Jr. Atrophie blanche: periodic painful ulcers of lower extremities—a clinical and histopathological entity. *Arch Dermatol.* 1966;93(2):187-193.
 81. Klein KL, Pittelkow MR. Tissue plasminogen activator for treatment of livedoid vasculitis. *Mayo Clin Proc.* 1992;67(10):923-933.
 82. Kallenberg CG. Key advances in the clinical approach to ANCA-associated vasculitis. *Nat Rev Rheumatol.* 2014;10(8):484-493.
 83. Schönermark U, Gross WL, de Groot K. Treatment of ANCA-associated vasculitis. *Nat Rev Nephrol.* 2014;10(1):25-36.
 84. Chen KR. Skin involvement in ANCA-associated vasculitis. *Clin Exp Nephrol.* 2013;17(5):676-682.
 85. Chen KR, Carlson JA. Clinical approach to cutaneous vasculitis. *Am J Clin Dermatol.* 2008;9:71-92.
 86. Jennette JC, Falk RJ. Small-vessel vasculitis. *N Engl J Med.* 1997;337:1512-1523.
 87. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg Strauss syndrome: clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore).* 1999;78:26-37.
 88. Guillevin L, Durand-Gasselin B, Cevallos R, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. *Arthritis Rheum.* 1999;42:421-430.
 89. Duna GF, Galperin C, Hoffman GS. Wegener's granulomatosis. *Rheum Dis Clin North Am.* 1995;21:949-986.
 90. Alkhan A, Hocker T. Vasculitides, vasculopathies, and other vascular disorders. In: *Review of Dermatology*. Philadelphia, PA: Elsevier Saunders; 2016. pp. 174-189.
 91. Smith RM. Update on the treatment of ANCA associated vasculitis. *Presse Med.* 2015;44(6 Pt 2):e241-e249.
 92. Ozaki S. ANCA-associated vasculitis: diagnostic and therapeutic strategy. *Allergol Int.* 2007;56(2):87-96.
 93. Bologna J, Jorizzo JL, Schaffer JV. *Cutaneous vasculitis. Dermatology*. Philadelphia, PA: Elsevier Saunders; 2012. pp. 385-410.
 94. Darteville A, Chaigne B, Moachon L, et al. Levamisole-induced vasculopathy: a systematic review. *Semin Arthritis Rheum.* 2019;48(5):921-926.
 95. Roberts JA, Chévez-Barrios P. Levamisole-induced vasculitis: a characteristic cutaneous vasculitis associated with levamisole-adulterated cocaine. *Arch Pathol Lab Med.* 2015;139(8):1058-1061.
 96. Radić M, Martinović Kaliterina D, Radić J. Drug-induced vasculitis: a clinical and pathological review. *Neth J Med.* 2012;70(1):12-17.
 97. Fries JF, Hunder GG, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Summary. *Arthritis Rheum.* 1990;33:1135-1136.
 98. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum.* 2013;65(1):1-11.
 99. Craven A, Robson J, Ponte C, et al. ACR/EULAR-endorsed study to develop Diagnostic and Classification Criteria for Vasculitis (DCVAS). *Clin Exp Nephrol.* 2013;17(5):619-621.
 100. Kallenberg CG. Advances in pathogenesis and treatment of ANCA-associated vasculitis. *Discov Med.* 2014;18(99):195-201.
 101. Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis.* 2009;68(3):310-317.
 102. Faurschou M, Westman K, Rasmussen N, et al. Brief Report: long-term outcome of a randomized clinical trial comparing methotrexate to cyclophosphamide for remission induction in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum.* 2012;64(10):3472-3477.
 103. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med.* 2010;363(3):221-232.
 104. Jones RB, Furuta S, Tervaert JW, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. *Ann Rheum Dis.* 2015;74(6):1178-1182.
 105. Hiemstra TF, Walsh M, Mahr A, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA.* 2010;304(21):2381-2388.
 106. Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med.* 2014;371(19):1771-1780.
 107. Charles P, Terrier B, Perrodeau É, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAIN-RITSAN2). *Ann Rheum Dis.* 2018;77(8):1143-1149.
 108. Harper L, Morgan MD, Walsh M, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis.* 2012;71(6):955-960.
 109. Jayne DR, Gaskin G, Rasmussen N, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol.* 2007;18(7):2180-2188.
 110. Pagnoux C, Mahr A, Hamidou MA, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med.* 2008;359(26):2790-2803.
 111. Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with anti-neutrophil cytoplasmic autoantibodies. *N Engl J Med.* 2003;349(1):36-44.
 112. Joy MS, Hogan SL, Jennette JC, Falk RJ, Nachman PH. A pilot study using mycophenolate mofetil in relapsing or resistant ANCA small vessel vasculitis. *Nephrol Dial Transplant.* 2005;20:2725-2732.
 113. Corne D, Corne Le Gall E, Specks U. Clinical trials in antineutrophil cytoplasmic antibody-associated vasculitis: what we have learnt so far, and what we still have to learn. *Nephrol Dial Transplant.* 2017;32(suppl 1):i37-i47.
 114. Jayne DR, Chapel H, Adu D, et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. *Q J Med.* 2000;93(7):433-439.
 115. Lamprecht P, Voswinkel J, Lilienthal T, et al. Effectiveness of TNF-alpha blockade with infliximab in refractory Wegener's granulomatosis. *Rheumatology (Oxford).* 2002;41(11):1303-1307.
 116. Birck R, Warnatz K, Lorenz HM, et al. 15- Deoxyspergualin in patients with refractory ANCA-associated systemic vasculitis: a six-month open-label trial to evaluate safety and efficacy. *J Am Soc Nephrol.* 2003;14(2):440-447.

117. Jayne DRW, Bruchfeld AN, Harper L, et al. Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. *J Am Soc Nephrol.* 2017;28(9):2756-2767.
118. Kim S, Marigowda G, Oren E, et al. Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome. *J Allergy Clin Immunol.* 2010;125:1336-1343.
119. Moosig F, Gross WL, Herrmann K, et al. Targeting interleukin-5 in refractory and relapsing Churg-Strauss syndrome. *Ann Intern Med.* 2011;155:341-343.
120. De Vita S, Quartuccio L, Isola M, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. *Arthritis Rheum.* 2012;64(3):843-853.

Hidradenitis suppurativa



Epidemiology, clinical presentation, and pathogenesis

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Learning objectives

After completing this learning activity, participants should be able to recognize the clinical features of hidradenitis suppurativa and describe the mechanism of hidradenitis suppurativa progression based on recent literature.

Disclosures

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Hidradenitis suppurativa (HS) is an inflammatory disorder that is characterized by chronic deep-seated nodules, abscesses, fistulae, sinus tracts, and scars in the axilla, inguinal area, submammary folds, and perianal area. This disfiguring condition is accompanied by pain, embarrassment, and a significantly decreased quality of life. Although the mechanism of HS has not been entirely elucidated, lesion formation is believed to center around follicular hyperkeratosis within the pilosebaceous-apocrine unit. Recent research has provided new insight into the role of cytokines in the pathogenesis of HS, helping close some existing knowledge gaps in the development of this condition. The first article in this continuing medical education series reviews HS epidemiology, clinical presentation, and classification. We also provide an update on the most recent understanding of HS pathogenesis, including the central role of inflammatory cytokines and other contributing factors, such as genetics, hormones, and pathogenic microorganisms. (J Am Acad Dermatol 2020;82:1045-58.)

Key words: hidradenitis; hidradenitis suppurativa; IL-17; pathogenesis; TNF- α .

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Hidradenitis suppurativa (HS) was first described by a French surgeon in 1839.¹ In 2009, the HS Foundation adopted a consensus definition: “HS is a chronic, inflammatory, recurrent, debilitating, skin follicular disease that usually presents after puberty with painful deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly, the axillary, inguinal, and anogenital regions.”² There is agreement that the diagnosis requires a history of ≥ 5 typical lesions (erythematous papules, nodules, or abscesses) in flexural sites,³ with a recurring nature over time.⁴

EPIDEMIOLOGY

Key points

- The prevalence of HS is unknown, but estimates range from 0.00033% to 4.10%
- HS most frequently occurs in young adults
- HS is more than twice as common in women compared with men, and is more common in African Americans and biracial individuals than whites

HS prevalence is unclear. Estimates range from 0.00033% to 4.10%.⁵ Higher estimates are derived from prospective⁶ and self-reported studies^{7,8}; lower estimates derive from registries.⁹⁻¹² A retrospective analysis of >48 million patients in the United States found an HS prevalence of 0.1%. The adjusted prevalence for women was more than twice that for men, and there was a 3-fold and 2-fold higher prevalence in African Americans and biracial individuals, respectively, compared with whites.¹³

HS incidence is also uncertain. The same retrospective study found an annual incidence of 11.4 cases per 100,000, with twice the incidence in women compared with men; in African Americans, it was 2.5 times that of whites.¹⁴ Data from 1968 to 2008 revealed an annual age- and sex-adjusted incidence of 6 cases per 100,000; women 20 to 29 years of age had the highest incidence.¹⁵ A 5-year retrospective cohort study from across the United States validated these findings: among 40,585 patients with HS, the majority (63.3%) were 18 to 44 years of age and were women (75.6%).¹⁶

QUALITY OF LIFE

Key points

- HS significantly decreases patients' quality of life
- Depression and pain are associated with HS
- HS leads to social and work impairment

HS dramatically decreases quality of life (QoL). Patients report embarrassment, self-consciousness, and an inability to participate in social and athletic activities.¹⁷ Depression, anxiety, pain, high body mass index (BMI), and work impairment are the main factors affecting QoL.^{18,19} Depression occurs in 5.9% to 42.9% of patients with HS^{15,19-22} in both pediatric¹⁸ and adult populations.^{15,17,21} Pain affects $\leq 97\%$ of patients²³⁻²⁵ and is significantly worse compared with psoriasis and other diseases.²⁶ Higher BMI ($> 25 \text{ kg/m}^2$) also impacts self-evaluated health, QoL, and work impairment.²⁷ Two studies found that 21.3% to 25.2% of patients with HS patients are unemployed^{17,28} and that 9.4% are out of work because of disability.¹⁷ Substance use is also common, occurring in 4% of patients with HS ($n = 32,625$) compared with 2% of patients without HS ($n = 9,581,640$; $P < .001$).²² The most common substances used were alcohol followed by opioids and cannabis.²² Of greatest concern, there is an increased risk of completed suicides in patients with HS,²⁹ which is greater than 2-fold the risk of suicide in patients with psoriasis.³⁰

PRESENTATION AND CLINICAL CLASSIFICATION

Key points

- HS is diagnosed by clinical features and history, and there are multiple scoring systems used for the classification of disease severity
- Lesions include deep-seated nodules, abscesses, and sinus tracts that rupture and form scars
- The Hurley staging system is the most widely used HS classification system
- There are several clinically distinct HS phenotypes

HS is diagnosed clinically; pathologic confirmation is unnecessary.³¹⁻³³ There are 3 criteria for diagnosis: characteristic lesions, predilection for flexural sites, and lesion recurrence.³⁴

While disease presentation varies,³⁵ characteristic lesions are deep-seated nodules that expand to form abscesses³⁶ that subsequently rupture and drain.³³ The initial lesions are “blind boils,” which can progress to draining sinuses, bridged scars, and open “tombstone” comedones.³³ Fibrosis results in scarring.³³ Lesions favor the axillae and the inguinal area, but also occur in the submammary folds, perineal area, buttocks, mons pubis, scalp, the postauricular area, and the back.^{37,38} There is often

a significant delay between symptom onset and the establishment of diagnosis (average 7.2 years), which underscores the need for familiarity with the above diagnostic criteria.³⁹

Most patients have >1 lesion at the time of diagnosis.³⁷ Lesions are usually accompanied by discomfort, pruritus, and pain^{23,36}; many patients experience prodromal pain symptoms.³³ Factors including heat, sweating, physical activity, shaving, and friction exacerbate symptoms.^{21,40} Acute exacerbations alternating with periods of quiescence is typical.³³

The most common HS classification system is the Hurley staging system,⁴¹ which is a 3-stage classification of disease severity designed to help select treatment⁴²; unfortunately, it fails to assess disease activity or treatment response. However, other classification and scoring methods exist. The modified Sartorius score quantifies disease intensity in a more clinically meaningful way on an open-ended scale.^{43,44} The Hidradenitis Suppurativa Severity Score Index also assesses disease activity and severity.^{45,46} The Hidradenitis Suppurativa Clinical Response is a dichotomized clinical tool that measures treatment response.⁴⁷⁻⁴⁹ The Physician's Global Assessment, commonly used for diseases like psoriasis and acne,^{50,51} has also been adapted into an HS-specific version.⁵² Table I summarizes these systems.

The Hurley staging system has been shown to have good interrater reliability and is considered an acceptable instrument for the classification of HS.⁴² The modified Sartorius score, Hidradenitis Suppurativa Severity Score Index, Hidradenitis Suppurativa Clinical Response, and HS Physician's Global Assessment have been found to have lower agreement between assessors.⁴² More recently, a refined Hurley staging system that subdivides stages I and II into mild (A), moderate (B), and severe (C), was proposed to help guide treatment.⁵³ This refined system more accurately reflects disease severity according to patient-reported QoL and physician-assessed Hidradenitis Suppurativa Severity Score Index.⁵⁴ There is also a validated HS severity self-assessment tool for survey research that allows patients to report disease severity without being seen by a physician. One study found a 66.7% agreement between physician-determined Hurley stage and self-determined Hurley stage via the HS severity self-assessment tool.⁵⁵

There are multiple HS phenotypes (Table II).⁴⁹ These distinct clinical subtypes are not based on disease severity; all 3 Hurley stages can occur in each

type. The regular type is the most common, and consists of patients who fulfill the diagnostic criteria for HS but who lack other specific characteristics.⁴⁹ The frictional furuncle type features lesions in frictional sites in patients who are overweight.⁴⁹ The conglobata type consists of cysts and acne conglobata primarily on the face and trunk in men who are not overweight.⁴⁹ The syndromic type features concomitant diseases, such as pyoderma gangrenosum and arthritis.⁴⁹ Finally, the ectopic type involves the face.⁴⁹ Although these phenotypes do not guide therapeutic decisions, consideration of these phenotypes may help optimize disease management.⁵⁶

COMORBIDITIES AND RISK FACTORS

Key points

- HS is associated with many comorbidities, most of which are inflammatory in nature
- Obesity is the most common comorbidity associated with HS
- There is a strong association between HS and tobacco smoking
- There is an increased prevalence of HS among psoriasis patients
- HS is a component of the follicular occlusion triad/tetrad

HS patients have an incredibly high comorbidity burden.^{57,58} Hypertension, obesity, dyslipidemia, thyroid disorder, arthropathies, psychiatric disorders, and polycystic ovarian syndrome have all been independently associated with HS (Table III).⁵⁷ While the exact connection between HS and its comorbidities remains unclear,⁵⁹ many associated disorders are also inflammatory.

Adverse cardiovascular outcomes (myocardial infarction, ischemic stroke, and cardiovascular-associated death) and all-cause mortality are significantly increased in patients with HS independent of age, sex, socioeconomic status, smoking, and medications.⁶⁰ Atherosclerosis has been associated with increased serum levels of C-reactive protein and tumor necrosis factor- α , which are also elevated in HS.⁶⁰

Metabolic syndrome (MetS), which includes diabetes mellitus, hypertension, dyslipidemia, and obesity, is associated with chronic inflammation⁶¹ and HS.^{33,62,63} Hospitalized and nonhospitalized patients with HS have an odds ratio of 3.89 and 2.08, respectively, of being diagnosed with MetS compared with healthy patients.⁶¹ Of the diseases comprising MetS, however, obesity is the most commonly associated: 50% to 75% of patients with HS are overweight

Table I. Hidradenitis suppurativa classification systems

Scoring system	Description					
Hurley score	Stage I	Single or multiple isolated abscesses without sinus tracts or scarring				
	Stage II	Recurrent abscesses with ≥ 1 sinus tracts and scarring, separated by normal skin				
	Stage III	Diffuse boils with multiple interconnected sinus tracts and no intervening normal skin.				
Modified Sartorius score	Anatomic regions involved	3 points per region: axilla, groin, gluteal, other				
	No. and scores of lesions	1 point for nodule, 6 points for fistula, for each region				
	Longest distance between 2 lesions	1 point if < 5 cm; 3 points if 5-10 cm, 9 points if > 10 cm. If 1 lesion, use same point system for size of lesion				
	Lesions clearly separated by normal skin	0 points if yes, 9 points if no				
HS Physicians' Global Assessment	Clear: 0	0 abscesses, 0 draining fistulas, 0 inflammatory nodules, 0 noninflammatory nodules				
	Minimal: 1	0 abscesses, 0 draining fistulas, 0 inflammatory nodules, presence of noninflammatory nodules				
	Mild: 2	0 abscesses, 0 draining fistulas, 1-4 inflammatory nodules, OR 1 abscess or draining fistula and 0 inflammatory nodules				
	Moderate: 3	0 abscesses, 0 draining fistulas, ≥ 5 inflammatory nodules OR 1 abscess or draining fistula and ≥ 1 inflammatory nodule OR 2-5 abscesses or draining fistulas and < 10 inflammatory nodules				
	Severe: 4	2-5 abscesses or draining fistulas and ≥ 10 inflammatory nodules				
	Very severe: 5	>5 abscesses or draining fistulas				
Hidradenitis Suppurativa Severity Index		No. of body sites	No. of erythematous surface area	No. of dressing changes during work hours	Pain (visual analog scale)	
	Stage 0	0	0	0	0-1	
	Stage 1	1	1	0	0-1	
	Stage 2	2	2-3	1	2-4	
	Stage 3	3	4-5	>1	5-7	
	Stage 4	≥ 4	>5	>1	8-10	
Hidradenitis Suppurativa Clinical Response	Hidradenitis Suppurativa Clinical Response achievers	$\geq 50\%$ reduction in the sum of abscesses and inflammatory nodules, no increase in the number of abscesses, and no increase in the number of draining fistulas from baseline				

or obese.⁵⁹ Obesity increases the proinflammatory response,²⁷ and high-BMI patients have higher Hurley scores, more affected areas, and worse self-reported severity compared with low-BMI patients.⁶⁴

There is also a strong relationship between tobacco and HS, although a causal relationship has not been established. The prevalence of smoking in patients with HS is estimated at 70% to 90%,⁶⁵ and the odds ratio of a new HS diagnosis increases by 90% among tobacco smokers compared with nonsmokers after adjusting for age, sex, race, and obesity.⁶⁶ Smoking also appears to correlate with

obesity: 75% of tobacco smokers diagnosed with HS are obese.⁶⁶

Psoriasis is also associated with HS. A study of 68,836 patients with psoriasis found that HS prevalence was increased in patients with psoriasis compared with age-, sex-, and ethnicity-matched control subjects (0.3% vs 0.2%).⁶⁷ This difference remains statistically significant after adjusting for smoking, obesity, and additional comorbidities. Psoriasis patients with coexistent HS are younger and have a higher prevalence of obesity and smoking.⁶⁷

Table II. Hidradenitis suppurativa phenotypes⁴⁹

Phenotype	Description
Regular	Patients fulfill the diagnostic criteria of HS Lack of additional specific characteristics Most common type
Frictional furuncle	Overweight patients Regular HS plus multiple deep nodules and abscesses on sites exposed to enhanced friction (abdomen, thighs, and buttocks)
Scarring folliculitis	Regular HS plus pustules, cysts, superficial nodules, depressed cribriform scarring, double ended comedones These lesions are frequently on buttocks, inguinal region, and pubic region Scarring of these lesions typically occurs
Conglobata	Commonly occurs in overweight patients who smoke Cyst formation and acne conglobata lesions on the back and the face This type is usually familial—initial γ -secretase mutations were found in this group Usually more severe (Hurley stage II-III)
Syndromic	Patients are usually men and are not overweight Patients have a syndromic constellation PASH syndrome PAPASH syndrome

HS, Hidradenitis suppurativa; PAPASH, pyogenic arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa; PASH, pyoderma gangrenosum, acne, and hidradenitis suppurativa.

Table III. Comorbidities and risk factors for hidradenitis suppurativa¹⁴⁰

Comorbidity/risk factor	Evidence level, grade of recommendation
Smoking	1, A
Cardiovascular disease	2, B
Metabolic syndrome	
Obesity	
Depression	
Diabetes mellitus	
Hypertension	
Hypertriglyceridemia	
Spondyloarthropathy	
Crohn disease	4, C

Several other conditions associated with a proinflammatory state have also been associated with HS. There is a 3.5% incidence of obstructive sleep apnea in patients with HS versus 2.5% in those without HS.⁶⁸ Inflammatory bowel disease (IBD), particularly Crohn disease (CD), also has possible epidemiologic and pathogenic connections with HS.^{69,70} Analysis from 4 studies found HS prevalence in IBD and CD patients to be 12.8% and 17.3%, respectively. Inflammatory arthritis also has a higher prevalence in HS populations compared with the general population.^{58,71} In a prospective study of 640 patients, 3.7% had comorbid spondylarthritis, and of those patients, HS preceded articular symptoms in >90%.⁷¹

Some dermatologic diseases share cutaneous pathology with HS. Hyperplasia of the pilosebaceous apparatus, follicular occlusion, and bacterial invasion are etiologic factors in acne conglobata and dissecting cellulitis as well as HS.⁷² Together, these conditions constitute the follicular occlusion triad⁷²; the addition of pilonidal cyst defines the follicular occlusion tetrad.⁷³ HS and acne can also be components of autoinflammatory syndromes. Pyoderma gangrenosum, acne, and hidradenitis suppurativa (PASH) is an established syndrome when all three conditions are present. If a patient has PASH with the addition of pyogenic arthritis, it is designated PAPASH.⁷⁴ Finally, chronic HS can transform into squamous cell carcinoma. The prevalence of squamous cell carcinoma associated with HS is approximately 4.6%.⁷⁵

PATHOGENESIS

Key points

- The primary event in HS is follicular hyperkeratosis, leading to rupture of the hair follicle and subsequent inflammation of apocrine glands
- TNF- α and interleukin-17 are key cytokines in HS pathogenesis
- Levels of TNF- α are higher in the lesional tissue of patients with HS than that of patients with psoriasis

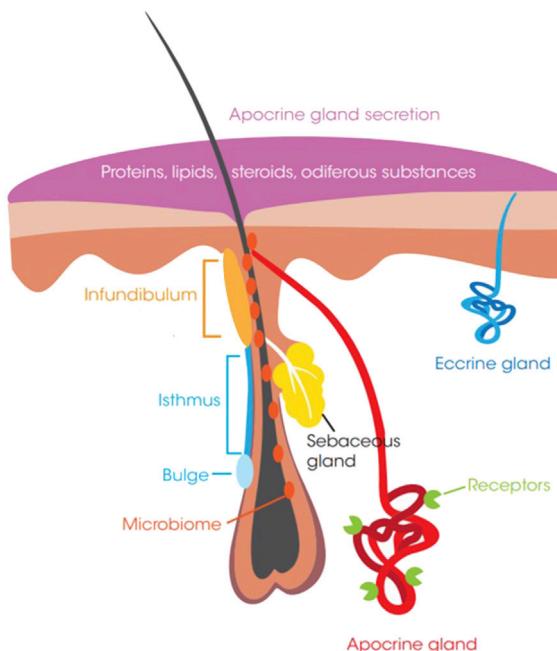


Fig 1. Pilosebaceous-apocrine unit. Adapted from Hoffman et al.⁷⁷

- **Levels of TNF- α in lesional HS skin and serum levels of interleukin-17 correlate with disease severity**
- **The role of sex hormones in HS remains unclear**
- **Thirty percent to 40% of patients with HS have ≥ 1 family member with the disease, supporting a genetic predisposition**

The mechanism of lesion formation in HS centers around the pilosebaceous—apocrine unit, which contains a hair follicle associated with sebaceous and apocrine glands. Sebaceous glands secrete sebum, a group of complex oils that lubricate the skin.⁷⁶ Apocrine glands drain oily sweat through a dermal duct that passes through the hair follicle by a coiled acrosyringium above the sebaceous gland (Fig 1).⁷⁷

Initially, apocrine gland inflammation was proposed as the primary event in HS.^{78–80} Newer research suggests that follicular hyperkeratosis occurs first, causing plugging and dilation that results in follicle rupture with subsequent inflammation, abscess, and sinus tract formation (Fig 2).^{80,81} Apocrine involvement appears secondary to dermal inflammation.⁸² Patients with HS have no change in apocrine gland size, density, or distribution compared with healthy control subjects,⁸³ but they do tend to have a reduced volume of sebaceous glands.^{82,84}

HS immunopathogenesis is complex and still being elucidated, but several cytokines appear to be particularly relevant (Fig 3).

TNF- α

TNF- α is secreted by innate and adaptive immune cells and is elevated in inflammatory diseases including rheumatoid arthritis, IBD, and psoriasis.^{85–87} TNF- α is significantly increased in patients with HS compared with healthy control subjects and patients with psoriasis,^{88,89} and TNF- α levels increase with increasing HS severity.⁸⁹

The role of TNF- α in HS is multifactorial.⁹⁰ First, TNF- α increases the ratio of T_H17 to regulatory T cells, which results in increased production of T_H17 cells' disease-relevant cytokines.⁸⁸ TNF- α inhibition in patients with HS decreases this ratio, reduces the polyfunctionality of CD4 $^{+}$ cells, and decreases IL-17-producing T cells, which ultimately reduces IL-22, interferon-gamma (IFN- γ), and IL-2-expressing CD4 $^{+}$ T cells.⁸⁸

Second, TNF- α acts on adipocytes and muscle cells to induce insulin-signaling defects⁹¹ and suppresses the secretion of adiponectin from adipocytes.⁹² Adiponectin is an antiinflammatory hormone that regulates glucose metabolism and insulin sensitivity.⁹³ It is negatively correlated with BMI; decreased circulating levels are associated with diabetes and MetS.^{93,94} Adiponectin levels are significantly decreased in patients with HS.⁹² Patients with HS have higher fasting serum glucose, insulin levels, and insulin resistance compared with control subjects, suggesting that HS, in part because of elevated TNF- α , might predispose to insulin resistance.⁹¹

Third, the relationship between smoking and HS is thought to involve TNF- α . Nicotine increases eccrine gland secretion, and nicotine excretion in sweat induces TNF- α release by keratinocytes and T_H17 cells. Nicotine directly stimulates macrophages to produce IL-1 β and TNF- α and increases the expression of matrix metalloproteinases (MMPs).⁹⁵ Nicotine induces infundibular epithelial hyperplasia, causing follicular occlusion and rupture.⁶⁶ Notably, nicotine acetylcholine receptors are found on all cells implicated in the pathogenesis of HS, including keratinocytes, sebocytes, mast cells, neutrophils, lymphocytes, and macrophages.⁶⁶

Fourth, the upregulation of Toll-like receptors (TLRs) and MMPs has been observed in HS. TLRs are important for generating innate immune responses. TLR4 helps activate gene expression resulting in production of proinflammatory

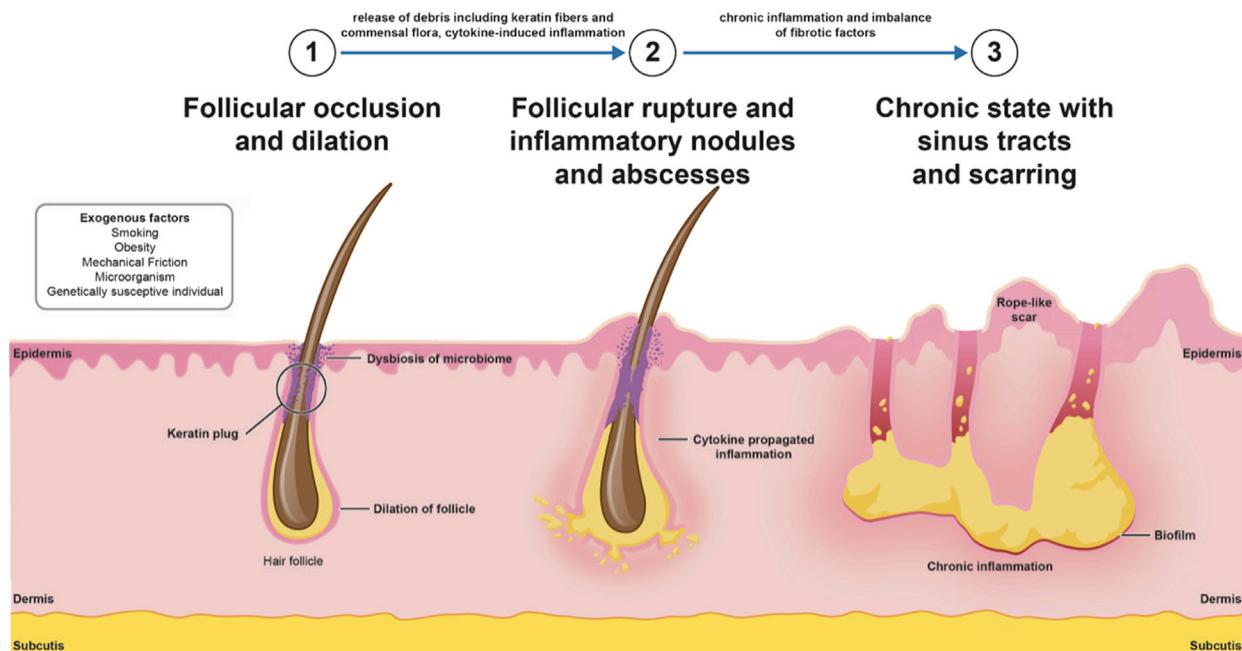


Fig 2. Postulated sequence of events underlying the pathophysiology of hidradenitis suppurativa. The first event is follicular occlusion with subsequent dilation. Endogenous factors in genetically predisposed individuals and exogenous factors (ie, smoking, friction, metabolic changes, and microbiome) contribute to occlusion of the follicular isthmus and early inflammation. The second event is rupture of the dilated follicle, propagation of cytokine-driven inflammation, and the formation of inflammatory nodules and abscesses. The third event is chronic inflammation and an imbalance of fibrotic factors that creates scarring and sinus tracts. Adapted from Vossen et al.⁸¹

cytokines including TNF- α , IL-1 β , and IL-6, as well as antiinflammatory cytokines, such as IL-10.⁹⁶ MMPs also activate inflammatory effectors and directly lead to tissue injury.⁹⁵ MMP2 is activated by TNF- α , and MMP9 is induced by TLRs, TNF- α , and IL-17. Elevations of these MMPs have been found in HS lesions.⁹⁵

There are still other signaling molecules that interact with TNF- α , though their roles are less well understood. For example, a relationship between TNF- α and mammalian target of rapamycin has been suggested.⁹⁷ Mammalian target of rapamycin complexes are major cellular regulators of survival, growth, and proliferation and are dysregulated in inflammatory diseases, including HS.⁹⁷ Complement factor C5a is another example. C5a primes overproduction of TNF- α ; plasma concentrations of C5a in patients with HS are higher compared with healthy control subjects.⁹⁸ Recent data demonstrate a dysregulation of complement-specific differentially expressed genes and proteins in HS lesions compared with nonlesional skin. C5a blood levels were elevated while other factors like C4b, C3, C3b, and iC3b were downregulated in patients with HS. In the skin transcriptome, other complement factors like

C1q and C2 were elevated while C7 was decreased. The role of complement dysregulation in patients with HS is still unclear.⁹⁹

IL-17

T_H17 cells develop from IL-23-stimulated CD4 $^{+}$ T cells and are the main producers of IL-17A. T_H17 cells are increased in lesional and perilesional HS skin compared with both autologous uninvolved skin and skin from healthy volunteers.⁸⁸ IL-17A levels are increased in patients with moderate-to-severe HS compared with healthy control subjects and correlate with disease severity independent of gender, age, and smoking.^{100,101} IL-17 levels are similarly increased in CD and ulcerative colitis,¹⁰² supporting a pathogenic connection between HS and IBD.¹⁰³

IL-17 induces the expression of IL-1 β , IL-6, and TNF- α ¹⁰⁴ through a mechanism involving the nod-like receptor protein 3 (NLRP3) inflammasome. Inflammasomes are protein complexes in macrophages and neutrophils that detect microorganisms and indicate endogenous stress. They activate caspase-1, which activates proinflammatory cytokines, such as IL-1 β and IL-18. IL-1 β is a pyrogen

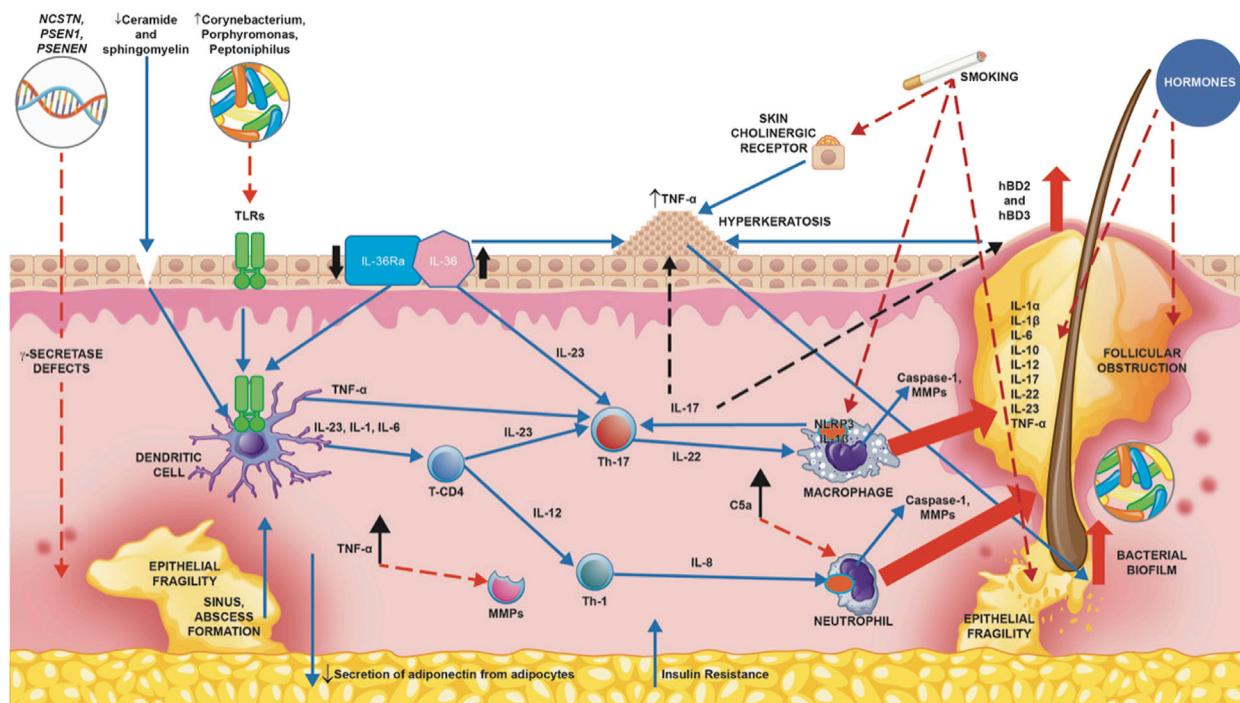


Fig 3. Postulated pathogenesis of hidradenitis suppurativa. Genetic defects affecting γ -secretase subunits result in abnormal immune system function and impaired maturation of hair follicle cells, resulting in an environment predisposed to epithelial fragility. Imbalances in interleukin (IL)-36:IL-36RA along with stimulation of cholinergic receptors from nicotine increase infundibular hyperkeratosis and follicular obstruction. Microbial dysbiosis and biofilm formation stimulate human beta-defensins that enhance follicular obstruction and inflammation. Alterations in sphingolipid composition, overexpression of Toll-like receptors from an altered microbiome, and imbalances in IL-36:IL-36RA stimulate dendritic cells and create a proinflammatory environment. Tumor necrosis factor- α (TNF- α) from keratinocytes and activated dendritic cells induces more hyperkeratosis, decreases adiponectin secretion from adipocytes, and increases the expression of matrix metalloproteases (MMPs). Complement factor C5a increases neutrophil migration and stimulates more production of TNF- α . IL-23 drives T_H17 differentiation and IL-17 overexpression. IL-17 induces expression of the NLRP3 inflammasome in neutrophils and macrophages, resulting in release of more inflammatory cytokines as well as caspases and MMPs into the follicular unit and perilesional skin. Smoking also stimulates NLRP3 expression. Hormones and high insulin levels worsen follicular obstruction and affect cytokine levels. Cytokine-driven feedback propagates and sustains chronic inflammation that results in formation of inflammatory nodules, abscesses, and eventually sinus tract and scar formation. Adapted from Cubilla et al.¹³⁹

and leukocyte-activating factor that further increases T_H17 cell levels.⁴⁰ IL-17 in turn increases macrophage production of IL-1 β and TNF- α , enhancing the immune response.⁹⁵ Elevated IL-1 β has been found in HS lesional and perilesional skin,^{40,89,90} and is considered a key inflammatory mediator in HS. Keratin fibers and keratinocyte debris also activate inflammasomes, and NLRP3 expression is elevated in HS.⁹⁵

Other cytokines

IL-12 and IL-23 are heterodimeric cytokines that share a common subunit (p40) and play a role in the

establishment of chronic inflammation.^{105,106} IL-23 is also involved in the development and maintenance of T_H17 cells. IL-23, and to a lesser degree IL-12, are secreted by activated macrophages in the papillary and reticular dermis.¹⁰⁶

IL-36, primarily expressed from keratinocytes and monocytes, is involved in innate and adaptive immunity.¹⁰⁷ Concentrations of IL-36 α , - β , and - γ are significantly higher in HS lesions compared with healthy adults.¹⁰⁷⁻¹⁰⁹ Activity of these proinflammatory cytokines is controlled by natural inhibitors, including the IL-36 receptor antagonist (IL-36RA). IL-36RA is not significantly expressed in HS lesional

skin, so IL-36 signaling might be unopposed.^{107,109} Interestingly, IL-36RA is increased in psoriasis, suggesting that an imbalance in the IL-36:IL-36RA ratio might contribute to the differing phenotypes of these conditions.¹⁰⁷

IL-6 is a proinflammatory cytokine that promotes B cell antibody production and is involved in multiple inflammatory conditions.¹¹⁰ Elevated levels of IL-6 and its receptor have been detected in HS skin,^{95,111} especially in Hurley stage II to III patients compared with healthy control subjects.¹¹²

Studies regarding the relevance of IFN- γ are inconsistent.^{88,113} A pilot study of HS patients and age-matched chronic wound patients demonstrated significantly elevated IFN- γ levels in HS effluent compared with chronic wounds.¹¹³ Increased expression of IFN- γ has also been found in HS lesional skin compared with the skin of healthy donors.¹¹⁴ An analysis of T cells from HS patient skin and blood, however, found no difference in IFN- γ production between patients with HS and healthy control subjects.⁸⁸

Hormones

Sebaceous glands have 2 types of androgen-converting enzymes: type II 5 α -reductase in hair follicles and type I in hair follicles and apocrine glands.^{80,115,116} 5 α -Reductase converts testosterone (T) to the more potent dihydrotestosterone (DHT). Both T and DHT bind androgen receptors on sebaceous glands, increasing sebum secretion and inflammation. Nonetheless, hyperandrogenism is usually absent in patients with HS^{80,117} and T and DHT levels in patients with HS do not differ compared with control subjects,^{80,118} suggesting that the effect of androgens in HS, if relevant, is local.⁸⁰

The role of female hormones in HS is also unclear.¹¹⁹ Up to 43% of female patients with HS experience worsening symptoms around menses.¹²⁰ Contraceptives containing progesterone appear to worsen HS, potentially because of their androgen-like effects.¹¹⁸ Alternatively, spironolactone, which is antiandrogenic, has been shown to decrease HS lesion count, PGA score, and pain.¹²¹

Sphingolipids

Sphingolipids are membrane lipid signaling molecules. There are 3 main types: ceramides, sphingomyelins, and glycosphingolipids. HS lesional skin demonstrates decreased expression of enzymes that generate ceramide and sphingomyelin as well as increased expression of enzymes that catabolize ceramide.¹²² Decreasing ceramide and

sphingomyelin levels disrupt the cutaneous barrier and cause immune activation.¹²²

Genetics

Thirty percent to 40% of patients with HS have ≥ 1 affected family member.^{123,124} *NCSTN*, *PSEN1*, and *PSENEN* genes are involved in γ -secretase production, which is essential for normal immune system function and maturation of hair follicle cells. In families with these mutations, HS follows an autosomal dominant inheritance pattern with incomplete penetrance,¹²³ and affected members tend to have a more severe phenotype.¹²⁵

Other genetic factors are also important in the pathogenesis of HS. These include the β -defensin gene cluster of chromosome band 8p23.1, which encodes the antimicrobial peptides human beta-defensins-2 and -3.¹²⁶ Single-nucleotide polymorphisms at the promoter region of the TNF gene,⁹⁶ as well as variations in microRNA expression, have also been correlated with HS.^{127,128}

BACTERIAL COLONIZATION

Key points

- HS patients have a unique skin microbiome
- Biofilms are a key feature of lesional skin, but distinct species have also been found
- There is a lack of consensus on which bacterial species are most common in HS lesions

The cutaneous microbiome is significantly different in HS lesional skin, nonlesional skin, and patients without HS.⁸¹ The lesional skin microbiome consists predominantly of *Corynebacterium*, *Porphyromonas*, and *Peptoniphilus* species,¹²⁹ while nonlesional skin has predominantly *Acinetobacter* and *Moraxella*.¹³⁰ *Corynebacterium* are Gram-positive aerobes that opportunistically infiltrate atypical tissue-like wounds.¹³¹ *Porphyromonas* are Gram-negative anaerobes that are typically found in the salivary microbiome and thrive as part of a polymicrobial community in inflammatory environments.¹³² *Peptoniphilus* are Gram-positive anaerobes that are commensals of the vagina and gut and that are commonly associated with diabetic skin or infections involving soft tissue, bone, joint, or surgical sites.¹³³ *Porphyromonas* and *Peptoniphilus* species have been associated with chronic wounds and therefore may impact the chronicity of HS.¹³⁰

Propionibacterium acnes is a skin commensal with bactericidal properties against other pathogens

that, along with *Staphylococcus epidermidis*, constitutes the microbiome of healthy adults.¹³⁰ *P acnes* is reduced in HS skin, potentially allowing pathogenic bacteria to flourish.¹³⁰ *S epidermidis* strains are decreased in HS lesional sites compared with non-lesional sites, too, but within the lesional sites, more strains were cultured from patients on antibiotics, and of those, *S epidermidis* was found to have reduced sensitivity to tetracycline and clindamycin, but higher sensitivity to rifampin.¹³⁴ Data involving the presence of *S aureus* in HS are inconsistent.¹³⁵ Some groups have observed *S aureus* in HS lesions, but others have not, likely because of the anaerobic nature deep within lesions.¹³⁶

In addition to the dysbiosis inherent in HS, colonization with biofilm-forming bacteria is common in HS, likely because of inflammation and rupture of the innate skin barrier.^{114,137,138} Biofilm aggregates occur in 67% to 75% of sinus tracts and infundibula, and are larger in lesional than perilesional skin.¹²⁹

In conclusion, HS is a debilitating condition that stems from follicular hyperkeratosis and apocrine gland inflammation. Patients are frequently smokers, obese, and report pain and a significantly decreased QoL. HS pathogenesis involves immune dysregulation with inflammatory cytokines, specifically TNF- α and IL-17, playing important roles, likely with an underlying genetic predisposition and distinct microbiome. Increased understanding of the immunopathogenesis has paved the way for the development of new targeted treatment options for this disease.

REFERENCES

- Chen W, Plewig G. Should hidradenitis suppurativa/acne inversa best be renamed as "dissecting terminal hair folliculitis"? *Exp Dermatol*. 2017;26:544-547.
- Shavit E, Alavi A, Bechara FG, et al. Proceeding report of the Second Symposium on Hidradenitis Suppurativa Advances (SHSA) 2017. *Exp Dermatol*. 2019;28(1):94-103.
- Ingram JR. Hidradenitis suppurativa: an update. *Clin Med*. 2016;16:70-73.
- Von Der Werth JM, Williams HC, Raeburn JA. The clinical genetics of hidradenitis suppurativa revisited. *Br J Dermatol*. 2000;142:947-953.
- Posso-De Los Rios CJ, Sarfo A, Ghias M, et al. Proceeding report of the third symposium on Hidradenitis Suppurativa advances (SHSA) 2018. *Exp Dermatol*. 2019;28:769-775.
- Jemec GB, Heidenheim M, Nielsen NH. The prevalence of hidradenitis suppurativa and its potential precursor lesions. *J Am Acad Dermatol*. 1996;35(2 pt 1):191-194.
- Vinding GR, Miller IM, Zarchi K, Ibler KS, Ellervik C, Jemec GBE. The prevalence of inverse recurrent suppuration: a population-based study of possible hidradenitis suppurativa. *Br J Dermatol*. 2014;170:884-889.
- Jemec GB. The symptomatology of hidradenitis suppurativa in women. *Br J Dermatol*. 1988;119:345-350.
- Albares MP, Belinchón I, Ramos JM, Sánchez-Payá J, Betloch I. Epidemiologic study of skin diseases among immigrants in Alicante, Spain [in Spanish]. *Actas Dermosifiliogr*. 2012;103:214-222.
- Sung S, Kimball AB. Counterpoint: analysis of patient claims data to determine the prevalence of hidradenitis suppurativa in the United States. *J Am Acad Dermatol*. 2013;69:818-819.
- Mahé A, IAH Cissé, Faye O, N'Diaye HT, Niamba P. Skin diseases in Bamako (Mali). *Int J Dermatol*. 1998;37:673-676.
- Cosmatos I, Matcho A, Weinstein R, Montgomery MO, Stang P. Analysis of patient claims data to determine the prevalence of hidradenitis suppurativa in the United States. *J Am Acad Dermatol*. 2013;68:412-419.
- Garg A, Kirby JS, Lavian J, Lin G, Strunk A. Sex- and age-adjusted population analysis of prevalence estimates for hidradenitis suppurativa in the United States. *JAMA Dermatol*. 2017;153:760-764.
- Garg A, Lavian J, Lin G, Strunk A, Alloo A. Incidence of hidradenitis suppurativa in the United States: a sex- and age-adjusted population analysis. *J Am Acad Dermatol*. 2017;77:118-122.
- Vazquez BG, Alikhan A, Weaver AL, Wetter DA, Davis MD. Incidence of hidradenitis suppurativa and associated factors: a population-based study of Olmsted County, Minnesota. *J Invest Dermatol*. 2013;133:97-103.
- Slyper M, Strunk A, Garg A. Incidence of sexual dysfunction among patients with hidradenitis suppurativa: a population-based retrospective analysis. *Br J Dermatol*. 2018;179:502-503.
- Delany E, Gormley G, Hughes R, et al. A cross-sectional epidemiological study of hidradenitis suppurativa in an Irish population (SHIP). *J Eur Acad Dermatol Venereol*. 2018;32:467-473.
- Tiri H, Jokelainen J, Timonen M, Tasanen K, Huilaja L. Somatic and psychiatric comorbidities of hidradenitis suppurativa in children and adolescents. *J Am Acad Dermatol*. 2018;79:514-519.
- Vangipuram R, Vaidya T, Jandarov R, Alikhan A. Factors contributing to depression and chronic pain in patients with hidradenitis suppurativa: results from a single-center retrospective review. *Dermatology*. 2016;232:692-695.
- Shavit E, Dreher J, Freud T, Halevy S, Vinker S, Cohen AD. Psychiatric comorbidities in 3207 patients with hidradenitis suppurativa. *J Eur Acad Dermatol Venereol*. 2015;29:371-376.
- Matusiak Ł. Profound consequences of hidradenitis suppurativa: a review. *Br J Dermatol*; 2019. <https://doi.org/10.1111/bjd.16603> [Epub ahead of print]. Accessed October 22, 2019.
- Garg A, Papagermanos V, Midura M, Strunk A, Merson J. Opioid, alcohol, and cannabis misuse among patients with hidradenitis suppurativa: a population-based analysis in the United States. *J Am Acad Dermatol*. 2018;79:495-500.e1.
- Matusiak Ł, Szczęch J, Kaaz K, Lelonek E, Szepietowski JC. Clinical characteristics of pruritus and pain in patients with hidradenitis suppurativa. *Acta Derm Venereol*. 2018;98:191-194.
- Patel ZS, Hoffman LK, Buse DC, et al. Pain, psychological comorbidities, disability, and impaired quality of life in hidradenitis suppurativa [corrected]. *Curr Pain Headache Rep*. 2017;21:49.
- Kouris A, Platsidaki E, Christodoulou C, et al. Quality of life and psychosocial implications in patients with hidradenitis suppurativa. *Dermatology*. 2016;232:687-691.
- Onderdijk AJ, van der Zee HH, Esmann S, et al. Depression in patients with hidradenitis suppurativa. *J Eur Acad Dermatol Venereol*. 2013;27:473-478.

27. Kjaersgaard Andersen R, Theut Riis P, Jemec GBE. Factors predicting the self-evaluated health of hidradenitis suppurativa patients recruited from an outpatient clinic. *J Eur Acad Dermatol Venereol.* 2018;32:313-317.
28. Gasparic J, Theut Riis P, Jemec GB. Recognizing syndromic hidradenitis suppurativa: a review of the literature. *J Eur Acad Dermatol Venereol.* 2017;31:1809-1816.
29. Thorlacius L, Cohen AD, Gislason GH, Jemec GBE, Egeberg A. Increased suicide risk in patients with hidradenitis suppurativa. *J Invest Dermatol.* 2018;138:52-57.
30. Tiri H, Huilaja L, Jokelainen J, Timonen M, Tasanen K. Women with hidradenitis suppurativa have an elevated risk of suicide. *J Invest Dermatol.* 2018;138:2672-2674.
31. Micheletti RG. Natural history, presentation, and diagnosis of hidradenitis suppurativa. *Semin Cutan Med Surg.* 2014;33(3 suppl):S51-S53.
32. Dhaou BB, Boussema F, Aydi Z, Baili L, Rokbani L. Hidradenitis suppurativa (Verneuil's disease). *J Saudi Soc Dermatol Dermatol Surg.* 2013;17:1-5.
33. Shalom G. Hidradenitis suppurativa: epidemiology, clinical features, associated comorbidities and treatment. *G Ital Dermatol Venereol.* 2017;152:46-57.
34. Vekic DA, Frew J, Cains GD. Hidradenitis suppurativa, a review of pathogenesis, associations and management. Part 1. *Australas J Dermatol.* 2018;59:267-277.
35. Hessam S, Scholl L, Sand M, Schmitz L, Reitenbach S, Bechara FG. A novel severity assessment scoring system for hidradenitis suppurativa. *JAMA Dermatol.* 2018;154:330-335.
36. Parulkar I, Haleem H, Paek SY. Epidemiologic and clinical features of hidradenitis suppurativa. *Semin Cutan Med Surg.* 2017;36:42-46.
37. Kim WB, Sibbald RG, Hu H, et al. Clinical features and patient outcomes of hidradenitis suppurativa: a cross-sectional retrospective study. *J Cutan Med Surg.* 2016;20:52-57.
38. Zouboulis CC, Del Marmol V, Mrowietz U, Prens EP, Tzellos T, Jemec GBE. Hidradenitis suppurativa/acne inversa: criteria for diagnosis, severity assessment, classification and disease evaluation. *Dermatology.* 2015;231:184-190.
39. Saunte DM, Boer J, Stratigos A, et al. Diagnostic delay in hidradenitis suppurativa is a global problem. *Br J Dermatol.* 2015;173:1546-1549.
40. Smith MK, Nicholson CL, Parks-Miller A, Hamzavi IH. Hidradenitis suppurativa: an update on connecting the tracts. *F1000Res.* 2017;6:1272.
41. Hurley HJ. Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa and familial benign pemphigus. Surgical approach. In: Roenigk RH, Roenigk Jr JJ, eds. *Dermatologic Surgery, Principles and Practice.* 2nd ed. New York: Marcel Dekker; 1989:623-646.
42. Thorlacius L, Garg A, Riis PT, et al. Inter-rater agreement and reliability of outcome measurement instruments and staging systems used in hidradenitis suppurativa. *Br J Dermatol.* 2019; 181:483-491.
43. Sartorius K, Lapins J, Emtestam L, Jemec GBE. Suggestions for uniform outcome variables when reporting treatment effects in hidradenitis suppurativa. *Br J Dermatol.* 2003;149:211-213.
44. Sartorius K, Emtestam L, Jemec GBE, Lapins J. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. *Br J Dermatol.* 2009;161:831-839.
45. Amano M, Grant A, Kerdell FA. A prospective open-label clinical trial of adalimumab for the treatment of hidradenitis suppurativa. *Int J Dermatol.* 2010;49:950-955.
46. Grant A, Gonzalez T, Montgomery MO, Cardenas V, Kerdell FA. Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. *J Am Acad Dermatol.* 2010;62:205-217.
47. Kimball AB, Jemec GBE, Yang M, et al. Assessing the validity, responsiveness and meaningfulness of the Hidradenitis Suppurativa Clinical Response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. *Br J Dermatol.* 2014;171:1434-1442.
48. Kimball AB, Sobell JM, Zouboulis CC, et al. HiSCR (Hidradenitis Suppurativa Clinical Response): a novel clinical endpoint to evaluate therapeutic outcomes in patients with hidradenitis suppurativa from the placebo-controlled portion of a phase 2 adalimumab study. *J Eur Acad Dermatol Venereol.* 2016;30:989-994.
49. van der Zee HH, Jemec GBE. New insights into the diagnosis of hidradenitis suppurativa: clinical presentations and phenotypes. *J Am Acad Dermatol.* 2015;73(5 suppl 1):S23-S26.
50. Cauli A, Gladman DD, Mathieu A, et al. Physician's Global Assessment in psoriatic arthritis: a multicenter GRAPPA study. *J Rheumatol.* 2018;45:1256-1262.
51. Pascoe VL, Enamandram M, Corey KC, et al. Using the Physician Global Assessment in a clinical setting to measure and track patient outcomes. *JAMA Dermatol.* 2015;151:375-381.
52. Zouboulis CC, Desai N, Emtestam L, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol.* 2015;29:619-644.
53. Horváth B, Janse IC, Blok JL, et al. Hurley staging refined: a proposal by the Dutch Hidradenitis Suppurativa Expert Group. *Acta Derm Venereol.* 2017;97:412-413.
54. Rondags A, van Straalen KR, van Hasselt JR, et al. Correlation of the refined Hurley classification for hidradenitis suppurativa with patient-reported quality of life and objective disease severity assessment. *Br J Dermatol.* 2019;180:1214-1220.
55. Senthilnathan A, Kolli SS, Cardwell LA, Richardson I, Feldman SR, Pichardo RO. Validation of a hidradenitis suppurativa self-assessment tool. *J Cutan Med Surg.* 2019; 23:388-390.
56. Jørgensen A-HR, Thomsen SF, Ring HC. Clinical phenotypes of hidradenitis suppurativa. *J Eur Acad Dermatol Venereol.* 2019;33:e111-e112.
57. Shlyankevich J, Chen AJ, Kim GE, Kimball AB. Hidradenitis suppurativa is a systemic disease with substantial comorbidity burden: a chart-verified case-control analysis. *J Am Acad Dermatol.* 2014;71:1144-1150.
58. Dauden E, Lazaro P, Aguilar MD, et al. Recommendations for the management of comorbidity in hidradenitis suppurativa. *J Eur Acad Dermatol Venereol.* 2018;32:129-144.
59. Menter A. Recognizing and managing comorbidities and complications in hidradenitis suppurativa. *Semin Cutan Med Surg.* 2014;33(3 suppl):S54-S56.
60. Egeberg A, Gislason GH, Hansen PR. Risk of major adverse cardiovascular events and all-cause mortality in patients with hidradenitis suppurativa. *JAMA Dermatol.* 2016;152:429-434.
61. Miller IM, Ellervik C, Vinding GR, et al. Association of metabolic syndrome and hidradenitis suppurativa. *JAMA Dermatol.* 2014;150:1273-1280.
62. Ergun T. Hidradenitis suppurativa and the metabolic syndrome. *Clin Dermatol.* 2018;36:41-47.
63. Lim ZV, Oon HH. Management of hidradenitis suppurativa in patients with metabolic comorbidities. *Ann Dermatol.* 2016; 28:147-151.
64. Theut Riis P, Saunte DM, Benhadou F, et al. Low and high body mass index in hidradenitis suppurativa patients-

- different subtypes? *J Eur Acad Dermatol Venereol.* 2018;32:307-312.
65. Micheletti R. Tobacco smoking and hidradenitis suppurativa: associated disease and an important modifiable risk factor. *Br J Dermatol.* 2018;178:587-588.
 66. Garg A, Papagermanos V, Midura M, Strunk A. Incidence of hidradenitis suppurativa among tobacco smokers: a population-based retrospective analysis in the U.S.A. *Br J Dermatol.* 2018;178:709-714.
 67. Kridin K, Shani M, Schonmann Y, et al. Psoriasis and hidradenitis suppurativa: a large-scale population-based study. *J Am Acad Dermatol;* 2019. <https://doi.org/10.1016/j.jaad.2018.11.036> [Epub ahead of print]. Accessed October 22, 2019.
 68. Wertenteil S, Strunk A, Garg A. Incidence of obstructive sleep apnea among patients with hidradenitis suppurativa: a retrospective population-based cohort analysis. *Br J Dermatol.* 2018;179:1398-1399.
 69. Principi M, Cassano N, Contaldo A, et al. Hydradenitis suppurativa and inflammatory bowel disease: an unusual, but existing association. *World J Gastroenterol.* 2016;22:4802-4811.
 70. Ramos-Rodriguez AJ, Timerman D, Khan A, Bonomo L, Hunjan MK, Lemor A. The in-hospital burden of hidradenitis suppurativa in patients with inflammatory bowel disease: a decade nationwide analysis from 2004 to 2014. *Int J Dermatol.* 2018;57:547-552.
 71. Richette P, Molto A, Viguier M, et al. Hidradenitis suppurativa associated with spondyloarthritis—results from a multicenter national prospective study. *J Rheumatol.* 2014;41:490-494.
 72. Miller IM, McAndrew RJ, Hamzavi I. Prevalence, risk factors, and comorbidities of hidradenitis suppurativa. *Dermatol Clin.* 2016;34:7-16.
 73. Vasanth V, Chandrashekhar BS. Follicular occlusion tetrad. *Indian Dermatol Online J.* 2014;5:491-493.
 74. Vinkel C, Thomsen SF. Autoinflammatory syndromes associated with hidradenitis suppurativa and/or acne. *Int J Dermatol.* 2017;56:811-818.
 75. Chapman S, Delgadillo D 3rd, Barber C, Khachemoune A. Cutaneous squamous cell carcinoma complicating hidradenitis suppurativa: a review of the prevalence, pathogenesis, and treatment of this dreaded complication. *Acta Dermato-venereol Alp Pannonica Adriat.* 2018;27:25-28.
 76. Makrantonaki E, Ganceviciene R, Zouboulis C. An update on the role of the sebaceous gland in the pathogenesis of acne. *Dermatoendocrinol.* 2011;3:41-49.
 77. Hoffman LK, Ghias MH, Lowes MA. Pathophysiology of hidradenitis suppurativa. *Semin Cutan Med Surg.* 2017;36:47-54.
 78. Jahns AC, Killasli H, Nosek D, et al. Microbiology of hidradenitis suppurativa (acne inversa): a histological study of 27 patients. *APMIS.* 2014;122:804-809.
 79. Melnik BC, Plewig G. Impaired Notch-MKP-1 signalling in hidradenitis suppurativa: an approach to pathogenesis by evidence from translational biology. *Exp Dermatol.* 2013;22:172-177.
 80. Khandalaval BN, Do MV. Finasteride in hidradenitis suppurativa: a "male" therapy for a predominantly "female" disease. *J Clin Aesthet Dermatol.* 2016;9:44-50.
 81. Vossen ARJ V, van der Zee HH, Prens EP. Hidradenitis suppurativa: a systematic review integrating inflammatory pathways into a cohesive pathogenic model. *Front Immunol.* 2018;9:2965.
 82. Kamp S, Fiehn AM, Stenderup K, et al. Hidradenitis suppurativa: a disease of the absent sebaceous gland?
 83. Sebaceous gland number and volume are significantly reduced in uninvolved hair follicles from patients with hidradenitis suppurativa. *Br J Dermatol.* 2011;164:1017-1022.
 84. Morgan WP, Hughes LE. The distribution, size and density of the apocrine glands in hidradenitis suppurativa. *Br J Surg.* 1979;66:853-856.
 85. Blok JL, Janse IC, Horváth B, Jonkman MF. Increased expression of integrin $\alpha 6\beta 4$ in the basement membrane zone lining the sebaceous glands in hidradenitis suppurativa. *Acta Derm Venereol.* 2015;95:994-996.
 86. Ślebioda TJ, Kmiec Z. Tumour necrosis factor superfamily members in the pathogenesis of inflammatory bowel disease. *Mediators Inflamm.* 2014;2014:325129.
 87. Moelants EAV, Mortier A, Van Damme J, Proost P. Regulation of TNF- α with a focus on rheumatoid arthritis. *Immunol Cell Biol.* 2013;91:393-401.
 88. Wcislo-Dziadecka D, Zbiciak-Nylec M, Brzezińska-Wcisło L, Mazurek U. TNF- α in a molecularly targeted therapy of psoriasis and psoriatic arthritis. *Postgrad Med J.* 2016;92:172-178.
 89. Moran B, Sweeney CM, Hughes R, et al. Hidradenitis suppurativa is characterized by dysregulation of the Th17: Treg cell axis, which is corrected by anti-TNF therapy. *J Invest Dermatol.* 2017;137:2389-2395.
 90. van der Zee HH, de Ruiter L, van den Broecke DG, Dik WA, Laman JD, Prens EP. Elevated levels of tumour necrosis factor (TNF)- α , interleukin (IL)-1 β and IL-10 in hidradenitis suppurativa skin: a rationale for targeting TNF- α and IL-1 β . *Br J Dermatol.* 2011;164:1292-1298.
 91. Frew JW, Hawkes JE, Krueger JG. A systematic review and critical evaluation of inflammatory cytokine associations in hidradenitis suppurativa. *F1000Res.* 2018;7:1930.
 92. Vilanova I, Hernández JL, Mata C, et al. Insulin resistance in hidradenitis suppurativa: a case-control study. *J Eur Acad Dermatol Venereol.* 2018;32:820-824.
 93. Malara A, Hughes R, Jennings L, et al. Adipokines are dysregulated in patients with hidradenitis suppurativa. *Br J Dermatol.* 2018;178:792-793.
 94. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J Clin Invest.* 2006;116:1784-1792.
 95. Shibata S, Tada Y, Hau C, et al. Adiponectin as an anti-inflammatory factor in the pathogenesis of psoriasis: induction of elevated serum adiponectin levels following therapy. *Br J Dermatol.* 2011;164:667-670.
 96. Shah A, Alhusayen R, Amini-Nik S. The critical role of macrophages in the pathogenesis of hidradenitis suppurativa. *Inflamm Res.* 2017;66:931-945.
 97. Savva A, Kanni T, Damoraki G, et al. Impact of Toll-like receptor-4 and tumour necrosis factor gene polymorphisms in patients with hidradenitis suppurativa. *Br J Dermatol.* 2013;168:311-317.
 98. Balato A, Caiazzo G, Annunziata MC, et al. Anti-TNF- α therapy modulates mTORC1 signalling in hidradenitis suppurativa. *J Eur Acad Dermatol Venereol.* 2019;33:e43-e45.
 99. Kanni T, Zenker O, Habel M, Riedemann N, Giamparellos-Bourboulis EJ. Complement activation in hidradenitis suppurativa: a new pathway of pathogenesis? *Br J Dermatol.* 2018;179:413-419.
 100. Hoffman LK, Tomalin LE, Schultz G, et al. Integrating the skin and blood transcriptomes and serum proteome in hidradenitis suppurativa reveals complement dysregulation and a plasma cell signature. *PLoS One.* 2018;13:e0203672.

100. Jiménez-Gallo D, de la Varga-Martínez R, Ossorio-García L, Collantes-Rodríguez C, Rodríguez C, Linares-Barrios M. Effects of adalimumab on T-helper-17 lymphocyte- and neutrophil-related inflammatory serum markers in patients with moderate-to-severe hidradenitis suppurativa. *Cytokine*. 2018;103:20-24.
101. Matusiak Ł, Szczęch J, Bieniek A, Nowicka-Suszko D, Szepietowski JC. Increased interleukin (IL)-17 serum levels in patients with hidradenitis suppurativa: implications for treatment with anti-IL-17 agents. *J Am Acad Dermatol*. 2017;76:670-675.
102. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med*. 2009;361:2066-2078.
103. Chen WT, Chi CC. Association of hidradenitis suppurativa with inflammatory bowel disease: a systematic review and meta-analysis. *JAMA Dermatol*; 2019. <https://doi.org/10.1001/jamadermatol.2019.0891> [Epub ahead of print]. Accessed October 22, 2019.
104. Theut Riis P, Thorlacius LR, Jemec GB. Investigational drugs in clinical trials for hidradenitis suppurativa. *Expert Opin Investig Drugs*. 2018;27:43-53.
105. Matusiak Ł, Jemec GB, Szepietowski JC. Pharmacological development in hidradenitis suppurativa. *Curr Opin Pharmacol*. 2019;46:65-72.
106. Schlapbach C, Hänni T, Yawalkar N, Hunger RE. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. *J Am Acad Dermatol*. 2011;65:790-798.
107. Di Caprio R, Balato A, Caiazzo G, et al. IL-36 cytokines are increased in acne and hidradenitis suppurativa. *Arch Dermatol Res*. 2017;309:673-678.
108. Hessam S, Sand M, Gambichler T, Skrygan M, Rüddel I, Bechara FG. Interleukin-36 in hidradenitis suppurativa: evidence for a distinctive proinflammatory role and a key factor in the development of an inflammatory loop. *Br J Dermatol*. 2018;178:761-767.
109. Thomi R, Kakeda M, Yawalkar N, Schlapbach C, Hunger RE. Increased expression of the interleukin-36 cytokines in lesions of hidradenitis suppurativa. *J Eur Acad Dermatol Venereol*. 2017;31:2091-2096.
110. Tanaka T, Kishimoto T. Targeting interleukin-6: all the way to treat autoimmune and inflammatory diseases. *Int J Biol Sci*. 2012;8:1227-1236.
111. Kelly G, Sweeney CM, Tobin A-M, Kirby B. Hidradenitis suppurativa: the role of immune dysregulation. *Int J Dermatol*. 2014;53:1186-1196.
112. Xu H, Xiao X, He Y, et al. Increased serum interleukin-6 levels in patients with hidradenitis suppurativa. *Postepy Dermatol Alergol*. 2017;34:82-84.
113. Banerjee A, McNish S, Shanmugam VK. Interferon-gamma (IFN- γ) is elevated in wound exudate from hidradenitis suppurativa. *Immunol Invest*. 2017;46:149-158.
114. Hotz C, Boniotto M, Guguen A, et al. Intrinsic defect in keratinocyte function leads to inflammation in hidradenitis suppurativa. *J Invest Dermatol*. 2016;136:1768-1780.
115. Randhawa HK, Hamilton J, Pope E. Finasteride for the treatment of hidradenitis suppurativa in children and adolescents. *JAMA Dermatol*. 2013;149:732-735.
116. Eicheler W, Dreher M, Hoffmann R, Happle R, Aumüller G. Immunohistochemical evidence for differential distribution of 5 alpha-reductase isoenzymes in human skin. *Br J Dermatol*. 1995;133:371-376.
117. Clark AK, Quinonez RL, Saric S, Sivamani RK. Hormonal therapies for hidradenitis suppurativa: review. *Dermatol Online J*. 2017;23.
118. Karagiannidis I, Nikolakis G, Sabat R, Zouboulis CC. Hidradenitis suppurativa/acne inversa: an endocrine skin disorder? *Rev Endocr Metab Disord*. 2016;17:335-341.
119. Riis PT, Ring HC, Themstrup L, Jemec GB. The role of androgens and estrogens in hidradenitis suppurativa - a systematic review. *Acta Dermatovenerol Croat*. 2016;24:239-249.
120. Vossen AR, van Straalen KR, Prens EP, van der Zee HH. Menses and pregnancy affect symptoms in hidradenitis suppurativa: a cross-sectional study. *J Am Acad Dermatol*. 2017;76:155-156.
121. Golbari NM, Porter ML, Kimball AB. Antiandrogen therapy with spironolactone for the treatment of hidradenitis suppurativa. *J Am Acad Dermatol*. 2019;80:114-119.
122. Dany M, Elston D. Gene expression of sphingolipid metabolism pathways is altered in hidradenitis suppurativa. *J Am Acad Dermatol*. 2017;77:268-273.e6.
123. Ingram JR. The genetics of hidradenitis suppurativa. *Dermatol Clin*. 2016;34:23-28.
124. Genetics Home Reference website. Noonan syndrome. Available at: <https://ghr.nlm.nih.gov/condition/noonan-syndrome>. Accessed October 22, 2019.
125. Pink AE, Simpson MA, Desai N, et al. Mutations in the γ -secretase genes NCSTN, PSENEN, and PSEN1 underlie rare forms of hidradenitis suppurativa (acne inversa). *J Invest Dermatol*. 2012;132:2459-2461.
126. Giambrelli-Bourboulis EJ, Platzer M, Karagiannidis I, et al. High copy numbers of β -defensin cluster on 8p23.1, confer genetic susceptibility, and modulate the physical course of hidradenitis suppurativa/acne inversa. *J Invest Dermatol*. 2016;136:1592-1598.
127. Hessam S, Sand M, Skrygan M, Gambichler T, Bechara FG. Inflammation-induced changes in the expression levels of components of the microRNA maturation machinery Drosha, Dicer, Drosha co-factor DGRC8 and Exportin-5 in inflammatory lesions of hidradenitis suppurativa patients. *J Dermatol Sci*. 2016;82:166-174.
128. Hessam S, Sand M, Skrygan M, Gambichler T, Bechara FG. Expression of miRNA-155, miRNA-223, miRNA-31, miRNA-21, miRNA-125b, and miRNA-146a in the inflammatory pathway of hidradenitis suppurativa. *Inflammation*. 2017;40:464-472.
129. Ring HC, Bay L, Nilsson M, et al. Bacterial biofilm in chronic lesions of hidradenitis suppurativa. *Br J Dermatol*. 2017;176:993-1000.
130. Ring HC, Thorsen J, Saunte DM, et al. The follicular skin microbiome in patients with hidradenitis suppurativa and healthy controls. *JAMA Dermatol*. 2017;153:897-905.
131. Zasada AA, Mosiej E. Contemporary microbiology and identification of *Corynebacteria* spp. causing infections in human. *Lett Appl Microbiol*. 2018;66:472-483.
132. Zenobia C, Hajishengallis G. *Porphyromonas gingivalis* virulence factors involved in subversion of leukocytes and microbial dysbiosis. *Virulence*. 2015;6:236-243.
133. Brown K, Church D, Lynch T, Gregson D. Bloodstream infections due to *Peptostreptococcus* spp.: report of 15 cases. *Clin Microbiol Infect*. 2014;20:O857-O860.
134. Ardon CB, Prens EP, Fuerst K, et al. Biofilm production and antibiotic susceptibility of *Staphylococcus epidermidis* strains from hidradenitis suppurativa lesions. *J Eur Acad Dermatol Venereol*. 2019;33:170-177.
135. Nikolakis G, Join-Lambert O, Karagiannidis I, Guet-Revillet H, Zouboulis CC, Nassif A. Bacteriology of hidradenitis suppurativa/acne inversa: a review. *J Am Acad Dermatol*. 2015;73(5 suppl 1):S12-S18.
136. Thomas C, Rodby KA, Thomas J, Shay E, Antony AK. Recalcitrant hidradenitis suppurativa: an investigation of demographics, surgical management, bacterial isolates, pharmacologic intervention, and patient-reported health outcomes. *Am Surg*. 2016;82:362-368.

137. Benzecri V, Grancini A, Guanzioli E, et al. Hidradenitis suppurativa/acne inversa: a prospective bacteriological study of 46 patients and review of the literature. *G Ital Dermatol Venereol*; 2019. <https://doi.org/10.23736/S0392-0488.18.05875-3> [Epub ahead of print]. Accessed October 22, 2019.
138. Negus D, Ahn C, Huang W. An update on the pathogenesis of hidradenitis suppurativa: implications for therapy. *Expert Rev Clin Immunol*. 2018;14:275-283.
139. Cubilla JAG, Abdalla BMZ, Criado PR, Oyafuso LK. Immunological pathways in hidradenitis suppurativa: current concepts and innovative therapies. *Clin Res Dermatol Open Access*. 2018;5:1-7.
140. Zouboulis CC, Bechara FG, Dickinson-Blok JL, et al. Hidradenitis suppurativa/acne inversa: a practical framework for treatment optimization - systematic review and recommendations from the HS ALLIANCE working group. *J Eur Acad Dermatol Venereol*. 2019;33:19-31.



Hidradenitis suppurativa

Current and emerging treatments

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Learning objectives

After completing this learning activity, participants should be able to list the treatment options available for patients with hidradenitis suppurativa, discuss emerging therapeutic options, and compare the utility and effectiveness of these methods.

Disclosures

Editors

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The treatment of hidradenitis suppurativa (HS) has remained challenging because of the many knowledge gaps regarding etiology. However, recent studies into the pathogenesis of HS have enabled the investigation of newer therapies. The second article in this continuing medical education series reviews the evidence for established therapies for HS, including anti-inflammatories, antibiotics, and surgery. New and emerging therapies that specifically target cytokines involved in HS pathogenesis will be covered. The potential therapeutic roles of anticytokine therapies, including both the expanded application of existing molecules as well as the specific development of novel therapies for HS are discussed. With increased attention on HS and with numerous clinical trials currently underway, we hope that the variety of treatment options for HS will be expanded. (*J Am Acad Dermatol* 2020;82:1061-82.)

Key words: adalimumab; antibiotics; hidradenitis; secukinumab; ustekinumab.

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The treatment of hidradenitis suppurativa (HS) remains challenging. Early studies were limited by their small sample size and the lack of placebo groups. With greater awareness of disease prevalence and improved understanding of immunopathogenesis, however, newer therapies are emerging.

ESTABLISHED THERAPIES

Key points

- **Antibiotics are used to decrease inflammation and to treat secondary infection**
- **Systemic tetracyclines, alone or in combination with other agents, are frequently used as first-line treatments**
- **Prednisone does not have much benefit alone, but may increase the response to adalimumab**
- **Surgery remains an important treatment for HS; wide excision is the only known curative procedure**
- **Weight loss and smoking cessation counseling should be recommended for patients with HS**

Antibiotics/anti-inflammatories

HS lesions are frequently colonized with bacteria and antibiotics have anti-inflammatory properties, supporting the dual therapeutic rationale for these agents. Only commonly used antibiotics for HS are discussed here.

Antibiotic monotherapy is often used as first-line treatment.^{1,2} A study of 46 patients with HS found that monotherapy with topical 1% clindamycin phosphate or systemic tetracycline (250 mg twice daily) both reduced the number of abscesses within 3 months and the number of nodules after 3 months.³ Bacterial presence at treatment onset did not affect the outcome. There was also no difference in pain, HS severity score, or Physician's Global Assessment (PGA) between the 2 groups, but the difference in participant global self-assessment outcome favored oral tetracyclines.^{1,3} There are no randomized, placebo-controlled trials of oral tetracyclines for patients with HS.

In moderate-to-severe disease, combination therapy is more common. Rifampin is a broad-spectrum antimicrobial that inhibits growth of most Gram-positive and some Gram-negative microorganisms.⁴ It has immunomodulatory effects via suppression of antigen-induced transformation of sensitized lymphocytes and suppression of T cell function, altering cell-mediated hypersensitivity.^{4,5} Clindamycin, a macrolide that inhibits protein synthesis, also modifies inflammation by suppressing complement-

derived chemotaxis of polymorphonuclear leukocytes.⁵

The rifampin-clindamycin combination is effective for HS treatment.⁶ A significant decrease in Sartorius score was found in most patients after 10 weeks. These results are consistent in the literature,⁷⁻¹⁰ supporting this combination as a frequently selected treatment.¹¹ Although generally well tolerated, studies have found adverse digestive symptoms in 13% to 43% of patients.⁶ Another combination consists of rifampin, moxifloxacin, and metronidazole.⁶ This combination has similarly shown success,^{9,11} particularly in patients with less severe disease,⁸ but is associated with adverse effects, including gastrointestinal symptoms, vaginal candidiasis, and tendinitis.⁶

Ertapenem is a broad-spectrum antibiotic that has demonstrated efficacy in treating HS.⁹ In 1 retrospective study of 36 patients with HS treated with 1 g of intravenous ertapenem for an average of 59 days (in addition to medications they were already taking), 35 patients showed improvement. However, 17 patients had serious complications including diarrhea, peripherally inserted central catheter line thrombosis and vaginitis.¹² Moreover, 30 patients relapsed in an average of 5.8 weeks. Another study of Hurley stage II/III patients receiving intravenous ertapenem found an improved Hurley stage by 1 point in 17 of 30 patients.⁷ Ertapenem might be used to achieve rapid improvement before surgery or other maintenance therapies, but should otherwise be considered for patients who are refractory to or contraindicated for other treatments.¹²

Although the intent of these therapies is to capitalize on both antiinflammatory and antibiotic properties, the antibiotic aspect of these medications always warrants consideration of antibiotic resistance. One study found patients using clindamycin were more likely to grow clindamycin-resistant *Staphylococcus aureus*.¹⁰ A study of 69 patients with HS demonstrated high resistance to monobactams (75%), tetracyclines (64%), and lincosamides (51%).¹³ Consequently, broad-spectrum combination treatment is considered the best option to limit resistance.⁶

Prednisone has also been tested as a therapeutic option for HS. In 1 study, 13 patients with recalcitrant HS were treated with 10 mg prednisone in addition to treatment they were currently receiving. Five patients showed remission after 4 to 12 weeks, and 3 maintained remission 6 months after prednisone discontinuation. Six patients showed improvement without complete remission and 2 patients had no response. Interestingly, 5 patients had no response

to adalimumab until prednisone was added, possibly because of the suppression of neutralizing antibodies.^{14,15} The effect of higher doses of prednisone has not been thoroughly investigated.

Intralesional corticosteroid therapy can be effective for isolated HS lesions.¹⁵ A case series with 33 patients with acute HS nodules or abscesses found a significant reduction in erythema, edema, suppuration, size, and patient-reported pain after intralesional triamcinolone treatment. This therapy presumably activates glucocorticoid receptors within lesions, resulting in the blockage of leukotriene synthesis and reduction of proinflammatory cytokines.¹⁶ However, the efficacy of intralesional corticosteroid therapy is refuted by a randomized, double-blind, placebo-controlled 3-arm trial evaluating the efficacy of intralesional triamcinolone injection. This study divided all lesions among 32 patients into 1 of 3 groups: triamcinolone 10 mg/mL, 40 mg/mL, or normal saline (placebo). There was no statistically or clinically significant difference in the number of days to lesion resolution in either treatment arm compared with the placebo arm.¹⁷

Table I provides a comprehensive review of medical therapies for HS.

Surgery

Surgery is an option in HS management. For mild disease, deroofing or laser treatment may alleviate symptoms. Incision and drainage may be used in the acute setting for patients presenting with painful fluctuant abscesses.¹⁸ For severe disease, wide excision is the only potentially curative treatment. Commonly used procedures are summarized in Table II.

Counseling

Lifestyle modification is paramount in HS management. Because obesity and increasing body mass index are associated with more severe disease, weight loss is strongly advised.^{19,20} Of 383 patients with HS who completed a survey before and after bariatric surgery, 35% fewer patients reported symptoms and the mean number of involved sites decreased from 1.93 to 1.22.¹⁹ Bariatric surgery has been debated, however, because of reports of worsening symptoms after surgery. One study described experiences of patients with HS posted on online forums and Facebook groups. About a third of patients discussing bariatric surgery noted worsening symptoms after surgery, seemingly because of the increase in skin folds.²¹

Smokers have a worse prognosis and poorer treatment outcomes; smoking cessation is thus advised for all patients with HS.^{13,22} In a

retrospective cohort study of 437 patients with HS, the frequency of ever being a smoker was 65%.²³ Tobacco was associated with treatment escalation (from topical to immunologic therapy or surgery).²³ Nonsmoking patients with HS have shown 2.8 times the odds of self-reported remission compared with smokers.²² In addition, former smokers or nonsmokers have a 3-fold higher rate of achieving a response to medical therapy compared with smokers.²² HS is also associated with an increased risk of adverse cardiovascular outcomes and all-cause mortality, further supporting the importance of smoking cessation.²⁴

BIOLOGIC THERAPIES

Key points

- Advances in the understanding of HS pathogenesis has guided studies to investigate the therapeutic role of biologics for this disease
- Tumor necrosis factor- α inhibitors are effective and safe for the treatment of HS; adalimumab is the only therapy for HS approved by the US Food and Drug Administration
- There are several ongoing clinical trials for newer biologic therapies targeting multiple cytokines
- It is likely that multiple immunologic pathways are implicated in HS progression, so complete treatment may need to target >1 pathway

Tumor necrosis factor- α inhibitors

Adalimumab (ADA) is the only drug for moderate-to-severe HS that has been approved by the US Food and Drug Administration.²⁵ ADA binds soluble and transmembrane TNF- α ¹⁵ and significantly reduces mammalian target of rapamycin (mTOR) activity in patients with HS.²⁶ Initial trials found a reduction in Sartorius score after 6 weeks.²⁷ In a larger trial of patients treated with ADA (40 mg weekly), 17.6% achieved a PGA score of 0 to 2 with at least a 2-grade improvement compared with baseline.^{27,28} Improvements in secondary outcomes, including increased quality of life and decreased pain, also occurred.²⁷ Two separate phase III multicenter, double-blind, placebo-controlled studies (PIONEER I and PIONEER II) with 633 combined patients with moderate-to-severe HS showed that 50.6% of patients receiving ADA 160 mg at week 0, 80 mg at week 2, and 40 mg weekly starting at week 4 achieved Hidradenitis Suppurativa Clinical Response (HiSCR) compared with only 26.8% of placebo at week 12.^{25,29} Two groups were defined: “responders” who achieved HiSCR, and “partial

Table I. Medical treatments for hidradenitis suppurativa, excluding biologics and surgery

Treatment	MOA	Severity (Hurley stage)*	Advantages†	Disadvantages†	Grade, II‡	Evidence level, strength of recommendation¶,§, *,#
Anti-inflammatories/antibiotics						
Topical clindamycin	Binds 50s bacterial subunit	I or II ³	<ul style="list-style-type: none"> Common for localized HS without deep abscesses Few AEs Inexpensive Standard treatment Large study of Hurley stage I patients experienced remission Inexpensive Well tolerated in most 	<ul style="list-style-type: none"> Requires constant application Ineffective in stage III disease or for multiple affected areas In women yeast infections, RB GI intolerance in some, possible hepatic issues Rifampin has many drug interactions; decreases the effectiveness of many medications 	B	IIb, B
Clindamycin/rifampin	Binds 50s bacterial subunit; inhibits DNA-dependent RNA polymerase	II or III ⁷¹			B	III, C
Oral tetracycline	Binds the 30s ribosomal subunit	I or II	<ul style="list-style-type: none"> Can be effective in more widespread lesions with frequent exacerbations 	<ul style="list-style-type: none"> Not available in all countries Has not shown significantly better effects than topical clindamycin⁷² 	B	II, B
Ertapenem	Beta-lactam antibiotic	I, II, or III	<ul style="list-style-type: none"> Limited reports show dramatic effect 	<ul style="list-style-type: none"> Expensive, little data Need IV access Long term use could select out for RB 	C	IV, C
Oral dapsone	Competitive inhibition of bacterial dihydropteroate synthase	I or II	<ul style="list-style-type: none"> May work where antibiotics fail 	<ul style="list-style-type: none"> Many potential AEs (neuropathy, hemolytic anemia, and methemoglobinemia) Response not durable; rapid relapse after use Consider giving with cimetidine 	C	IV, C

Minocycline/rifampin	Inhibits 30s subunit; Inhibits DNA-dependent RNA polymerase	I or II ⁷³	<ul style="list-style-type: none"> May be more effective than clindamycin/rifampin Generics inexpensive 	<ul style="list-style-type: none"> In women yeast infections, RB Extended release minocycline is expensive GI intolerance, possible hepatic issues Minocycline can cause headaches and rare side effects (including HSS) Rifampin has many drug interactions; decreases the effectiveness of many medications 	C	NR
Fluoroquinolones/ metronidazole/ rifampin (triple therapy)	Inhibits ligase activity of type II topoisomerases, gyrase and topoisomerase IV; Produces intermediate compounds and free radicals that are cytotoxic to facultative anaerobic bacteria; Inhibits DNA-dependent RNA polymerase	II or III	<ul style="list-style-type: none"> Might work when clindamycin/rifampin and minocycline/rifampin fail Inexpensive 	<ul style="list-style-type: none"> Tendon rupture CNS issues, particularly in the elderly Yeast infections, RB GI upset Metronidazole can cause sacral neuropathy Must avoid alcohol 	NR	IV, C
Topical dapson	Inhibits myeloperoxidase and eosinophil-peroxidase within neutrophils and eosinophils, respectively	I or II	<ul style="list-style-type: none"> Few AEs Soothing vehicle 	<ul style="list-style-type: none"> Expensive Not effective for majority of patients 	NR	NR

Continued

Table I. Cont'd

Treatment	MOA	Severity (Hurley stage)*	Advantages [†]	Disadvantages [†]	Grade, ^{II,‡}	Evidence level, strength of recommendation ^{¶,§, ,¶,#}
Immunosuppressives						
Prednisone	Glucocorticoid receptor agonist; Inhibits proinflammatory cytokine production, decreases number of circulating lymphocytes, induces cell differentiation, and stimulates T cell apoptosis	II or III	• May augment adalimumab therapy ¹⁴	• Sexual AE • Gynecomastia • Sparse evidence	C	IV, D
Intralesional corticosteroids	Glucocorticoid receptor agonist; Inhibits release of phospholipase A2; causes vasoconstriction; has direct inhibitory effect on DNA and inflammatory transcription factors	NED	• Quick acting • Can have cumulative effect abating or burning out HS	• Rare adrenal suppression • Limited duration of effectiveness of 2-4 weeks • Does not always expedite lesion resolution • Painful	C	IV, D
Cyclosporine	Calcineurin inhibitor; binds cyclophilin; blocks T-cell activation by preventing IL-2 transcription	II or III	• Few reports show tremendous anti-inflammatory effectiveness • Safer to use for months over oral corticosteroids	• Requires laboratory and vital sign monitoring • Can promote SCC • Renal AEs • Hypertension	E ⁷⁴	IV, D
Dimethyl fumarate	Activates the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway, involved in the cellular response to oxidative stress; Impairs IL-12 and IL-23 production by dendritic cells and macrophages	II or III ⁷⁴	• Has been effective in decreasing inflammation in psoriasis vulgaris patients ⁷⁵	• Unproven for HS	E ⁷⁴	NR

Hydroxychloroquine	May impair complement-dependent antigen-antibody reactions; inhibits locomotion of neutrophils and chemotaxis of eosinophils; increases pH, which interferes with lysosomal degradation of hemoglobin	NED	<ul style="list-style-type: none"> • Pilot study in progress • No published data⁷⁶ 	NR	NR	
Hormonal therapy Spironolactone	Competitive aldosterone receptor antagonist in cortical collecting tubule of nephron	I or II	<ul style="list-style-type: none"> • Inexpensive • May reduce menstrual flares • Low doses may be as effective as higher doses (helpful for patients with tolerability issues)⁷⁷ 	<ul style="list-style-type: none"> • Diuretic • Increases K⁺ • May require laboratory monitoring • May affect menses • Rare neural and muscular AEs 	C	IV, D
OCP (as a class)	Progestogen negatively feeds back on hypothalamus, decreases pulse frequency of GnRH, decreases secretion of FSH and LH; estrogen stabilizes uterus endometrium and negatively feeds back to the anterior pituitary to decrease FSH secretion	I or II	<ul style="list-style-type: none"> • Inexpensive, except branded products with drospirenone which may be best type of OCP for females with HS 	<ul style="list-style-type: none"> • Increased risk of blood clots in particular if drospirenone is part of OCP 	D ⁷⁸	IV, D

Continued

Table I. Cont'd

Treatment	MOA	Severity (Hurley stage)*	Advantages [†]	Disadvantages [†]	Grade, ^{II,‡}	Evidence level, strength of recommendation ^{§,§§,¶}
Cyproterone acetate and ethynodiolide	Cyproterone acetate is antiandrogenic and progestogenic, with weak partial glucocorticoid activity, weak inhibition of steroidogenesis, and an agonist at the pregnane X receptor; ethynodiolide is an agonist of the estrogen receptors	I or II	<ul style="list-style-type: none"> Inexpensive May reduce menstrual flares 	<ul style="list-style-type: none"> Not available in US Risk of increased clotting 	C ⁷⁹	IV, D
Finasteride	Competitive inhibitor of type 2 5 α -reductase	I or II	<ul style="list-style-type: none"> Multiple cases have shown improvement in 4 weeks⁵² 	<ul style="list-style-type: none"> Sexual AEs Gynecomastia Recurrence after treatment cessation⁵² 	D	IV, D
Dutasteride	Synthetic 4-azasteroid compound that is a selective inhibitor of both the type 1 and type 2 isoforms of steroid 5 α -reductase	NED	<ul style="list-style-type: none"> More effective testosterone blocker than finasteride 	<ul style="list-style-type: none"> AEs similar and greater than finasteride More risk of gynecomastia Uncertain effect of blocking DHT1 More expensive than finasteride 	NR	IV, D
Leuprorelin acetate, flutamide, degarelix gonadotropin-releasing hormone agonist	GnRH analog with agonist properties when pulsatile and antagonist when continuous; Nonsteroidal competitive inhibitor at androgen receptors	II or III ⁷³	<ul style="list-style-type: none"> Strong hormonal suppression 	<ul style="list-style-type: none"> Not proven for HS Extreme hormonal AEs 	NR	IV, D

Retinoids						
Isotretinoin	13-cis-retinoic acid, binds to and activates nuclear retinoic acid receptors	NED	<ul style="list-style-type: none"> Helped >20% of patients May have greater effect in younger patients with acne⁵⁶ 	<ul style="list-style-type: none"> Most patients have no response Xerosis Needs iPledge participation Requires laboratory monitoring Many potential AEs Similar AEs as isotretinoin except more prolonged risk of birth defects Expensive Few studies 	B	IV, D
Acitretin, oral alitretinoin, or etretinate	Acitretin is the free acid of etretinate, which is less lipophilic and has a shorter terminal half-life than etretinate; alitretinoin is an endogenous retinoid related to vitamin A	II or III	<ul style="list-style-type: none"> Might resolve follicular occlusion May have other positive immunologic effects Does not require iPledge participation 		B	IV, C
Antidiabetics						
Metformin	Biguanide; inhibits hepatic gluconeogenesis and the action of glucagon; decreases gluconeogenesis; increases glycolysis and peripheral glucose uptake (increased insulin sensitivity)	I or II	<ul style="list-style-type: none"> May decrease Sartorius score and improve QoL Few side effects 	<ul style="list-style-type: none"> Mixed results on efficacy 	D ¹⁶	NR
Glucagon-like peptide-1 analogues/agonists	Increased glucose-dependent insulin release and satiety; decreased glucagon release and gastric emptying	NED	<ul style="list-style-type: none"> Limited data 	<ul style="list-style-type: none"> Limited data on efficacy 	NR	NR
Other therapies						
Zinc gluconate 90 mg	Zinc salt of gluconic acid, with two anions of gluconate for each zinc (II) cation	I ⁷³	<ul style="list-style-type: none"> Inexpensive Limited strong data May decrease Sartorius score and improve QoL 	<ul style="list-style-type: none"> Not for severe disease Copper should accompany it Relapse with reduction in dose 	C	III, C

Continued

Table I. Cont'd

Treatment	MOA	Severity (Hurley stage)*	Advantages [†]	Disadvantages [†]	Grade, ^{‡,§,‡}	Evidence level, strength of recommendation ^{¶,§,¶,#}
Botulinum toxin 3 times daily wash + antibacterial soap + sodium fusi- date 2% ointment	Heat-labile toxin that inhibits acetylcholine release at the neuromuscular junction Sodium fusidate is a bacterial protein synthesis inhibitor that prevents turnover of elongation factor G from the ribosome; inhibits protein translation in Gram- positive bacteria	NED; case reports of efficacy in II and III ^{80,81} I ⁶⁶	<ul style="list-style-type: none"> Might alter neural factors Alters skin flora because of decreased sweating Prospective trial found decreased pain and itching as well as complete healing of many lesions⁶⁶ 	<ul style="list-style-type: none"> Expensive, unproven 	E ⁸⁰ B	IV, D NR
IVIG	Derived from the pooled human plasma of thousands of donors; intact IgG molecules with trace amounts of IgA, soluble CD4, CD8, HLA molecules, and certain cytokines; IgG subclasses (IgG1, IgG2, IgG3, and IgG4) in IVIG products have a distribution similar to that found in normal human plasma	NED	<ul style="list-style-type: none"> Might work if all else fails 	<ul style="list-style-type: none"> Expensive, unproven 	D ⁸²	NR

PDGF, GCSF	PDGF induces vascular remodeling, smooth muscle cell migration, and stimulates fibroblast growth for collagen synthesis; GCSF is a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells	NED; only 1 case report ⁸³	<ul style="list-style-type: none"> Promote healing 	<ul style="list-style-type: none"> Expensive, unproven 	E ⁸³	NR
Benzoyl peroxide	Releases free radical oxygen species; sebostatic, comedolytic, and inhibitory to <i>Propionibacterium acnes</i> in vivo	NED	<ul style="list-style-type: none"> Established acne treatment Prospective multicenter trial in progress^{13,67} 	<ul style="list-style-type: none"> No published data¹³ 	NR	NR

AE, Adverse event; C5a, complement factor 5a; cAMP, cyclic adenosine monophosphate; CNS, central nervous system; DHT1, dihydrotestosterone 1; GCSF, granulocyte-macrophage colony-stimulating factor; GI, gastrointestinal; GnRH, gonadotropin-releasing hormone; HLA, human leukocyte antigen; HSS, hypersensitivity syndrome; IgA, immunoglobulin A; IgG, immunoglobulin G; IL, interleukin; IVAB, intravenous antibiotics, in particular ertapenem and ceftriaxone; IVIG, intravenous immunoglobulin; K, potassium; MTX, methotrexate; NED, not enough data; NR, not reported; OCP, oral contraceptive pill; PDE4, phosphodiesterase 4; PDGF, platelet-derived growth factor; PKA, protein kinase A; QoL, quality of life; RB, resistant bacteria; SCC, squamous cell carcinoma.

¹As defined by Guyatt G, Oxman AD, Vist GE, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-926.

[#]Evidence level: Ia = metaanalysis of randomized controlled trials; Ib = randomized controlled trial; IIa = controlled study without randomization; IIb = quasiexperimental study; III = nonexperimental descriptive studies, such as comparative, correlation, and case-control studies; IV = expert committee reports or opinion or clinical experience of respected authorities, or both.

^{**}Strength of recommendation: A = category I evidence; B = category II evidence or extrapolated from category I evidence; C = category III evidence or extrapolated from category I or II evidence; D = category IV evidence or extrapolated from category II or III evidence.

^{*}As defined by Alkhani A, Sayed C, Alavi A, et al. North American clinical management guidelines for hidradenitis suppurativa: a publication from the United States and Canadian Hidradenitis Suppurativa Foundations: part II: Topical, intralesional, and systemic medical management. J Am Acad Dermatol 2019;81:91-101.

[†]As defined by Scheinfeld N. Hidradenitis suppurativa: a practical review of possible medical treatments based on over 350 hidradenitis patients. Dermatol Online J 2013;19:1.

[‡]As defined by Zouboulis et al.⁷²

[§]As defined by Gullive W, Zouboulis C, Prens E, Jemec GB, Tzellos T. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa. Rev Endocr Metab Disord 2016;17:343-351.

^{||}Grading criteria: A = ≥1 prospective, randomized, double-blind, controlled trial without major design flaws; B = prospective clinical trial with ≥20 subjects; C = clinical trial with <20 subjects or ≥20 cases in the literature; D = series with ≥5 subjects who responded; E = anecdotal case reports with <5 subjects.

Table II. Surgical therapies for hidradenitis suppurativa

Procedure	Severity (Hurley stage)	Advantages	Disadvantages	Evidence level, strength of recommendation ^{a†}
Surgery				
Deroofing	I or II ^{18,84}	<ul style="list-style-type: none"> • Minimally invasive • Preserves unaffected tissues⁸⁵ • Provides immediate relief^{84,86} 	<ul style="list-style-type: none"> • Does not permanently remove inflammation • High rate of recurrence and infection^{84,86} 	IV, D
Incision and drainage	I or II ⁸⁶	<ul style="list-style-type: none"> • Minimally invasive • Provides immediate relief from a tense abscess 	<ul style="list-style-type: none"> • Cannot be performed on solid lesions⁸⁶ • High rate of recurrence and infection^{84,86} 	III, C
Excision with primary closure	II or III (occasionally I) ⁸⁷	<ul style="list-style-type: none"> • Low morbidity • Rapid wound healing • High patient satisfaction rate⁸⁸ 	<ul style="list-style-type: none"> • Moderate recurrence rate⁸⁹ • Postoperative complications may include suture dehiscence, bleeding, and infection⁸⁸ • Moderate recurrence rate⁸⁷ 	III, C
Excision with second intention healing	II or III (occasionally I) ⁸⁷	<ul style="list-style-type: none"> • No entrapment of epithelial strands or debris, as can occur after primary closure⁸⁷ • Favorable cosmetic results⁹⁰ • Only known treatment that can be curative¹⁸ • Associated with the lowest rates of recurrence⁸⁴ • Early excision allows for the best chance of reduced pain and disability⁸⁴ 	<ul style="list-style-type: none"> • Associated with greater postoperative morbidity⁸⁵ 	IIb, B
Wide excision	II or III (occasionally I) ⁸⁷	<ul style="list-style-type: none"> • Associated with greater postoperative morbidity⁸⁵ 		IIb, B
Reconstruction with flap plasty	II or III (occasionally I) ⁸⁷	<ul style="list-style-type: none"> • Considered the best option for closing wounds if repair is indicated¹⁸ 	<ul style="list-style-type: none"> • Associated with greater postoperative morbidity⁸⁵ 	Ia/Ila, A/B
STEEP	II or III ⁹¹	<ul style="list-style-type: none"> • Spares subcutaneous fat • Low recurrence rates • Relatively short healing time⁹¹ 	<ul style="list-style-type: none"> • Contracture formation possible⁹¹ 	IV, D ^{91,92}

Laser			
Nd:YAG	I or II ⁹³		Ib, A
Intralesional laser (630-nm)	Hurley stage unclear; modified Sartorius score range 8-59 ⁹⁶		NED
IPL	I or II ⁹³		IV, D
CO ₂	II or III ⁹³		Ib, A
		<ul style="list-style-type: none"> • Reduces the number of hair follicles and sebaceous glands in the treated areas⁹³ • Decreases inflammation and scarring of lesions^{93,84} • May prevent new eruptions⁹⁴ • Less invasive than surgery⁹⁵ • Improved effect with photosensitizers, such as methylene blue gel, psoralen bath solution, or with activation by ultraviolet A • Decreases inflammation of lesions • Less invasive than surgery⁹⁵ • Tissue sparing ability • Heal with less disfiguring consequences compared with surgical excision⁹³ 	
		<ul style="list-style-type: none"> • Many patients experience pain related to treatment • Some patients report no change in symptoms after treatment⁹⁴ 	
		<ul style="list-style-type: none"> • Increased depth of lesions make it less effective for HS compared with other skin conditions like acne⁶ • Requires multiple treatments • Can cause erythema, irritation, or burning⁹⁷ • Recurrence likely • Complications include scar contracture, restricted range of motion, and delayed wound healing⁸⁴ • Limited evidence showing success⁹³ 	

CO₂, Carbon dioxide; IPL, intense pulsed light; Nd:YAG, neodymium-doped:yttrium aluminum garnet; NED, not enough data; STEEP, skin-tissue sparing excision with electrosurgical peeling.

*As defined by Gullive W, Zouboulis C, Prens E, Jemec GB, Tzellos T. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa. Rev Endocr Metab Disord 2016;17:343-51. Evidence level: Ia = metaanalysis of randomized controlled trials; Ib = randomized controlled trial; IIa = controlled study without randomization; IIb = quasiexperimental study; III = nonexperimental descriptive studies, such as comparative, correlation, and case-control studies; IV = expert committee reports or opinion or clinical experience of respected authorities, or both.

[†]As defined by Guyatt G, Oxman AD, Vist GE, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6. Strength of recommendation: A = category I evidence; B = category II evidence or extrapolated from category I evidence; C = category III evidence or extrapolated from category I or II evidence; D = category IV evidence or extrapolated from category II or III evidence.

responders" who achieved a $\geq 25\%$ reduction in the number of total abscesses.³⁰ In an open-label extension of both trials, all patients were followed for ≥ 96 weeks. Of the 88 patients receiving 40 mg ADA weekly, HiSCR was improved at week 36 (62.5% HiSCR) and maintained at week 168 (52.3% HiSCR).³⁰ Of a subset of responders and partial responders, the HiSCR rate was improved at week 36 (79.4%) and maintained by week 168 (57.1%).³⁰ In both the responders and partial responders, there was a clinically significant improvement in quality of life at week 72. Even if patients did not meet HiSCR at week 12, the open-label extension results suggest patients might still benefit from long-term use.³⁰ In October 2018, ADA was approved by the US Food and Drug Administration for the treatment of HS in patients ≥ 12 years of age.³¹

ADA efficacy might be related to mTORC1 signaling,²⁶ which is important for innate and adaptive immunity and T_H17 differentiation.³² In a study of 13 patients given the standard HS dose of ADA, *MTOR* gene expression was significantly reduced in lesional skin at week 16.²⁶ mTORC1 phosphorylates the effector protein S6 kinase beta-1 (S6K1), and therefore this study also analyzed S6K1 and activated P-S6K1 protein levels. After 16 weeks, both S6K1 and P-S6K1 levels were significantly reduced in patients with HS.²⁶

Infliximab is a chimeric monoclonal antibody that inhibits TNF- α by binding soluble and bound TNF- α , reducing circulating TNF- α and inducing apoptosis in cells with bound TNF- α .^{15,25,29} In a phase II randomized, double-blind, crossover study, 38 patients with moderate to severe HS received 5 mg/kg of intravenous infliximab on weeks 0, 2, 4, 6, 14, and 22. By week 8, 60% of patients had a 25% to $< 50\%$ decrease in HS severity compared with 5.6% of patients in the placebo group.²⁵ The infliximab group also demonstrated reduced inflammatory markers compared with the placebo group at week 8 as well as significant improvements in mean Dermatology Life Quality Index (DLQI) and visual analog scores.^{25,27} However, "wearing off effects" occurred during the maintenance period 4 weeks after each infusion,¹³ suggesting that shorter intervals between infusions might be more effective.

Etanercept is a recombinant human TNF- α receptor p75-Fc fusion protein that competitively binds membrane-bound TNF- α receptors. In a phase II open-label trial of 15 patients receiving etanercept 50 mg weekly for 12 weeks, 10 participants completed the 12-week treatment period, while 5 participants withdrew before completion. The results showed no clinically significant decrease in DLQI after treatment. Although 29% of patients

reported moderate improvement in their disease, no participants had complete remission at 12 weeks.³³

Golimumab is a human anti-TNF- α monoclonal antibody that binds to soluble and membrane-bound TNF- α . One published case describes a 51-year-old woman with severe HS, type II diabetes, and psoriatic arthritis. Initial treatment with 40 mg ADA every-other-week and 15 mg methotrexate weekly for her psoriatic arthritis had no impact on her HS. A subsequent change to anakinra 100 mg daily for 5 months flared both her HS and arthritis. A trial of golimumab 50 mg once a month for 8 months flared her HS further, though her arthritis improved.³⁴

Interleukin-17 inhibitors

Secukinumab is a monoclonal antibody against interleukin-17A (IL-17A). A published case of a 47-year-old man describes patient-reported improvements in abscess and inflammatory nodule count as well as pain score, but these were not paralleled by the physician's clinical scores.^{25,35} Another report of a 24-year-old woman describes an almost complete resolution of nodules at 8 weeks after secukinumab 300 mg weekly for 1 month. Throughout the treatment period, there was a continuous reduction in HSS, serum amyloid A level, white blood cell count, and C-reactive protein level.³⁶ Serum amyloid A is an acute-phase protein that increases significantly in response to inflammatory stimuli. The treatment-induced reduction in serum amyloid A and C-reactive protein suggests a decrease in inflammation. A single-arm, open-label, pilot study of secukinumab for patients with HS has been completed,³⁷ and a phase III, multicenter, randomized, double-blind, placebo-controlled study is underway.³⁸

Ixekizumab is another monoclonal antibody that selectively binds IL-17A. One published case describes a 46-year-old man with HS and comorbid psoriasis and psoriatic arthritis who had a decrease in Sartorius score (54 to 16) and DLQI (20 to 3) after 4 weeks of treatment with ixekizumab (160 mg at week 0, 80 mg every-other-week for 12 weeks, then 80 mg every 4 weeks).³⁹ At 20 weeks, efficacy was maintained and there were no side effects.

IL-12/23 inhibitors

Ustekinumab is a monoclonal antibody against IL-12/IL-23, which function within the T_H1 and T_H17 pathways, respectively.²⁵ One phase II, prospective, uncontrolled, open-label study of ustekinumab treatment in 17 patients with moderate-to-severe HS suggests limited benefit.^{40,41} Guselkumab is a monoclonal antibody that specifically targets IL-23. A

phase II, multicenter, randomized, placebo-controlled, double-blind, proof of concept study to evaluate guselkumab for the treatment of moderate-to-severe HS is underway.⁴²

Other biologics

Anakinra is a humanized monoclonal antibody targeting the IL-1 receptor. A study of 20 patients with HS found 7 of 9 patients in the treatment group receiving 100 mg anakinra subcutaneously once daily for 12 weeks achieved HiSCR compared with 3 of 10 patients receiving placebo.⁴³ An open-label phase II, nonrandomized trial with 6 moderate-to-severe patients with HS demonstrated a significant reduction of Sartorius score after daily anakinra for 8 weeks.^{25,44} In a double-blind, randomized, placebo-controlled trial with 20 Hurley stage II or III patients, HiSCR improved in 78% of patients in the anakinra arm compared with 30% in the placebo arm at week 12.^{25,45} However, at 24 weeks, the HiSCR difference was not significant between the treatment and placebo groups.²⁵ A significant decrease in serum levels of interferon-gamma and an increase in IL-22 was also observed in the treatment group after 12 weeks.⁴³

MABp1 is a monoclonal antibody against IL-1 α . A prospective, double-blind, 1:1 randomized, placebo-controlled study in 20 moderate-to-severe patients with HS was completed.⁴⁶ All patients either failed or had a contraindication to ADA. Sixty percent of MABp1-treated patients achieved HiSCR at week 12 compared with 10% of placebo patients.^{16,46} MABp1 efficacy was maintained at week 24, while there was no maintenance of efficacy in the placebo group. More than 80% (85.7%) of MABp1-treated patients reported improvement in visual analog scores versus 20% of the placebo group. In the MABp1 group, ultrasonography found decreased neovascularization and lesion depth while serum analysis demonstrated decreased circulating IL-8 and production of IL-8 by whole blood.⁴⁶

Growing evidence suggests that multiple immunologic pathways are implicated in HS; simultaneously targeting different pathways might provide better outcomes,⁴⁷ but there is controversy regarding the safety of using multiple biologics concurrently. In rheumatoid arthritis, concomitant therapy with etanercept and anakinra resulted in more adverse events.⁴⁷ However, rheumatoid arthritis analyses may not be applicable to HS.⁴⁷ Moreover, 2 biologics have been safely and effectively used for the treatment of other diseases (eg, TNF- α and IL-12/23 therapy for psoriasis and palmoplantar pustulosis),⁴⁷⁻⁴⁹ and anecdotal evidence suggests that this

method of therapy has been successful in patients with HS.⁴⁷ Indeed, combination therapies using multiple immunosuppressive agents like ADA plus mycophenolate or methotrexate appear to provide better responses than ADA alone (authors' unpublished data).

Table III summarizes other biological therapies and new small molecules for HS.

OTHER THERAPIES

Key points

- Ethinyloestradiol, noregestrol, and cyproterone acetate have not been effective for HS treatment, but finasteride might decrease symptoms
- Systemic retinoids might decrease symptoms in younger patients with HS with acne and lower body weight
- For mild HS, a combination of antibacterial soap, warm compresses, and sodium duside 2% ointment may decrease lesion size and symptoms

Hormonal therapies

The evidence for hormonal therapy in HS is limited by small sample sizes, variable outcome measures and methods, and reporting bias.⁵⁰ The only randomized controlled, double-blinded, cross-over study of hormonal therapy in HS compared 50 μ g ethinyloestradiol/500 μ g noregestrol on days 5 to 25 of the menstrual cycle to 50 μ g ethinyloestradiol on days 5 to 25 and 50 μ g cyproterone acetate on days 5 to 14 of the menstrual cycle.⁵¹ Both groups had decreased plasma testosterone and visual analogue scales, and there was no clinically significant difference between the 2 treatments.^{8,51} However, both groups had significantly decreased HS severity; 29% of patients cleared after having continuous disease for ≤ 20 years.⁵¹

Finasteride is a selective competitive inhibitor of type II 5 α -reductase.^{52,53} Case reports have reported improvement of moderate-to-severe HS within 4 weeks of finasteride treatment, but recurrences were reported after treatment cessation.⁵²

Spiromolactone is a potassium-sparing diuretic that has antiandrogenic properties. It blocks mineralocorticoid receptors, inhibiting androgen production, and has moderate affinity for both progesterone and androgen receptors.⁵⁴ In a small case series of patients with HS with mild-to-moderate disease, 17 of 20 patients taking spironolactone 100 to 150 mg daily showed reduced PGA after 3 months. No cases were completely cleared and only 3 were severe at baseline.^{8,55} This

Table III. Other biologic therapies and new small molecules for hidradenitis suppurativa

Drug and dose (if applicable)	MOA	Study no.	Trial type	Patients, n	Disease severity	Outcome
Etanercept 50 mg SQ	Fusion protein that binds and inhibits both TNF- α and TNF- β	NCT00107991	Phase II open-label; 12 weeks	15	Moderate to severe	Failed to show a clinically significant decrease in PGA score and DLQI at 12 weeks ⁹⁸
CJM-112	Monoclonal antibody against IL-17A	NCT02421172	Phase II randomized, double-blind, placebo-controlled, multiple dose study	66	Moderate to severe	No published results ⁹⁹
Bimekizumab	Monoclonal antibody against IL-17A and IL-17F	NCT03248531	Phase II multicenter double-blind placebo-controlled trial comparing with adalimumab	157	Moderate to severe	No published results ¹⁰⁰
Ustekinumab 45 mg or 90 mg on weeks 0, 4, 16, and 28	Monoclonal antibody against p40 subunit of IL-12 and IL-23	NCT01704534	Phase II prospective, uncontrolled, open-label study; 40 weeks	17	Moderate to severe	Sartorius score was markedly (n = 6), moderately (n = 8), and mildly improved (n = 1), no change, or worsening (n = 2); mean Sartorius score of the whole population decreased from a baseline of 112.12 to 60.18 after 40 weeks ⁴⁰ ; in addition, by week 40, 8 of 17 patients achieved HiSCR-50
MEDI8968	Antibody to the IL-1 receptor	NCT01838499	Phase IIa Randomized, Double-Blind, Placebo-controlled, Multicenter Study	224	Moderate to Severe	23.6% of patients in the MEDI8968 group had improved PGA compared with 18.5% of patients in the placebo group; 43.6% of patients dropped out of the experimental group because of a lack of improvement and trial terminated early because of a lack of efficacy ¹⁶

Bermekimab 400 mg Adalimumab	Monoclonal antibody against IL-1 α Human monoclonal antibody against TNF- α	NCT03512275	Phase II multicenter open-label study	20	Moderate to severe	No published results ¹⁰¹
		PIONEER I (NCT01468207)	Phase III multicenter, double-blinded, placebo-controlled, randomized trial	307	Mild to severe	41.8% of patients receiving ADA compared with 26.0% of patients in the placebo group achieved a clinical response ($P = .003$) ²⁹
		PIONEER II (NCT01468233)	Phase III multicenter, double-blinded, placebo-controlled, randomized trial	326	Mild to severe	58.9% of patients receiving ADA compared with 27.6% of patients in the placebo group achieved a clinical response ($P = .001$); patients receiving ADA had significantly greater improvement in lesions, pain, and modified Sartorius score compared with the placebo group ²⁹
		NCT02904902	Phase III multicenter, open-label, single arm study	15	Moderate to severe	No published results ¹⁰²
		NCT02808975	Phase IV, double- blind, randomized, placebo-controlled, multicenter study	200	Moderate to severe	No published results ¹⁰³
IFX 5 mg/kg at weeks 0, 2, 6, then every 8 weeks thereafter	Chimeric monoclonal antibody against TNF- α	NCT03001115	Postmarketing cohort study	300	Severe	No published results ¹⁰⁴
		NCT00795574	Phase II, randomized, double-blind, placebo-controlled crossover trial	38	Moderate to severe	60% of patients treated with IFX showed a 25% to <50% improvement, 26.7% showed a $\geq 50\%$ improvement, and 13.3% showed a <25% improvement in HSSI score 8 weeks after the initial dose ¹⁰⁵

Continued

Table III. Cont'd

Drug and dose (if applicable)	MOA	Study no.	Trial type	Patients, n	Disease severity	Outcome
Anakinra 100 mg/ 0.67 mL in- jected SQ once daily	Humanized mono- clonal antibody against the IL-1 receptor	NCT01516749	Phase II, open-label, proof-of-concept, nonrandomized study	6	Moderate to severe	Patients showed a significant reduction of Sartorius score after anakinra was given daily for 8 weeks ($P = .024$) ⁴⁴
		NCT01558375	Phase II, double-blind, randomized, controlled clinical trial	20	Moderate to severe	HiSCR improved at week 12 in 78% of patients in the anakinra arm compared with 30% in the placebo arm ⁴³
Secukinumab 300 mg every 2 weeks or every 4 weeks	Monoclonal antibody against IL-17A	NCT03713632	Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel group study	Estimated enrollment: 471	Moderate to severe	No published results ³⁸
Guselkumab	Monoclonal antibody against IL-23	NCT03628924	Phase II multicenter, randomized, placebo-controlled, double-blind, proof-of-concept study	Estimated enrollment: 180	Moderate to severe	No published results ⁴²
Apremilast	PDE4 inhibitor that blocks cAMP degradation, which drives activation of PKA. In turn, it re- duces production of TNF- α , IL-12p40, and IL-17, and in- creases IL-10.	NCT03049267	Phase I double-blind, randomized placebo-controlled clinical trial	20	Moderate	No published results ¹⁰⁶
		NCT02695212 10 mg/day 1-6, 30 mg twice daily at day 6 onwards	Phase II single center open-label clinical trial	20	Moderate	No published results ¹⁰⁷
		N/A; no clinical trial underway	Case series	9	Moderate to severe	Significant improvement in Sartorius score in addition to decreased VAS pain score and DLQI ¹⁰⁸
IFX-1	Monoclonal antibody against C5a	NCT03001622	Phase II open-label clinical trial	12	Moderate to severe	No published results ¹⁰⁹
INCB054707	JAK inhibitor	NCT03569371	Phase II open-label, single arm study	10	Moderate to severe	No published results ¹¹⁰

C5a, Complement factor 5a; cAMP, cyclic adenosine monophosphate; DLQI, Dermatology Life Quality Index; HiSCR, Hidradenitis Suppurativa Clinical Response; HSSI, Hidradenitis Suppurativa Severity Index; IFX, infliximab; IL, interleukin; JAK, Janus kinase; MOA, mechanism of action; PDE4, phosphodiesterase 4; PGA, Physician's Global Assessment; PKA, protein kinase A; SQ, subcutaneous; TNF, tumor necrosis factor; VAS, visual analog scale.

medication may benefit women who report flares associated with menses.⁸

Retinoids

Retinoids have long been used for HS despite their questionable efficacy.¹³ One chart review investigated the response of 25 patients with HS (11 with Hurley stage I, 7 with stage II, and 7 with stage III) to isotretinoin, with an average dose of 0.45 mg/kg/day for 6.8 months.⁵⁶ Eight patients had no response, 8 had a partial response, and 9 had a complete response. Acne was most prevalent in complete responders and least common in nonresponders. Moreover, out of the complete responders, two-thirds of patients had Hurley stage I disease, and one third of patients had stage II.⁵⁶ Complete responders were an average of 7.5 years younger than nonresponders. Response was also better in patients who weighed less.⁵⁶ This study suggests that isotretinoin may benefit less severe patients with acne who are younger and weigh less.

Although isotretinoin is not recommended by the European Treatment Guidelines for HS, it might be helpful for patients with inflammatory, migratory, and furunculoid lesions.⁵⁷ A few studies from 1-2 decades ago found a response rate to isotretinoin in Patients with HS of about 16%.⁵⁷ A more recent review found a relatively high response rate to acitretin/etretinate among patients with HS (7 independent studies comprising a total of 32 patients demonstrated a significant response in 65.6%).^{57,58} Isotretinoin appears to be ineffective for treating sinus tracts and tunnels.⁵⁹

Antidiabetic medications

Antidiabetic drugs, specifically metformin, have garnered attention because they inhibit the proliferation of proinflammatory cytokines of human keratinocytes in vitro through an mTOR signaling pathway.⁶⁰ Metformin decreases hepatic glucose production and improves insulin sensitivity by increasing peripheral glucose uptake and utilization,^{61,62} and it has been shown to act as an antiandrogenic agent that may influence the expression of genes involved in HS.⁶²

A pilot study found metformin effective in treating recalcitrant HS.⁶³ In addition, 22 women and 3 men treated with metformin showed a statistically significant reduction in average Sartorius score of 7.64 at week 12 and 12.78 at week 24.^{8,62} Other metformin studies in patients with HS have yielded mixed results.¹³ Glucagon-like peptide-1 analogues and agonists (eg, liraglutide) have also been considered for HS treatment. Although there is less research on

the efficacy of these drugs,⁶⁴ some studies suggest potential benefit.²⁰

Zinc glutamate has a regulatory role in innate and adaptive immunity and may have a potential benefit in patients with HS.¹³ In a small pilot study of patients with Hurley stage I and II HS, zinc glutamate was somewhat effective, but relapses occurred when the dose was reduced from 90 mg to 20 to 60 mg.¹³ A combination of oral zinc gluconate and topical triclosan was evaluated for HS treatment in a retrospective study of 66 patients. After 3 months of treatment, Sartorius score and DLQI were reduced from 32.5 to 25 and 12.5 to 8, respectively.⁶⁵

Topicals

Few studies have investigated washes for HS treatment. One prospective trial of 627 patients with Hurley stage I axillary disease tested the efficacy of a three times daily wash with antibacterial soap, warm compress for 10 minutes, and the application of topical sodium dusidate 2% ointment. Patients did not shave. Before treatment, 100% of patients reported armpit pain and 77% had itching. Complete healing was reported in 361 patients at week 2 and 114 patients at week 4.⁶⁶

Benzoyl peroxide is an established acne treatment that is being tested for HS. One prospective 16-week multicenter, single-blinded, randomized controlled trial is comparing provodine topical cream and 10% benzoyl peroxide in 25 patients with HS. There are no published data from this trial to date.^{13,67}

In conclusion, at the time of this article's submission, there were 33 HS active clinical trials (ie, not yet recruiting, recruiting, enrolling by invitation, or active but not recruiting).⁶⁸ The British Association of Dermatologists guidelines for the management of HS⁶⁹ and the North American clinical management guidelines for HS⁵⁰ have recently been updated. Although the treatment of HS remains difficult, a clearer understanding of the immunopathogenesis of this disease will likely lead to more efficacious therapies. With so many trials currently enrolling patients or doing so on the horizon,⁷⁰ practitioners will hopefully have more tools in their armamentarium supported by more rigorously derived data.

REFERENCES

1. Ingram JR, Woo PN, Chua SL, et al. Interventions for hidradenitis suppurativa. *Cochrane Database Syst Rev*. 2015; 10:CD010081.
2. Ingram JR, McPhee M. Management of hidradenitis suppurativa: a U.K. survey of current practice. *Br J Dermatol*. 2015; 173:1070-1072.
3. Jemec GB, Wendelboe P. Topical clindamycin versus systemic tetracycline in the treatment of hidradenitis suppurativa. *J Am Acad Dermatol*. 1998;39:971-974.

4. Pradhan S, Madke B, Kabra P, Singh AL. Anti-inflammatory and immunomodulatory effects of antibiotics and their use in dermatology. *Indian J Dermatol.* 2016;61:469-481.
5. van der Zee HH, Boer J, Prens EP, Jemec GBE. The effect of combined treatment with oral clindamycin and oral rifampicin in patients with hidradenitis suppurativa. *Dermatology.* 2009;219:143-147.
6. Robert E, Bodin F, Paul C, et al. Non-surgical treatments for hidradenitis suppurativa: a systematic review. *Ann Chir Plast Esthet.* 2017;62:274-294.
7. Bettoli V, Join-Lambert O, Nassif A. Antibiotic treatment of hidradenitis suppurativa. *Dermatol Clin.* 2016;34:81-89.
8. Orenstein LA, Micheletti RG. Medical management of hidradenitis suppurativa. *Semin Cutan Med Surg.* 2017;36:62-66.
9. Andersen RK, Jemec GBE. Treatments for hidradenitis suppurativa. *Clin Dermatol.* 2017;35:218-224.
10. Fischer AH, Haskin A, Okoye GA. Patterns of antimicrobial resistance in lesions of hidradenitis suppurativa. *J Am Acad Dermatol.* 2017;76:309-313.e2.
11. Scheinfeld N. Why rifampin (rifampicin) is a key component in the antibiotic treatment of hidradenitis suppurativa: a review of rifampin's effects on bacteria, bacterial biofilms, and the human immune system. *Dermatol Online J.* 2016;22.
12. Braunberger TL, Nartker NT, Nicholson CL, et al. Ertapenem - a potent treatment for clinical and quality of life improvement in patients with hidradenitis suppurativa. *Int J Dermatol.* 2018;57:1088-1093.
13. van Straalen KR, Schneider-Burrus S, Prens EP. Current and future treatment of hidradenitis suppurativa [E-pub ahead of print]. *Br J Dermatol.* <https://doi.org/10.1111/bjde.16768>. Accessed October 23, 2019.
14. Wong D, Walsh S, Alhusayen R. Low-dose systemic corticosteroid treatment for recalcitrant hidradenitis suppurativa. *J Am Acad Dermatol.* 2016;75:1059-1062.
15. Shanmugam VK, Zaman NM, McNish S, Hant FN. Review of current immunologic therapies for hidradenitis suppurativa. *Int J Rheumatol.* 2017;2017:8018192.
16. Theut Riis P, Thorlaciusr LR, Jemec GB. Investigational drugs in clinical trials for hidradenitis suppurativa. *Expert Opin Investig Drugs.* 2018;27:43-53.
17. University of North Carolina Chapel Hill. A randomized controlled trial evaluating the efficacy of intralesional triamcinolone in hidradenitis suppurativa. Available at: <https://clinicaltrials.gov/ct2/show/NCT02781818>. Accessed October 23, 2019.
18. Scuderi N, Monfrecola A, Dessy LA, Fabbrocini G, Megna M, Monfrecola G. Medical and surgical treatment of hidradenitis suppurativa: a review. *Skin Appendage Disord.* 2017;3:95-110.
19. Kromann CB, Ibler KS, Kristiansen VB, Jemec GBE. The influence of body weight on the prevalence and severity of hidradenitis suppurativa. *Acta Derm Venereol.* 2014;94:553-557.
20. Jennings L, Nestor L, Molloy O, Hughes R, Moriarty B, Kirby B. The treatment of hidradenitis suppurativa with the glucagon-like peptide-1 agonist liraglutide. *Br J Dermatol.* 2017;177:858-859.
21. Golbari NM, Lee Porter M, Kimball AB. Response to: remission of hidradenitis suppurativa after bariatric surgery. *JAAD Case Rep.* 2018;4:278-279.
22. Garg A, Papagermanos V, Midura M, Strunk A. Incidence of hidradenitis suppurativa among tobacco smokers: a population-based retrospective analysis in the U.S.A. *Br J Dermatol.* 2018;178:709-714.
23. Garg A, Besen J, Legler A, Lam CS. Factors associated with point-of-care treatment decisions for hidradenitis suppurativa. *JAMA Dermatol.* 2016;152:553-557.
24. Micheletti R. Tobacco smoking and hidradenitis suppurativa: associated disease and an important modifiable risk factor. *Br J Dermatol.* 2018;178:587-588.
25. Maarouf M, Clark AK, Lee DE, Shi VY. Targeted treatments for hidradenitis suppurativa: a review of the current literature and ongoing clinical trials. *J Dermatolog Treat.* 2018;29:441-449.
26. Balato A, Caiazzo G, Annunziata MC, et al. Anti-TNF α therapy modulates mTORC1 signalling in hidradenitis suppurativa. *J Eur Acad Dermatol Venereol.* 2019;33:e43-e45.
27. van Rappard DC, Mekkes JR, Tzellos T. Randomized controlled trials for the treatment of hidradenitis suppurativa. *Dermatol Clin.* 2016;34:69-80.
28. Kimball AB, Kerdel F, Adams D, et al. Adalimumab for the treatment of moderate to severe hidradenitis suppurativa: a parallel randomized trial. *Ann Intern Med.* 2012;157:846-855.
29. Kimball AB, Okun MM, Williams DA, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. *N Engl J Med.* 2016;375:422-434.
30. Zouboulis CC, Okun MM, Prens EP, et al. 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. *J Am Acad Dermatol.* 2019;80:60-69.e2.
31. Humira [package insert]. North Chicago, IL: AbbVie Inc.
32. De Vita V, Melnik BC. The magnitude of mTORC1 signalling may predict the response to isotretinoin treatment in patients with hidradenitis suppurativa. *Dermatology.* 2017;233:399-400.
33. Lee RA, Dommash E, Treat J, et al. A prospective clinical trial of open-label etanercept for the treatment of hidradenitis suppurativa. *J Am Acad Dermatol.* 2009;60:565-573.
34. van der Zee HH, Prens EP. Failure of anti-interleukin-1 therapy in severe hidradenitis suppurativa: a case report. *Dermatology.* 2013;226:97-100.
35. Thorlacius L, Theut Riis P, Jemec GBE. Severe hidradenitis suppurativa responding to treatment with secukinumab: a case report. *Br J Dermatol.* 2018;179:182-185.
36. Schuch A, Fischer T, Boehner A, Biedermann T, Volz T. Successful treatment of severe recalcitrant hidradenitis suppurativa with the interleukin-17A antibody secukinumab. *Acta Derm Venereol.* 2018;98:151-152.
37. Tufts Medical Center. Exploratory trial evaluating cosentyx (secukinumab) for patients with moderate-to-severe hidradenitis suppurativa. Available at: <https://clinicaltrials.gov/ct2/show/NCT03099980>. Accessed October 23, 2019.
38. Novartis Pharmaceuticals. Study of efficacy and safety of two secukinumab dose regimens in subjects with moderate to severe hidradenitis suppurativa (HS) (SUNRISE). Available at: <https://clinicaltrials.gov/ct2/show/NCT03713632>. Accessed October 23, 2019.
39. Odorici G, Pellacani G, Conti A. Ikekizumab in hidradenitis suppurativa: a case report in a psoriatic patient [E-pub ahead of print]. *G Ital Dermatol Venereol.* <https://doi.org/10.23736/S0392-0488.18.06135-7>. Accessed October 23, 2019.
40. Blok JL, Li K, Brodmerkel C, Horváthovich P, Jonkman MF, Horváth B. Ustekinumab in hidradenitis suppurativa: clinical results and a search for potential biomarkers in serum. *Br J Dermatol.* 2016;174:839-846.
41. University Medical Center Groningen. A proof of concept study to evaluate the effectiveness of ustekinumab in hidradenitis suppurativa (HITS). Available at: <https://clinicaltrials.gov/ct2/show/NCT01704534>. Accessed October 23, 2019.

42. Janssen Research and Development. A study to evaluate the efficacy, safety, and tolerability of guselkumab for the treatment of participants with moderate to severe hidradenitis suppurativa (HS) (NOVA). Available at: <https://clinicaltrials.gov/ct2/show/NCT03628924>. Accessed October 23, 2019.
43. Tzanetakou V, Kanni T, Gitrakou S, et al. Safety and efficacy of anakinra in severe hidradenitis suppurativa: a randomized clinical trial. *JAMA Dermatol*. 2016;152:52-59.
44. University of California San Francisco. Anakinra as a treatment for hidradenitis suppurativa. Available at: <https://clinicaltrials.gov/ct2/show/NCT01516749>. Accessed October 23, 2019.
45. University of Athens. Anakinra in hidradenitis suppurativa. Available at: <https://clinicaltrials.gov/ct2/show/NCT01558375>. Accessed October 23, 2019.
46. Kanni T, Argyropoulou M, Spyridopoulos T, et al. MABp1 targeting IL-1 α for moderate to severe hidradenitis suppurativa not eligible for adalimumab: a randomized study. *J Invest Dermatol*. 2018;138:795-801.
47. Naik HB, McGinness A, Shinkai K. Concurrent anticytokine biologics for the management of severe hidradenitis suppurativa: are they safe and effective? *Cutis*. 2018;101:163-164, 176.
48. Babalola O, Lakdawala N, Strober BE. Combined biologic therapy for the treatment of psoriasis and psoriatic arthritis: a case report. *JAAD Case Rep*. 2015;1:3-4.
49. Torre KM, Payette MJ. Combination biologic therapy for the treatment of severe palmoplantar pustulosis. *JAAD Case Rep*. 2017;3:240-242.
50. Alkhani A, Sayed C, Alavi A, et al. North American clinical management guidelines for hidradenitis suppurativa: a publication from the United States and Canadian Hidradenitis Suppurativa Foundations: part II: topical, intralesional, and systemic medical management. *J Am Acad Dermatol*. 2019; 81:91-101.
51. Mortimer PS, Dawber RP, Gales MA, Moore RA. A double-blind controlled cross-over trial of cyproterone acetate in females with hidradenitis suppurativa. *Br J Dermatol*. 1986; 115:263-268.
52. Khandalaval BN, Do MV. Finasteride in hidradenitis suppurativa: a "male" therapy for a predominantly "female" disease. *J Clin Aesthet Dermatol*. 2016;9:44-50.
53. Randhawa HK, Hamilton J, Pope E. Finasteride for the treatment of hidradenitis suppurativa in children and adolescents. *JAMA Dermatol*. 2013;149:732-735.
54. Karagiannis I, Nikolakis G, Sabat R, Zouboulis CC. Hidradenitis suppurativa/acne inversa: an endocrine skin disorder? *Rev Endocr Metab Disord*. 2016;17:335-341.
55. Lee A, Fischer G. A case series of 20 women with hidradenitis suppurativa treated with spironolactone. *Australas J Dermatol*. 2015;56:192-196.
56. Huang CM, Kirchhof MG. A new perspective on isotretinoin treatment of hidradenitis suppurativa: a retrospective chart review of patient outcomes. *Dermatology*. 2017;233:120-125.
57. Boer J. Are there indications for isotretinoin treatment of hidradenitis suppurativa? *Dermatology*. 2017;233:111-112.
58. Zouboulis CC, Desai N, Emtestam L, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol*. 2015;29:619-644.
59. Lipsker D, Severac F, Freysz M, et al. The ABC of hidradenitis suppurativa: a validated glossary on how to name lesions. *Dermatology*. 2016;232:137-142.
60. Liu Y, Yang F, Ma W, Sun Q. Metformin inhibits proliferation and proinflammatory cytokines of human keratinocytes in vitro via mTOR-signaling pathway. *Pharm Biol*. 2016;54: 1173-1178.
61. Vilanova I, Hernández JL, Mata C, et al. Insulin resistance in hidradenitis suppurativa: a case-control study. *J Eur Acad Dermatol Venereol*. 2018;32:820-824.
62. Bubna AK. Metformin - for the dermatologist. *Indian J Pharmacol*. 2016;48:4-10.
63. Verdolini R, Clayton N, Smith A, Alwash N, Mannello B. Metformin for the treatment of hidradenitis suppurativa: a little help along the way. *J Eur Acad Dermatol Venereol*. 2013; 27:1101-1108.
64. Emtestam L, Sartorius K. Interleukin-36 cytokine family signalling in hidradenitis suppurativa. *Br J Dermatol*. 2018; 178:591-592.
65. Hessam S, Sand M, Meier NM, Gambichler T, Scholl L, Bechara FG. Combination of oral zinc gluconate and topical triclosan: an anti-inflammatory treatment modality for initial hidradenitis suppurativa. *J Dermatol Sci*. 2016;84: 197-202.
66. Shirah BH, Shirah HA. Effective modified conservative tissue preserving protocol to treat stage I axillary hidradenitis suppurativa: a prospective cohort study of 627 patients with five years follow-up. *J Dermatolog Treat*. 2017;28:458-463.
67. Henry Ford Health System. An investigation into the efficacy of providone topical cream as compared to 10% benzoyl peroxide wash for the treatment of hidradenitis suppurativa. Available at: <https://clinicaltrials.gov/ct2/show/NCT01818167>. Accessed October 23, 2019.
68. clinicaltrials.gov. website. Available at: https://clinicaltrials.gov/ct2/results?cond=Hidradenitis+Suppurativa&Search=Apply&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=. Accessed October 23, 2019.
69. Ingram JR, Collier F, Brown D, et al. British Association of Dermatologists guidelines for the management of hidradenitis suppurativa (acne inversa) 2018. *Br J Dermatol*. 2019;180: 1009-1017.
70. U.S. National Library of Medicine. Hidradenitis suppurativa. Available at: <https://clinicaltrials.gov/ct2/results?cond=Hidradenitis+Suppurativa&term=&cnty=&state=&city=&dist=>. Accessed February 12, 2019.
71. Hamby R, Kirby B. Prolonged clindamycin and rifampicin for hidradenitis suppurativa: resist to prevent resistance. *Br J Dermatol*. 2019;180:702-703.
72. Zouboulis CC, Bechara FG, Dickinson-Blok JL, et al. Hidradenitis suppurativa/acne inversa: a practical framework for treatment optimization - systematic review and recommendations from the HS ALLIANCE working group. *J Eur Acad Dermatol Venereol*. 2019;33:19-31.
73. Scheinfeld N. Hidradenitis suppurativa: a practical review of possible medical treatments based on over 350 hidradenitis patients. *Dermatol Online J*. 2013;19:1.
74. Deckers IE, Prens EP. An update on medical treatment options for hidradenitis suppurativa. *Drugs*. 2016;76:215-229.
75. Melnik BC, John SM, Chen W, Plewig G. T helper 17 cell/regulatory T-cell imbalance in hidradenitis suppurativa/acne inversa: the link to hair follicle dissection, obesity, smoking and autoimmune comorbidities. *Br J Dermatol*. 2018;179:260-272.
76. University of Pittsburgh. Hydroxychloroquine for the treatment of hidradenitis suppurativa. Available at: <https://clinicaltrials.gov/ct2/show/NCT03275870>. Accessed October 23, 2019.
77. Golbari NM, Porter ML, Kimball AB. Antiandrogen therapy with spironolactone for the treatment of hidradenitis suppurativa. *J Am Acad Dermatol*. 2019;80:114-119.

78. Massachusetts General Hospital. A study to examine the safety and efficacy of drospirenone and ethinyl estradiol (YAZ) versus placebo in HS. Available at: <https://clinicaltrials.gov/ct2/show/NCT00722800>. Accessed October 23, 2019.
79. Ingram JR, Woo PN, Chua SL, et al. Interventions for hidradenitis suppurativa: a Cochrane systematic review incorporating GRADE assessment of evidence quality. *Br J Dermatol.* 2016;174:970-978.
80. Khoo ABS, Burova EP. Hidradenitis suppurativa treated with Clostridium botulinum toxin A. *Clin Exp Dermatol.* 2014;39:749-750.
81. Shi W, Schultz S, Strouse A, Gater DR. Successful treatment of stage III hidradenitis suppurativa with botulinum toxin A. *BMJ Case Rep.* 2019;12:e226064.
82. Goo B, Chung HJ, Chung WG, Chung KY. Intramuscular immunoglobulin for recalcitrant suppurative diseases of the skin: a retrospective review of 63 cases. *Br J Dermatol.* 2007;157:563-568.
83. Sharon-Guidetti A, Ziv Y, Kummer E, Yogeve R, Halevy A. Granulocyte-macrophage colony-stimulating factor for perianal hidradenitis suppurativa: report of a case. *Dis Colon Rectum.* 2006;49:682-684.
84. Smith MK, Nicholson CL, Parks-Miller A, Hamzavi IH. Hidradenitis suppurativa: an update on connecting the tracts. *F1000Res.* 2017;6:1272.
85. Scholl L, Hessam S, Bergmann U, Bechara FG. Surgical treatment of sinus tracts and fistulas in perianal hidradenitis suppurativa. *J Cutan Med Surg.* 2018;22:239-241.
86. Janse I, Bieniek A, Horváth B, Matusiak Ł. Surgical procedures in hidradenitis suppurativa. *Dermatol Clin.* 2016;34:97-109.
87. Deckers IE, Dahi Y, van der Zee HH, Prens EP. Hidradenitis suppurativa treated with wide excision and second intention healing: a meaningful local cure rate after 253 procedures. *J Eur Acad Dermatol Venereol.* 2018;32:459-462.
88. van Rappard DC, Mooij JE, Mekkes JR. Mild to moderate hidradenitis suppurativa treated with local excision and primary closure. *J Eur Acad Dermatol Venereol.* 2012;26:898-902.
89. Mehdizadeh A, Hazen PG, Bechara FG, et al. Recurrence of hidradenitis suppurativa after surgical management: a systematic review and meta-analysis. *J Am Acad Dermatol.* 2015;73(5 suppl 1):S70-S77.
90. Bieniek A, Matusiak Ł, Chlebicka I, Szepietowski JC. Secondary intention healing in skin surgery: our own experience and expanded indications in hidradenitis suppurativa, rhinophyma and non-melanoma skin cancers. *J Eur Acad Dermatol Venereol.* 2013;27:1015-1021.
91. Blok JL, Spoo JR, Leeman FWJ, Jonkman MF, Horváth B. Skin-tissue-sparing excision with electrosurgical peeling (STEEP): a surgical treatment option for severe hidradenitis suppurativa Hurley stage II/III. *J Eur Acad Dermatol Venereol.* 2015;29:379-382.
92. Blok JL, Boersma M, Terra JB, et al. Surgery under general anaesthesia in severe hidradenitis suppurativa: a study of 363 primary operations in 113 patients. *J Eur Acad Dermatol Venereol.* 2015;29:1590-1597.
93. John H, Manoloudakis N, Stephen Sinclair J. A systematic review of the use of lasers for the treatment of hidradenitis suppurativa. *J Plast Reconstr Aesthet Surg.* 2016;69:1374-1381.
94. Mahmoud BH, Tierney E, Hexsel CL, Pui J, Ozog DM, Hamzavi IH. Prospective controlled clinical and histopathologic study of hidradenitis suppurativa treated with the long-pulsed neodymium:yttrium-aluminum-garnet laser. *J Am Acad Dermatol.* 2010;62:637-645.
95. Negus D, Ahn C, Huang W. An update on the pathogenesis of hidradenitis suppurativa: implications for therapy. *Expert Rev Clin Immunol.* 2018;14:275-283.
96. Valladares-Narganes LM, Rodríguez-Prieto MA, Blanco-Suárez MD, Rodríguez-Lage C, García-Doval I. Treatment of hidradenitis suppurativa with intralesional photodynamic therapy using a laser diode attached to an optical cable: a promising new approach. *Br J Dermatol.* 2015;172:1136-1139.
97. Theut Riis P, Saunte DM, Sigsgaard V, Wilken C, Jemec GBE. Intense pulsed light treatment for patients with hidradenitis suppurativa: beware treatment with resorcinol. *J Dermatolog Treat.* 2018;29:385-387.
98. University of Pennsylvania. Etanercept for treatment of hidradenitis. Available at: <https://clinicaltrials.gov/ct2/show/NCT00107991>. Accessed October 23, 2019.
99. Novartis Pharmaceuticals. Efficacy, safety, and pharmacokinetics study of CJM112 in hidradenitis suppurativa patients. Available at: <https://clinicaltrials.gov/ct2/show/NCT02421172>. Accessed October 23, 2019.
100. UCB Pharma. A study to test the efficacy, safety and pharmacokinetics of bimekizumab in subjects with moderate to severe hidradenitis suppurativa. Available at: <https://clinicaltrials.gov/ct2/show/NCT03248531>. Accessed October 23, 2019.
101. XBiotech Inc. A study of bermekimab in patients with hidradenitis suppurativa. Available at: <https://clinicaltrials.gov/ct2/show/NCT03512275>. Accessed October 23, 2019.
102. AbbVie. Open-label study of adalimumab in Japanese subjects with hidradenitis suppurativa. Available at: <https://clinicaltrials.gov/ct2/show/NCT02904902>. Accessed October 23, 2019.
103. AbbVie. Safety and efficacy of Humira (Adalimumab) for hidradenitis suppurativa (HS) peri-surgically (SHARPS Study) (SHARPS). Available at: <https://clinicaltrials.gov/ct2/show/NCT02808975>. Accessed October 23, 2019.
104. AbbVie. Post-marketing surveillance of adalimumab in Korean hidradenitis suppurativa subjects (HS rPMS). Available at: <https://clinicaltrials.gov/ct2/show/NCT03001115>. Accessed October 23, 2019.
105. Grant A, Gonzalez T, Montgomery MO, Cardenas V, Kerdel FA. Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. *J Am Acad Dermatol.* 2010;62:205-217.
106. Erasmus Medical Center. Short-term Safety, efficacy and mode of action of apremilast in moderate suppurative hidradenitis (SMASH). Available at: <https://clinicaltrials.gov/ct2/show/NCT03049267>. Accessed October 23, 2019.
107. Florida Academic Dermatology Centers. Single center study of apremilast for the treatment of hidradenitis suppurativa (HS). Available at: <https://clinicaltrials.gov/ct2/show/NCT02695212>. Accessed October 23, 2019.
108. Weber P, Seyed Jafari SM, Yawalkar N, Hunger RE. Apremilast in the treatment of moderate to severe hidradenitis suppurativa: a case series of 9 patients. *J Am Acad Dermatol.* 2017;76:1189-1191.
109. InflaRx GmbH. Studying complement inhibition in patients with moderate to severe hidradenitis suppurativa. Available at: <https://clinicaltrials.gov/ct2/show/NCT03001622>. Accessed October 23, 2019.
110. Incyte Corporation. A study of the safety of INCB054707 in participants with hidradenitis suppurativa. Available at: <https://clinicaltrials.gov/ct2/show/NCT03569371>. Accessed October 23, 2019.

Vulvar diseases



Approach to the patient

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Learning objectives

After completing this learning activity, participants should be able to increase the thoroughness and comfort in the performance of the genital exam for both patient and provider; distinguish normal anatomic variations from disease processes in children and adults; and choose appropriate bedside testing that can increase diagnostic accuracy.

Disclosures

Editors

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Patients with vulvar dermatoses often delay seeking medical treatment because of anxiety and embarrassment. Moreover, women frequently self-treat with various home remedies and see multiple clinicians before presenting to a dermatologist. Despite serving as the primary providers for patients with vulvovaginal symptoms, gynecologists typically receive limited training in the causes and management of these conditions. Dermatologists are experts in the evaluation and management of cutaneous disease and should be the caretakers of all skin, including the genitalia. Vulvar disorders are underrecognized by dermatologists for numerous reasons: inadequate training, lack of comfort with both interview and examination techniques, and unfamiliarity with normal anatomic variations. The first article in this continuing medical education series on vulvar dermatoses reviews the fundamentals, approach, and techniques that can be used to ensure a successful visit for both patient and provider. (J Am Acad Dermatol 2020;82:1277-84.)

Key words: female genitalia; genital; patient education; physical examination; vulvar dermatology; vulvology.

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Vulvar diseases are an underserved category within dermatology and are not commonly a focus within dermatology training centers/programs. In fact, in a 2012 survey of International Society for the Study of Vulvovaginal Diseases multispecialty vulvar disorder experts, only 19% received formal vulvar disease training during residency and 11% during fellowship.¹ Anogenital itching and pain, the most common presenting symptoms, may be attributable to inflammatory dermatoses, infections, neoplasms, hormonal changes, and neuropathies, often with psychologic comorbidities. Indeed, most chronic anogenital symptoms are multifactorial in origin. Dermatologists are ideally suited to provide comprehensive evaluation and management for patients with chronic anogenital symptoms given the clinicians' ability to generate a broad differential diagnosis, perform judicious point-of-care diagnostic testing, and formulate a manageable treatment plan in partnership with the patient.

INTERVIEWING THE PATIENT

Key points

- **Obtaining a thorough patient history is vital to visit success**
- **Patients should complete a focused vulvar questionnaire before the visit when possible**
- **Patients with vulvar disorders have a significantly impaired quality of life**

Obtaining a thorough directed patient history can be achieved using a systematic approach. The interview process may be streamlined using a written questionnaire completed by the patient in advance of the visit (Supplement I; available at <https://doi.org/10.17632/t89rwxnrpt.1>). The dermatologist may then review the patient's information and tailor in-person interviewing to the most high-yield topics and second-level questions. The interview should aim to clarify symptom nature (pruritus vs pain), modifying factors (alleviating, exacerbating), and previous treatment (prescribed, self-directed). The interviewer should demonstrate and verbalize empathy in acknowledging the patient's symptoms and impact on quality-of-life. When a previsit questionnaire cannot be obtained, extended visits or multiple visits may be offered to facilitate comprehensive interview, examination, and counseling.

Vulvar symptoms may be localized or generalized and may involve the vulva or perianal skin. The two most common vulvar complaints are pruritus and pain. Patients with pruritus generally report a need to scratch/manipulate the affected skin that results in some degree of temporary relief. Patients who

scratch vigorously may subsequently experience pain caused by secondary erosions and fissures. Pain may be described by patients as burning, rawness, stinging, or aching; in contrast to patients with pruritus, patients with vulvar pain tend to avoid and minimize contact with their anogenital skin.

In attempting to alleviate vulvar symptoms, patients may apply various products and "remedies" to their vulvas and vaginas. Patients should be encouraged to divulge all modes and methods of treatment that they use for their genitalia. Questionnaires should query patient hygiene, grooming habits, and the use of personal care products and medications (nonprescription and prescription). In one survey of women, 84% reported grooming their pubic hair, most commonly for sex (56%), vacation (46%), or a health care professional visit (40%).²

Douching, sometimes called vaginal washing, is a personal care practice reportedly used regularly by 12% of females in the United States; it is more commonly used by African American women.³ Women report that they douche to feel clean after menses (66%), for general hygiene (44%), to cleanse before or after sex (37%), to reduce vaginal odor (27%), or because they thought it was normal to douche (19%).⁴ Paradoxically, women often deny douching when questioned in the health care setting because they have been told to avoid this practice by a health care provider. Douching has been associated with multiple adverse effects, including early preterm birth,⁵ ectopic pregnancy,⁶ and an increased incidence of bacterial vaginosis.^{5,7}

In addition to conventional feminine hygiene products, patients have reported cleaning their vulvas with excessive water washes, Lysol (which was once marketed for feminine hygiene and potential contraception), frozen bottles, and even performing "vajacials" (facials for the vagina).⁸ Patients may not readily disclose all practices and treatments, and providers should ask about home remedies if patients fail to improve with standard therapies.

It is equally important to assess for depression, sexual discomfort, anxiety, and suicidal ideation.^{9,10} Because of the sensitivity of these conditions, cultivating trust and reinforcing confidentiality between dermatologist and patient is of paramount importance. When a previsit questionnaire is available, summarizing a patient's previous treatment course may lead to higher patient satisfaction.¹¹

Finally, counseling patients using terminology and language that they understand and use themselves leads to more successful interventions and higher patient satisfaction.¹¹

PHYSICAL EXAMINATION

Key points

- The vulva should be examined in an organized, standardized fashion
- Using age-appropriate language and tone is essential
- Having a conversation with children and parents before the examination can alleviate anxiety and physical stress

Before the visit, dermatologists should prepare office staff to room patients with vulvar symptoms because sensitive information will often be discussed as part of the chief complaint. At the beginning of the visit, the patient should be fully informed of the process and who will be involved. If medical students, residents, or fellows are present in clinic, patients should be informed of the rationale for their involvement. Having a medical assistant or nurse in the room during the examination can make the patient feel more at ease and provide medicolegal protection for the provider.

Once the patient intake process has been completed, the patient should remove all clothing, including undergarments. The best position in which to evaluate patients differs between adults and prepubertal children.

Adult examination. Examination of an adult woman is most easily accomplished in the dorsal lithotomy position using footrests. This positioning allows for optimal visualization of all anogenital anatomic structures. The head of the bed should be positioned at a 30° to 45° angle so that the provider can maintain eye contact and speak to the patient face-to-face during the examination. This position also allows the provider to demonstrate sites of disease and techniques for medication application to the patient using a handheld mirror. Adult patients may need to raise one or both knees toward their chest in order to adequately visualize the perianal skin and the gluteal cleft.

After the examination, the patient should be asked to localize their symptoms by pointing, as symptoms are often disparate from clinical abnormalities.

Pediatric examination. Ensuring a comfortable and safe environment for prepubertal children who require a genital examination is critical. Children 3 to 5 years of age may have difficulty identifying when touching requests are inappropriate, particularly when asked by people that they deem as “good.”¹² For this reason, before the examination, we advocate a conversation that explains the purpose of the examination and gives the child a feeling of agency over her body. In a soothing, calm voice, the

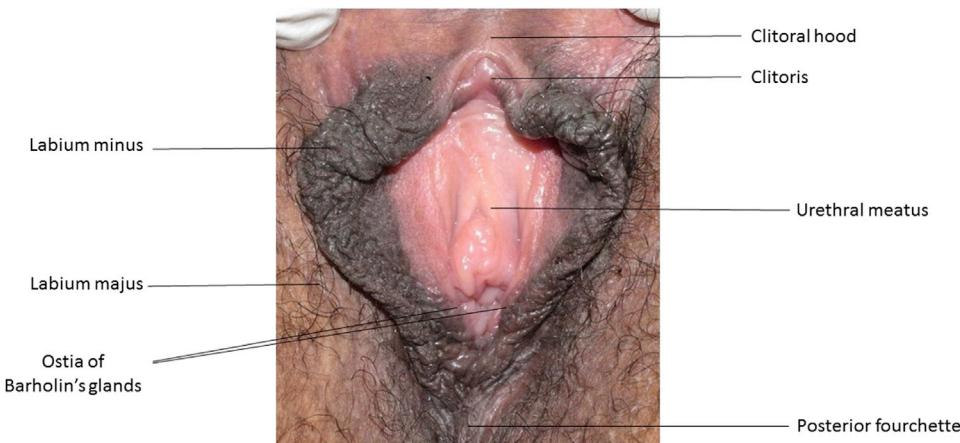


Fig 1. Child positioning.

dermatologist should explain his/her role as a doctor who specializes in examining “bottoms” and wants to help make the child’s problem better. The dermatologist should formally ask permission of both the parent and child before starting the examination. A child should never be examined against her will; if necessary, an examination under anesthesia can be performed. Before the examination, the dermatologist should show and allow the child to hold any instruments he/she may use (swabs, flashlights, etc.) in order to reduce the child’s anxiety.¹³

Several body positions can be used for optimal visualization of the vulva of a prepubertal child. The child may lie on her back on the examination table, put her feet together, and gently abduct the knees in a “frog-leg” position (Fig 1). To visualize the entire vulva including the hymen, the provider should place his/her hands on the bilateral buttocks and then retract posteriorly. This movement will also avoid inadvertent, painful separation of labial adhesions. The dermatologist should state “now you will feel my glove on your bottom” when initiating the examination; it is considered best to avoid using certain terms such as “relax” or “fingers” that may trigger victims of abuse.¹³ For a pediatric patient, one can have the child lie back over a parent’s knee with her hips flexed and knees apart, which naturally separates the buttocks thereby obviating the need for separation by the examiner. When evaluating a child, the parent/guardian can serve as the chaperone for examination.

During a pediatric examination, if abuse is suspected, early referral to the child abuse team (if available) and reporting to child protective services is imperative. We do not advocate asking more intensive screening questions of the child unless one has training specific to abuse victims. When health professionals suspect abuse in adult women, detailed histories should be gathered and observations documented.¹⁴ Almost all states require health professionals to report reasonable suspicions of elder abuse to Adult Protective Services.

**Fig 2.** Vulvar anatomy.

VISIT DOCUMENTATION

Key point

- **Photographs are beneficial for examination, documentation, and for communication with other providers and should be stored within the patient's medical record when possible**

Referring providers may not be familiar with the dermatology lexicon; therefore, diagrams or clinical photographs integrated into the patient medical record can be helpful. Physicians should preface clinical vulvar photography by explaining that every new patient has a baseline photograph taken to facilitate subsequent monitoring of disease activity and treatment response. Most clinical practices administer photography consent forms at a patient's initial visit. Many electronic medical records can incorporate and store photographs in a Health Information Portability and Accountability Act of 1996 (HIPAA)—compliant manner within the patient's chart, obviating the need for and potential hazards of standalone storage systems. Institutions and providers should define the security policy for sensitive clinical photographs, including genital photographs. At one institution known to the authors, urologic, gynecologic, and child abuse photography access is limited to providers in those specialties.

NORMAL VARIATION IN VULVAR ANATOMY

Key point

- **Vulvar anatomy changes with age and hormonal status**

Recognizing normal vulvar anatomy is the first step in being able to recognize abnormal vulvar anatomy and signs of disease (Fig 2). Furthermore, appreciating the different types of epithelia that occur within the vulva (keratinized skin, modified

mucous membrane, and true mucous membrane) can help to develop/hone a differential diagnosis because certain conditions have a predilection for the keratinized skin (eg, atopic dermatitis, contact dermatitis, or psoriasis) whereas others have a predilection for the modified (eg, lichen sclerosus) or true mucous membranes (eg, erosive lichen planus).

Consistently performing the external genital examination in a standardized order minimizes the risk of missing an important finding. We suggest that the keratinized, hair-bearing skin of the medial thighs, inguinal folds, labiocrural folds, mons pubis, and labia majora be examined first. Attention should then turn to the partially keratinized, modified mucous membranes consisting of the interlabial sulci (the crease between the labia majora and labia minora), labia minora, clitoral hood, and posterior fourchette.

Labia minora should be evaluated for symmetry, signs of scarring (eg, reduction in mass, lateral agglutination to the labia minora) as well as signs of active inflammation (eg, erythema, edema, fissure, erosion, and ulcer).¹⁵ Significant normal variation in size, shape, pigmentation, and symmetry of the labia minora can occur between patients and within an individual patient. Visible labia minora (Fig 3) are just as common as labia minora "hidden" by the labia majora, although patients with the former are more likely to perceive their genitalia as being abnormal¹⁶; this may manifest as a form of body dysmorphic disorder, leading some patients to seek labiaplasty.

The clitoral hood (prepuce) should be assessed for retractability and the ability to visualize the clitoral body; the inability to completely retract the clitoral hood suggests the presence of agglutination (fusion or scarring), which often results from inflammatory dermatoses. Similarly, the posterior fourchette (ie, the 6 o'clock position of the introitus) should be assessed for elasticity and scarring as well as signs of active inflammation (see above). Fissures



Fig 3. Normal vulva.

commonly occur at the posterior fourchette as a result of mechanical trauma (eg, intercourse, examination). The characteristics of the vaginal introitus mucosa and urethral meatus should be noted recognizing that the degree of “normal” vulvar and introitus erythema can vary significantly over time and between patients.¹⁷ Finally, the perineum, a common site for treatment-refractory lichen sclerosus, the perianal skin, and the gluteal cleft should be examined^{18,19}; the perianal skin is not naturally exposed in a dorsal lithotomy position.

Vulvar anatomy changes with age and changes in hormonal status. During pregnancy, vulvar hyperpigmentation, venous congestion, and soft tissue swelling commonly occur; these changes generally resolve postpartum. Pelvic organ dysfunction can occur after delivery, in the presence or absence of perineal injury, with associated incontinence or dyspareunia. During menopause, pubic hair may thin and gray, subcutaneous fat may atrophy, and the modified and true mucous membranes may become pale and exhibit decreased secretions. Lactobacilli may decrease in number leading to an elevated vaginal pH.^{20,21}

In children, the length of the vulva is disproportionately composed of the clitoris. Before adrenarche, there may be no pubic hair and the labia minora are smaller. Labial adhesions are more common in prepubertal girls and may be reversible with treatment, as opposed to in adults, where scarring is permanent.^{19,22}

Benign vulvar findings that often prompt dermatology consultation include vulvar papillae (often

mistaken for condyloma acuminata), ectopic sebaceous glands (ie, Fordyce spots), and angiokeratomas.

DIAGNOSTIC TESTING

Key points

- Point-of-care diagnostic testing plays an important role in the evaluation and treatment of vulvar dermatoses
- Knowledge of the basic normal saline wet mount and potassium hydroxide preparation is helpful for point-of-care diagnosis
- Vulvar biopsy specimens should be considered and obtained in patients when abnormal signs exist on examination

Point-of-care microscopy, including normal saline wet mount and potassium hydroxide (KOH) preparation can assist with the diagnosis of patients who present with vulvovaginal pruritus and pain. Such testing should be considered in all women with vulvovaginal symptoms and should not be limited to those who present with “abnormal discharge.” The normal saline wet mount can be informative and provides information regarding vaginal epithelial cell maturity, the degree of inflammation, and the presence of normal lactobacilli. A KOH preparation can detect the presence of fungal elements in a cost-conscious manner. A drop of 0.9-M sodium chloride and 10-mM potassium hydroxide should be placed onto separate glass slides. Vaginal swab specimens should be obtained by inserting a cotton-tipped applicator into secretions of the proximal vagina until adequately moistened. A separate applicator should then be rubbed onto each prepared slide, followed by placement of a coverslip.

Normal saline wet mount evaluation of a fully estrogenized vagina will demonstrate predominantly mature vaginal squamous epithelial cells (vs immature squamous, or parabasal, cells), ≤ 1 white blood cell per epithelial cell ($\leq 1:1$ ratio) on high-power field, and abundant lactobacilli (Fig 4). When lactobacilli are present, the vaginal fluid has a pH of < 5 . Immature, parabasal cells may be observed in several settings, namely estrogen insufficiency (eg, atrophic vagina), inflammatory vaginitis (eg, desquamative inflammatory vaginitis), and erosive conditions (eg, lichen planus, pemphigus vulgaris) or foreign body reaction.

The KOH preparation then should be examined for fungal elements, which may manifest as pseudohyphae (eg, *Candida albicans*; Fig 5) or budding yeast. The budding forms of non-*C. albicans* yeast species may be better visualized on normal saline wet mount. Given the low sensitivity and specificity of KOH

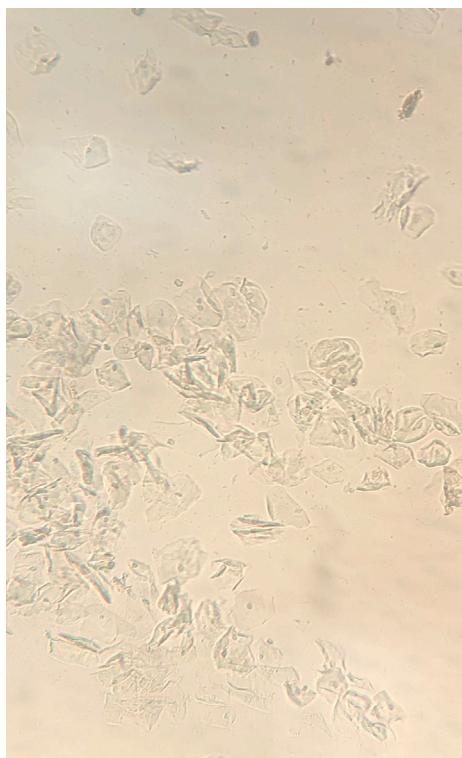


Fig 4. Normal wet mount.

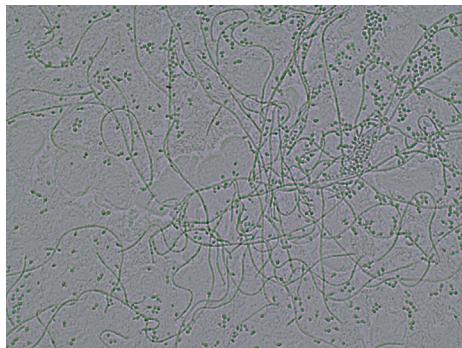


Fig 5. *Candida albicans*.

preparation microscopy, a vaginal swab for fungal culture may increase the diagnostic yield.

Vulvar biopsy specimens should be considered and obtained in patients when abnormal signs exist on examination to help narrow the differential diagnosis and when there is concern for malignancy. Features on examination that may be concerning for malignancy include localized hyperkeratosis, persistent ulceration, localized nodularity/induration, and a failure to respond to standard treatment. Patients often report itching or pain at sites without primary lesions; obtaining a biopsy specimen of normal-appearing skin is not helpful and should be avoided.

Sampling genital skin may be done with either the punch, shave, or snip techniques. Snip biopsy is a

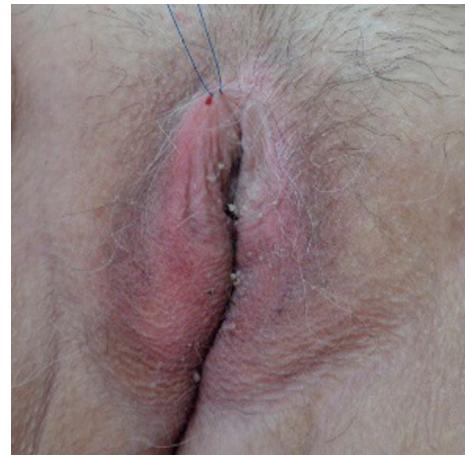


Fig 6. Biopsy position.

useful technique that may be preferred given ease of this procedure on mucous membranes. A suture is placed to provide tension on skin/mucosa (Fig 6) and tissue is then sampled using gradle or iris scissors. Although any suture can be used for this biopsy, the authors prefer polypropylene suture given the low coefficient of friction and ease of seeing the color against skin and hair in this area. Aluminum chloride can be used to achieve hemostasis with subsequent application of white petrolatum.

When malignancy is suspected, obtaining a punch biopsy specimen is preferred to ensure adequate depth of the sample; hemostasis can be achieved using gel foam or absorbable suture.

PATIENT EDUCATION AND VULVAR CARE INSTRUCTIONS

Key points

- Patients should be educated on sites of disease and strategies for topical medication application to the vulva with demonstration during the visit
- Written instructions, clinical photographs, and education handouts can improve patient understanding and adherence to treatment

Patient education is crucial. Studies show that patients prefer both written and verbal instructions from their physicians.^{23,24} Detailed instructions are vital because most women are not familiar with visually inspecting or applying topical therapies to their vulvas. Demonstrating the quantity of and locations for medication use is imperative for treatment success and is more memorable than verbal instruction alone. Such demonstration can easily be accomplished during the physical examination using a small, lentil-sized amount of petrolatum. A pea-sized amount of ointment will cover an area larger



Fig 7. Topical corticosteroid-induced purpura and atrophy.

Table I. Guidelines for vulvar care

Wash only once a day, with clear water. Avoid soap when irritated. Pat dry, do not use a hairdryer
Use tampons if tolerated rather than pads, because local wet conditions plus friction from sanitary pad use can cause irritant contact dermatitis in certain patients ²⁵
Douching is not needed and does not promote vaginal health; if necessary for psychological reasons, avoid commercial douches with additives, and use a homemade recipe of a half teaspoon of vinegar per cup of water
Moisturizers such as white petrolatum are useful to apply before urination if patients have dysuria or healing vulvar ulcers
Avoid Spandex and wear loose-fitting clothing if vulvar irritation is present

than two palms. Taking the additional time to demonstrate medication quantity and areas for application will help to avoid side effects such as corticosteroid-induced atrophy (Fig 7).

Recall, retention, and visit satisfaction are improved when verbal instruction is supplemented with written patient handouts.²³ Handouts on common vulvar conditions can educate patients about the conditions, disease course/progression, as well as treatments and potential adverse effects; such handouts can be found on <https://www.issvd.org> and <https://www.naspag.org/>. Daily care practices vary widely among patients, and written patient guidelines outlining optimal vulvar care are beneficial (Table I).

Providing the patient with labeled clinical photographs for at-home use can be a helpful

treatment reference. When caring for pediatric patients, it is preferable to provide the parents with a schematic diagram (Supplement 2; available at <https://doi.org/10.17632/t89rwxnrpt.1>) that highlights areas for medication use.

A careful and thoughtful history and examination combined with verbal and written patient education provides management of symptoms and alleviation of anxiety in women with chronic vulvovaginal symptoms, even when the underlying causes are not obvious or curable.

REFERENCES

1. Venkatesan A, Farsani T, O'Sullivan P, Berger T. Identifying competencies in vulvar disorder management for medical students and residents: a survey of US vulvar disorder experts. *J Low Genit Tract Dis.* 2012;16:398-402.
2. Rowen TS, Gaither TW, Awad MA, Osterberg EC, Shindel AW, Breyer BN. Pubic hair grooming prevalence and motivation among women in the United States. *JAMA Dermatol.* 2016;152:1106-1113.
3. Grimley DM, Annang L, Foushee HR, Bruce FC, Kendrick JS. Vaginal douches and other feminine hygiene products: women's practices and perceptions of product safety. *Matern Child Health J.* 2006;10:303-310.
4. Ness R, Hillier S, Richter H, et al. Why women douche and why they may or may not stop. *Sex Transm Dis.* 2003;30:71-74.
5. Luong ML, Libman M, Dahhou M, et al. Vaginal douching, bacterial vaginosis, and spontaneous preterm birth. *J Obstet Gynaecol Can.* 2010;32:313-320.
6. Martino JL, Vermund SH. Vaginal douching: evidence for risks or benefits to women's health. *Epidemiol Rev.* 2002;24:109-124.
7. Alcaide ML, Rodriguez VJ, Brown MR, et al. High levels of inflammatory cytokines in the reproductive tract of women with BV and engaging in intravaginal douching: a cross-sectional study of participants in the Women Interagency HIV Study. *AIDS Res Hum Retroviruses.* 2017;33:309-317.
8. Savin J. What it's really like to get a "vagina facial." Cosmopolitan. September 1, 2015. Available at: <https://www.cosmopolitan.com/uk/beauty-hair/beauty-trends/a38229/vagina-facial-review/>. Accessed December 28, 2019.
9. Cheng H, Oakley A, Conaglen JV, Conaglen HM. Quality of life and sexual distress in women with erosive vulvovaginal lichen planus. *J Low Genit Tract Dis.* 2017;21:145-149.
10. Lawton S, Littlewood S. Vulval skin conditions: disease activity and quality of life. *J Low Genit Tract Dis.* 2013;17(2):117-124.
11. Rowland-Morin PA, Carroll JG. Verbal communication skills and patient satisfaction. A study of doctor-patient interviews. *Eval Health Prof.* 1990;13:168-185.
12. Kenny MC, Wurtelle SK. Children's abilities to recognize a "good" person as a potential perpetrator of childhood sexual abuse. *Child Abuse Negl.* 2010;34:490-495.
13. Habeshian K, Fowler K, Gomez-Lobo V, Marathe K. Guidelines for pediatric anogenital examination: insights from our vulvar dermatology clinic. *Pediatr Dermatol.* 2018;35:693-695.
14. Dong XQ. Elder abuse: systematic review and implications for practice. *J Am Geriatr Soc.* 2015;63:1214-1238.
15. Selim MA, Hoang MP. A histologic review of vulvar inflammatory dermatoses and intraepithelial neoplasm. *Dermatol Clin.* 2010;28:649-667.
16. Lykkebo AW, Drue HC, Lam JUH, Guldberg R. The size of labia minora and perception of genital appearance. *J Low Genit Tract Dis.* 2017;21:198-203.

17. Edwards L. Genital anatomy. In: Edwards L. *Genital Dermatology Atlas*, 2 ed. Philadelphia, PA: Lippincott, Williams and Wilkins; 2011:1-10.
18. Haefner HK. Vulvar anatomy. In: Black M, Ambros-Rudolph C, Edwards L, Lynch P, eds. *Obstetric and Gynecologic Dermatology*. London: Mosby Elsevier; 2008:123-132.
19. Wilkinson EJ, Stone IK. *Atlas of Vulvar Disease*. 3rd ed. Philadelphia, PA: Lippincott, Williams and Wilkins; 2012.
20. Braude P, Hamilton-Fairley D. Hormonal Changes during puberty, pregnancy, and the menopause. In: Black M, Ambros-Rudolph C, Edwards L, Lynch P, eds. *Obstetric and Gynecologic Dermatology*. London: Mosby Elsevier; 2008:3-12.
21. Cohen Sacher B. The normal vulva, vulvar examination, and evaluation tools. *Clin Obstet Gynecol*. 2015;58:442-452.
22. Edwards L. Pediatric genital disease. In: Edwards L, ed. *Genital Dermatology Atlas*. 2 ed. Philadelphia, PA: Lippincott, Williams and Wilkins; 2011:245-267.
23. Hong J, Nguyen TV, Prose NS. Compassionate care: enhancing physician–patient communication and education in dermatology. *J Am Acad Dermatol*. 2013;68:364.e1-364.e10.
24. Uhlenhake EE, Kurkowski D, Feldman SR. Conversations on psoriasis—what patients want and what physicians can provide: a qualitative look at patient and physician expectations. *J Dermatol Treat*. 2010;21:6-12.
25. Wakashin K. Sanitary napkin contact dermatitis of the vulva: location-dependent differences in skin surface conditions may play a role in negative patch test results. *J Dermatol*. 2007;34:834-837.



Vulvar diseases

Conditions in adults and children

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Learning objectives

After completing this learning activity, participants should be able to recognize common vulvar conditions in children and adults; identify treatment strategies for common vulvar diseases; and compare and contrast common cutaneous conditions in genital skin compared to presentations on other parts of the body.

Disclosures

Editors

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Planners

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The most problematic vulvovaginal conditions are familiar to dermatologists but may exhibit distinct clinical features or medication management because of the anatomic location. The second article in this continuing medical education series focuses on management pearls for treating vulvar diseases. We highlight key conditions, such as lichen sclerosus, erosive lichen planus, and vulvodynia. In addition, we review conditions that dermatologists may be less familiar with, such as plasma cell vulvitis, desquamative inflammatory vaginitis, vulvar aphthae, and low estrogen states. Nearly 1 in 6 women experience undiagnosed and untreated vulvovaginal discomfort at some point in their lives. Physicians who treat vulvar disorders will improve the quality of life of countless women. (J Am Acad Dermatol 2020;82:1287-98.)

Key words: genital dermatology; lichen planus; lichen sclerosus; vulvar dermatology; vulvology.

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Abbreviations used:

DIV:	desquamative inflammatory vulvitis
EVLP:	eruptive vulvovaginal lichen planus
GSM:	genitourinary syndrome of menopause
LP:	lichen planus
LS:	lichen sclerosus
SCC:	squamous cell carcinoma

Vulvar conditions are an underserved part of medical care. Dermatologists can positively impact women's lives through a willingness to evaluate and treat patients with anogenital dermatoses. Common dermatologic conditions may exhibit different clinical features on the genitalia when compared with nongenital skin (Table I). This review provides the general dermatologist with the tools to evaluate and treat some of the more common and challenging conditions that involve the vulva.

LICHEN SCLEROSUS

Key points

- First-line therapy is a daily ultrapotent topical corticosteroid until the texture normalizes
- Maintenance therapy with a midpotency topical corticosteroid, such as daily triamcinolone ointment 0.1%, or an ultrapotent agent, such as clobetasol ointment 0.05%, 3 times weekly decreases the risk of squamous cell carcinoma
- Treatment should be ongoing rather than according to symptoms

Lichen sclerosus (LS) is a chronic inflammatory condition that preferentially affects the anogenital region. Autoimmune and genetic factors are accepted etiologic components in vulvar LS because of the clustering of associated autoimmune diseases, increased presence of autoantibodies, and presence of LS in about 10% of family members.^{1,2}

LS most commonly affects prepubertal and postmenopausal women (Fig 4). Hypopigmented or depigmented patches with cigarette paper texture, petechiae, fissures, and erosions are hallmark features of active disease (Fig 5). Agglutination of the labia minora, phimosis of the clitoral hood, and hypertrophic plaques are evidence of more advanced disease (Fig 6). Up to 5% of women with LS develop vulvar squamous cell carcinoma (SCC), but treatment substantially decreases this risk and prevents scarring.^{3,4} Vaginal LS has rarely been reported; its association with vaginal SCC is unclear.³

Treatment for LS with ultrapotent topical corticosteroids is always beneficial, but a small number of

Table I. Frequent pearls and pitfalls of treating patients with vulvar dermatoses

Atopic dermatitis/lichen simplex chronicus

Pearl

Class I steroids such as clobetasol or halobetasol ointment daily, reevaluate monthly
Recommending medication use until the skin is normal, then tapering frequency or potency
Nighttime sedation

Pitfall

Using low-potency corticosteroids when the condition is active/severe
Stopping treatment too soon
Overwashing and unnecessary topicals

Psoriasis

Pearl

Mid- to high-potency steroids during the week, with breaks on weekends
Calcineurin inhibitors as maintenance when skin is clear

Pitfall

Confusion with candidiasis (Fig 1)
Using low-potency corticosteroids
Stopping treatment too soon

Contact dermatitis

Pearl

Asking about ALL topicals applied to the skin
Referring for or patch testing when patient is not improving

Pitfall

Forgetting to ask about washing frequency and agents (Fig 2)
Forgetting to address incontinence (Fig 3)



Fig 1. Inverse psoriasis mimicking candidiasis. Note the well-defined dull red plaques. Patients are often treated multiple times for fungal infections before the diagnosis is made.

patients may not respond adequately to first-line therapy. Most therapeutic failures are related to inadequate duration of treatment or intermittent symptomatic treatment only (Table II). Emerging potential therapies include fractional CO₂ laser



Fig 2. Irritant and allergic contact dermatitis to benzocaine. Note the deep, well-defined ulcerations. This patient was using benzocaine to treat vulvar psoriasis.



Fig 3. Irritant contact dermatitis from incontinence. Poorly defined erythematous plaques should prompt questions about incontinence.

and platelet-rich plasma; however, the current evidence does not indicate the prevention of SCC.⁵⁻⁷ A randomized, double-blind, placebo-controlled trial of autologous platelet-rich plasma intradermal injections for the treatment of vulvar LS showed no significant difference between groups. Furthermore, treated patients demonstrate increased postprocedure inflammation on histology. The authors suggest that these negative results indicate that vulvar LS is not adequately treated with autologous platelet-rich plasma.⁸



Fig 4. Pediatric lichen sclerosus. Note the figure-of-eight depigmentation with "cigarette paper" texture, a larger clitoral hood, the lack of hair, and a smaller labia minora compared with the adult vulva.



Fig 5. Lichen sclerosus. In addition to the depigmented, shiny plaques, note the subtle linear fissures in the anterior vulva skin folds. These can be painful.

EROSIVE LICHEN PLANUS

Key points

- Treat erosive vulvovaginal lichen planus with ultrapotent daily topical corticosteroids



Fig 6. Hyperkeratotic lichen sclerosus. This patient has thick white plaques studded with angulated erosions anteriorly. Note thickening of the perineum, a common site for refractory disease.

- **Women with erosive vaginal lichen planus require aggressive management, including compounded vaginal corticosteroid suppositories and vaginal dilators to prevent stenosis**
- **Chronic therapy is required for optimal control and should be individualized**

Erosive vulvovaginal lichen planus (EVVLP) is a common, painful, erosive condition found most often in postmenopausal women and is usually accompanied by oral disease. In a review of 72 patients with EVVLP, >92% of patients presented with burning or pain; 50% were found to have pruritus.⁹ Esophageal involvement with stenosis and pain has been recognized with increasing frequency; less often, eye and ear involvement with scarring can occur. LP of dry, keratinized skin is uncommonly (<25%) associated with EVVLP. Classic EVVLP demonstrates erosions, sometimes with reticulated white borders (Fig 7). However, erosions are usually nonspecific and indistinguishable morphologically from the much less common mucous membrane pemphigoid and pemphigus vulgaris. An oral examination is more likely than the vulva to show the diagnostic white striae of LP to help secure the diagnosis. Atrophic, erythematous patches of LP can be confused with differentiated vulvar intraepithelial neoplasia. Advanced disease produces scarring with loss of the labia minora, narrowing or

Table II. Lichen sclerosus management

Primary therapy

Superpotent corticosteroid (clobetasol 0.05% ointment, halobetasol 0.05% ointment, betamethasone dipropionate in augmented vehicle ointment) twice daily until the texture normalizes, with follow up every 6–8 weeks; usually requiring about 4 months

Intraleisional triamcinolone acetonide 10 mg/cc into any thick or stubborn areas monthly to induce healing
Tacrolimus 0.1% ointment or pimecrolimus cream added if a corticosteroid provides insufficient improvement. Use is limited by burning with application, FDA warning for SCC, and cost, but the decrease in SCC in well-managed LS almost certainly is outweighed by the theoretical risk of using tacrolimus or pimecrolimus

Maintenance: data shows ongoing maintenance decreases the risk of SCC. Do not treat according to symptoms

Superpotent corticosteroid once, 3 times a week, or Midpotency corticosteroid, such as triamcinolone 0.1% ointment daily, or

Tacrolimus 0.1% ointment or pimecrolimus cream twice daily

Nonspecific measures

Patient education on the chronic nature of LS, as well as on vulvar care and minimizing washing and irritants

Estrogen replacement for postmenopausal women with introital symptoms or introital LS (see section on atrophic vagina)

Nighttime sedation for women who are itchy and scratching at night to prevent further damage to the vulva, until itching is controlled

For recalcitrant disease, consider (all therapies unstudied except for case reports and small trials)

Evaluate the anogenital skin for residual disease, atrophic vagina, and consider vulvodynia triggered by the LS

Fractional CO₂ laser

Platelet rich plasma: no evidence of benefit beyond anecdotal

Level of evidence IA.⁵⁶ FDA, U.S. Food and Drug Administration; LS, lichen sclerosus; SCC, squamous cell carcinoma.

even closure of the introitus, and burying of the clitoris (Fig 8). Such scarring may also result from LS, pemphigus vulgaris, and mucous membrane pemphigoid. Patients suspected of having EVVLP who do not exhibit pathognomonic white reticulation should have a biopsy specimen obtained for histologic confirmation and exclusion of autoimmune bullous disorders. Clinicopathologic correlation is essential because biopsy specimens rarely yield a definitive diagnosis of LP but rather a histologic description of lichenoid dermatitis.

Unlike LS, vaginal involvement is common in EVVLP and manifests as erythematous patches or



Fig 7. Erosive vulvovaginal lichen planus. Note the well-demarcated, symmetrical erosions. When biopsy specimens are obtained, take the sample from the junction of the erosion to capture the transition between eroded and epithelialized skin.



Fig 8. Obliteration of normal architecture from erosive vulvovaginal lichen planus.

erosions. The resulting seropurulent vaginal discharge may cause an irritant contact mucositis at the introitus. Normal saline wet mount of vaginal fluid shows sheets of white blood cells and round immature squamous cells shed from the base of

Table III. Lichen planus management

Vulva

Superpotent corticosteroid (clobetasol 0.05% ointment, etc) twice daily until erosions and white areas heal, and symptoms abate, with follow-up every 6-8 weeks. Then taper to least frequent dosing, or lowest potency corticosteroid that maintains control

Intraleisional triamcinolone acetonide 10 mg/mL into any thick or stubborn erosions monthly to induce healing

Occasionally, for severe disease, prednisone 40-60 mg daily initially to gain control of the disease

Tacrolimus 0.1% ointment or pimecrolimus cream added if a corticosteroid provides insufficient improvement. Use is limited by burning with application, FDA warning for SCC, and cost, but the decrease in SCC in well-managed LP almost certainly is outweighed by the theoretical risk of using tacrolimus or pimecrolimus

Vagina (if erosions are present or purulent vaginal secretions while estrogenized)

Hydrocortisone acetate 200 mg or 300 mg compounded vaginal suppositories nightly, taper to least frequent dosing that maintains control

Consider tacrolimus 0.1% ointment inserted or compounded into suppository if LP is recalcitrant

Estrogen if postmenopausal (see section on atrophic vagina)

Weekly fluconazole 150-200 mg to prevent Candidiasis while on vaginal corticosteroid or advise patient of higher risk of yeast

Insertion of largest comfortable size dilator 3 times weekly to ensure patency of the vagina and serve as early warning for narrowing, unless sexually active

For recalcitrant disease

Ensure estrogen replacement, no symptomatic side effects to corticosteroids, and that skin changes of LP persist, otherwise consider vulvodynia triggered by LP

Systemic therapies often used for erosive mucosal LP include methotrexate ≤ 25 mg weekly, hydroxychloroquine 200 mg twice daily, mycophenolate mofetil ≤ 1 g 3 times daily, cyclosporine, azathioprine, cyclophosphamide, and tumor necrosis factor blockers. None regularly produce improvement, all are sometimes useful for individual women, but in all cases, treatment for several months may be required to see the benefit

Level of evidence II^b.¹¹ FDA, U.S. Food and Drug Administration; LP, lichen planus; SCC, squamous cell carcinoma.

erosions. Vaginal disease often results in vaginal narrowing, foreshortening, or complete obliteration.

The management of EVLP is successful in most women. Patients with severe EVLP or multiple sites of mucosal erosive LP involvement may present a greater challenge (Table III).

An ultrapotent topical corticosteroid ointment applied twice daily produces healing of erosions and reduces pain in most women.¹⁰ Recalcitrant erosions can be treated with intralesional corticosteroid injection using triamcinolone acetonide 10 mg/mL. EVVLP sometimes requires systemic treatment for disease control, and ≤40% of patients may require a combination of topical and systemic therapy.^{11,12} For severe disease, some dermatologists use prednisone or intramuscular triamcinolone for rapid symptom control before switching to other corticosteroid-sparing agents for long-term maintenance. Systemic medications used for EVVLP include azathioprine, cyclosporine, cyclophosphamide, hydroxychloroquine, methotrexate, mycophenolate mofetil, tacrolimus, and tumor necrosis factor- α blockers. Other than systemic corticosteroids, none show consistently predictable benefit, but they may improve symptoms. Use is based on experience and open-label series.

If LP involves the vaginal as well as vulvar mucosa, dermatologists should use intravaginal corticosteroids. Hydrocortisone acetate 25 mg rectal suppositories used in the vagina are usually of insufficient potency for benefit; therefore, compounded suppositories, such as hydrocortisone acetate 200 mg or 300 mg or tacrolimus ointment 0.1% can be used vaginally at bedtime. The frequency of any corticosteroid preparation should be reduced with improvement to minimize systemic absorption and resulting complications. Because intravaginal corticosteroid use predisposes to the development of vulvovaginal candidiasis, the use of oral fluconazole 200 mg weekly or clotrimazole vaginal cream twice weekly is encouraged for prophylaxis.

In order to maintain patency of the vagina, women with EVVLP should be advised to have vaginal intercourse or use a vaginal dilator with regular frequency (several times per week) once their pain is adequately improved. This can also help to identify early narrowing of the vagina before dysfunction occurs. Graduated dilators can be obtained online. Rarely, vaginal introital narrowing can result in acute urinary retention that requires surgical correction.

Patients with poorly controlled EVVLP are at risk for vulvar SCC, with an estimated malignant transformation rate of 2.3%.¹² A retrospective review of 38 cases of LP-associated vulvar SCC demonstrated that patients developed tumors on the vulvar vestibule (between the clitoris and the urethra), clitoral hood, labium minus, and in the interlabial sulcus.¹³

We recommend close follow-up every 6 months at minimum to be individualized based on disease severity and treatment strategy.



Fig 9. Plasma cell vulvitis. This patient had burning with urination and the examination revealed a striking red/orange patch. This will be missed unless the labia minora are separated during examination.

PLASMA CELL VULVITIS

Key points

- **Plasma cell vulvitis (Zoon vulvitis) is an uncommon but distinctive dermatosis of unknown cause that must be distinguished from EVVLP and differentiated vulvar intraepithelial neoplasia**
- **The management of plasma cell vulvitis consists primarily of chronic ultrapotent or intralesional corticosteroids and moderately improves but rarely resolves**

Plasma cell vulvitis, also called Zoon vulvitis, is a distinctive, idiopathic dermatosis. Plasma cell mucositis can also affect the oral cavity and the glans penis. Plasma cell vulvitis does not affect children.

Plasma cell vulvitis distinctively exhibits well-demarcated, red/orange patches involving the periurethral mucosa and vestibule (Fig 9), often extending to the medial labia minora. Burning and irritation are common. When a biopsy specimen is obtained, the histologic examination classically shows an epithelium with flattened “lozenge-shaped” epithelial cells and an inflammatory infiltrate containing ≥20% plasma cells. Treatment should be initiated with ultrapotent topical corticosteroid ointments, such as clobetasol or halobetasol, twice daily, with intralesional triamcinolone acetonide 10 mg/mL if there is insufficient improvement. Tacrolimus ointment 0.1%, pimecrolimus cream 1%, and ablative CO₂ laser have also been used.^{14,15}

DESQUAMATIVE INFLAMMATORY VAGINITIS

Key points

- **Desquamative inflammatory vaginitis is a unique idiopathic inflammatory mucositis that occurs only in the vagina**



Fig 10. Desquamative inflammatory vaginitis.

- The diagnosis is made clinically after excluding infection, specific erosive skin disease, and estrogen deficiency
- Management involves intravaginal corticosteroids or clindamycin cream requiring recurrent or chronic dosing

Desquamative inflammatory vaginitis (DIV) is a unique vaginal mucositis that presents with purulent copious discharge as well as introital itching, irritation, and dyspareunia. Examination reveals vaginal and introital erythema, and, often, erythema and edema of the labia minora resulting from contact with irritating vaginal fluid (Fig 10). DIV does not exhibit erosions of the vagina, vulva, or oral cavity. Normal saline wet mount shows a marked increase in white blood cells and an increase in the proportion of round, parabasal squamous epithelial cells (Fig 11). Lactobacilli are absent, and the vaginal fluid pH is therefore >5 . Molecular testing should be performed for gonorrhea, chlamydia, and trichomoniasis to rule out infectious causes of purulent cervicitis. As estrogen deficiency can present comparably, postmenopausal women not already on estrogen replacement therapy should be given a diagnostic trial of intravaginal estrogen with reevaluation 1 month later.

DIV treatment consists of vaginal hydrocortisone suppositories or clindamycin vaginal cream, 1 applicator full daily at bedtime with follow-up in one month.¹⁶ The dosing frequency and amount of medication can be tapered to the least frequent and smallest amount needed to maintain comfort. Many

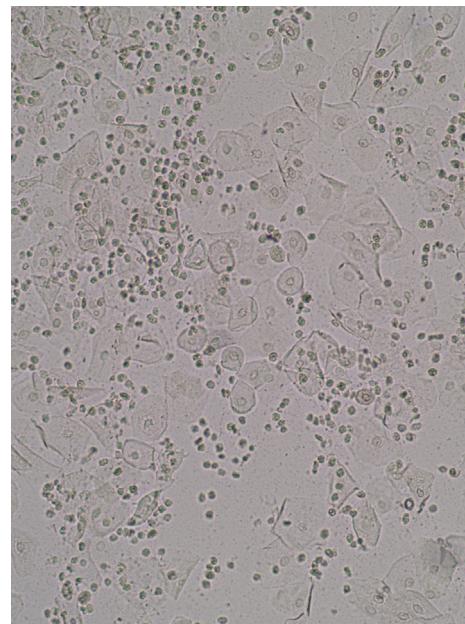


Fig 11. Desquamative inflammatory vaginitis, wet mount.

providers use adjunctive weekly fluconazole to prevent secondary vulvovaginal candidiasis.

VULVAR CROHN'S DISEASE

Key points

- Metastatic Crohn's disease of the vulva characteristically presents with vulvar edema or distinctive knife-cut ulcerations
- The course of metastatic cutaneous Crohn's disease may diverge from that of intestinal disease
- Fecal calprotectin level can be useful in making the diagnosis

Anogenital Crohn's disease requires familiarity with its distinctive ulcer morphology and a high index of suspicion when confronted with edema and draining nodules. The cutaneous presentation is protean: classic contiguous Crohn's disease presents with perianal fistulae, while nonpitting edema of the labia majora (Fig 12), knife-cut ulcerations of skin creases (Fig 13), violaceous nodules, and firm perianal tags are characteristic findings seen in metastatic cutaneous disease.¹⁷⁻²⁰ Chronic vulvar edema may lead to lymphangiectasias, firm skin tags, or verrucoid nodules. Genital ulcerations were the most common vulvar finding in a large series of adult patients with Crohn's disease.²¹ In children, asymptomatic labial edema or induration is the most common presentation of metastatic Crohn's disease.²²⁻²⁵ When additional clinical information is needed, histopathology demonstrates granulomatous inflammation, differentiating it from other forms



Fig 12. Metastatic Crohn's disease, vulvar edema.

of ulcers (herpes simplex virus, aphthae, or syphilis). Fecal calprotectin levels demonstrate 87% specificity and 99% sensitivity for inflammatory bowel disease and can be used as a screening test for intestinal inflammation.²⁶⁻²⁸ We recommend referral to a gastroenterology specialist when vulvar Crohn's disease is suspected; fecal calprotectin should be obtained while awaiting referral because a level $>250 \mu\text{g}/\text{mg}$ predicts a high likelihood of inflammatory bowel disease.²⁶

Treatment of vulvar Crohn's disease, in both adults and children, focuses on managing the underlying Crohn's disease, regardless of whether intestinal involvement is present.

VULVAR APHTHAE

Key points

- The diagnosis of aphthous ulcers (Lipschutz ulcers, non-sexually acquired genital ulcerations) should be considered in the appropriate clinical context after exclusion of infectious etiologies
- Herpes simplex virus infection in an immunosuppressed person can be indistinguishable from an aphthous ulcer
- Most patients with oral and genital aphthae do not meet diagnostic criteria for Behçet disease because this condition requires objective documentation of multisystem disease including the eye, gut, vessels, joints, or central nervous system



Fig 13. Metastatic Crohn's disease, knife-cut ulceration.

- The treatment of aphthous ulcers includes oral and topical corticosteroids and acute pain control, as well as suppression of recurrent outbreaks

Vulvar ulcers often are acutely painful. The differential diagnosis is vast, although the list of likely possibilities in Western countries is rather limited. The morphologic distinction between erosions and ulcers is critical when formulating a differential diagnosis. Erosions result from loss of the epithelium only and classically result from herpes simplex virus infection and noninfectious erosive mucosal diseases, such as EVVLP. Ulcers require deeper, more extensive tissue loss, characterized by a white fibrin base on mucous membranes, and have a smaller differential diagnosis.

Aphthous ulcers are reactive mucosal ulcerations; this entity is a diagnosis of exclusion but does demonstrate a typical clinical presentation and morphology allowing for prompt presumptive diagnosis. Occurring most often in girls between 9 and 18 years of age, vulvar aphthae are typically well-demarcated and deep, sometimes necrotic or accompanied by marked edema (Fig 14). Most patients experience a prodrome of flu-like symptoms, sore throat, and fever. Aphthae have a predilection for the medial labia minora and vestibule (Fig 15),²⁹⁻³¹ but sometimes involve the labia majora.^{32,33} Aphthae result from a reactive, immunologic reaction and may be associated with an acute viral infection (ie, Epstein–Barr virus).^{29,34-37} In most cases, however, no infectious relationship is identified.



Fig 14. Aphthous ulcer causing profound edema of labia minus.

The isolated presence of genital and oral aphthae does not constitute a diagnosis of Behçet disease. Behçet disease requires objective documentation of multisystem inflammation, including the eye, joints, central nervous system, and gastrointestinal tract.³⁸⁻⁴⁰ A thorough review of systems is indicated as a screening mechanism for all patients with aphthae, and those with frequently recurrent ulcers or symptoms of additional organ involvement should be referred for ophthalmologic and rheumatologic evaluations.

Sexually acquired infections should be considered in all patients with vulvar ulcers, and decisions regarding sexually transmitted disease testing should be made after carefully considering the individual patient's sexual history, risk factors, and clinical presentation.^{31,41} The abrupt onset and morphology of aphthae often suggests the correct diagnosis. Initial treatment includes acute pain management with sitz baths, topical anesthetics, and nonopioid and narcotic analgesics. Ultrapotent topical corticosteroid ointments may be useful, but most cases require oral prednisone 40 mg to 60 mg per day until healing begins.⁴²⁻⁴⁴ Frequent, recurrent outbreaks deserve suppression. Oral doxycycline 100 mg daily may prevent recurrences and has a favorable side effect profile but is contraindicated in children <8 years of age.^{33,36,42,44,45} In addition, oral dapsone, colchicine, thalidomide, and tumor necrosis factor antagonists have demonstrated efficacy in the suppression of aphthae recurrences.⁴⁶⁻⁴⁸



Fig 15. Aphthous ulcer. Lesions are larger and often more painful than oral aphthae.

ATROPHIC VAGINA

Key points

- Atrophic vagina, now renamed the genitourinary syndrome of menopause, results from estrogen deficiency and can manifest as vaginal dryness, itching, burning, dyspareunia, and urinary symptoms
- Symptomatic women are readily treated with intravaginal or systemic estrogen

Atrophic vagina is an older term used to describe a vaginal low-estrogen state in adult women and has been renamed genitourinary syndrome of menopause (GSM) when women are symptomatic.⁴⁹ GSM occurs in postmenopausal women occurring either naturally or after surgical or chemically induced menopause and in breastfeeding women. Without adequate estrogen, the vaginal epithelium atrophies and exhibits decreased moisture and elasticity (Fig 16), which predisposes to the development of vaginal erosions with resulting purulent vaginal secretions and erythema. GSM symptoms include vaginal dryness, itching, irritation, burning, and dyspareunia as well as urinary urgency, increased frequency, dysuria, and recurrent urinary tract infections.

The diagnosis of atrophic vaginitis or atrophic vagina involves the detection of immature parabasal squamous epithelial cells with (vaginitis) or without increase in leukocytes on normal saline wet mount in the clinical setting of estrogen deficiency.



Fig 16. Genitourinary syndrome of menopause. Patient's vagina has a pale, white, firm dry texture. This responds rapidly to local estrogen replacement.

Table IV. Atrophic vagina management

Topical estrogens

Estradiol cream or conjugated equine estrogen cream, 0.5-4 g/day (at night) for 2 weeks, then 0.5-1 g 1 to 3 times/week

Estradiol vaginal tablets, 1 10- μ g tablet nightly for 2 weeks, then maintenance therapy 1-3 times/week

Estradiol ring 2 mg changed every 3 months after initial insertion

For patients who cannot or will not use estrogen

Moisturizers and lubricants for sexual activity

Hydrocortisone acetate 25 mg rectal suppositories per vagina

Oral ospemifene: estrogen agonist for clotting and endometrial cancer, antagonist for breast tissue

Vaginal prasterone (dihydroepiandrosterone) 6.5 mg/day (at night—but this is an estrogen precursor)

Fractional CO₂ laser

Levels of evidence: vaginal estrogen, IIA;⁵⁷ nonhormone, III.⁵⁸

The optimal management of GSM consists of estrogen replacement (Table IV). Whereas systemic estrogen replacement is beyond the scope of this continuing medical education article, the use of topical/intravaginal estrogens are within the purview of all dermatologists. Women are at increased risk for the development of vulvovaginal candidiasis with estrogen replacement. Although this may occur at any time, anecdotally this often occurs in the first few weeks of treatment; physicians should consider

Table V. Vulvodynia management

Nonspecific measures

Patient education, handouts

Avoidance of irritants and management of any abnormalities, such as estrogen deficiency or dermatoses

Lidocaine 2% jelly

Pelvic floor evaluation and physiotherapy

Medications for neuropathic pain

Topical agents

Lidocaine 5% ointment at introitus at night

Amitriptyline 2% compounded 3 times/day

Amitriptyline 2%/baclofen 2% compounded 3 times/day

Amitriptyline 2%/baclofen 2%/ketamine 2% compounded 3 times/day

Gabapentin 4% or 6% compounded 3 times/day

Diazepam vaginal suppositories or oral tablets per vagina 10 mg/day

Oral agents

Duloxetine, beginning at 20 mg titrating up to 60 mg/day

Venlafaxine sustained/extended release, beginning at 37.5 mg, titrating to 150 mg 4 times/day

Tricyclic medications beginning at 5-10 mg, titrating as high as 150 mg at bedtime

Gabapentin beginning at 100 mg, titrating as high as 1200 mg 3 times/day

Pregabalin beginning at 25 mg, titrating as high as 300 mg 2 times/day

Topiramate beginning at 25 mg bid and increasing up to 100 mg 2 times/day

Counseling

Cognitive behavioral therapy

Sex therapy

Other, less used therapies

Botulinum toxin, hypnotherapy, and acupuncture

Levels of evidence: pelvic floor physical therapy, IIA;^{52,58} cognitive behavioral therapy, IB;⁵⁹ neuromodulating agent, IV.⁵²

prescribing fluconazole 200 mg weekly. Lack of adherence to prescribed intravaginal estrogen therapy may result from patient concerns regarding potential cancer risk, logistical challenges related to vaginal insertion, difficulty in cleaning applicators, and confusion regarding topical vulvar versus intravaginal use. Potential benefits, risks, and tips for optimal use should be reviewed with the patient upon initiation of treatment.

VULVODYNIA

Key points

- **Vulvodynia is a common underrecognized syndrome of vulvar pain of ≥ 3 months' duration without a definable cause**
- **Obtaining routine biopsy specimens of focal areas of pain or redness are not informative and should be avoided**

• **Vulvodynia represents a central neuropathic pain/processing disorder accompanied by pelvic floor muscle dysfunction and comorbid anxiety/depression to varying degrees**

The prevalence of vulvodynia in the United States is estimated to be 8%.^{50,51} Its etiology is multifactorial, and research and clinical experience suggest that hypertonic pelvic floor muscle dysfunction is a strong factor.^{52,53} Neuropathic pain is recognized as well, with women responding to medications for neuropathy; central processing rather than peripheral neuropathy is postulated because these patients nearly always exhibit comorbidities or associated pain syndromes, including headaches, temporomandibular joint disorder, interstitial cystitis, fibromyalgia, pelvic pain, and irritable bowel syndrome, etc. Finally, many women with vulvodynia exhibit depression, anxiety, and psychosexual dysfunction in variable degrees.^{54,55}

A diagnosis of vulvodynia requires a history of chronic vulvar discomfort in the context of a normal vulvar examination and normal saline wet mount. Evidence of typical comorbidities of associated pain syndromes can also be helpful but is not required. In fact, one study shows that a diagnosis of vulvodynia can be made with fairly good reliability on the basis of a mailed questionnaire.⁵¹ Even when a skin disease or infection is identified, this does not eliminate vulvodynia as a secondary condition, because chronic inflammatory vulvovaginal diseases can serve as triggers for the development of vulvodynia.

In addition to a thorough vulvar examination, the evaluation of women with chronic vulvar pain generally includes mapping of the area of pain using a cotton-tipped applicator. Attention to pelvic floor dysfunction (through pelvic floor physical therapy), neuropathic pain (through topical, intravaginal, or systemic medications), and coincident anxiety/depression (through therapy or medical management) produce remarkable improvement in most patients (Table V). When pain is strictly limited to the vestibule/introitus (vestibulodynia), women refractory to other treatment modalities may be candidates for surgical excision. With careful attention to each of the factors that play a role in vulvodynia, most women experience marked improvement and find they can reclaim activities of daily living.

Nearly 1 in 6 women experience undiagnosed and untreated vulvovaginal discomfort during their lives. As an integral part of the treatment team, dermatologists who care for patients with vulvar disorders can improve the quality of life for countless women.

REFERENCES

1. Terlou A, Santegoets LAM, van der Meijden WI, et al. An autoimmune phenotype in vulvar lichen sclerosus and lichen planus: a Th1 response and high levels of microRNA-155. *J Invest Dermatol.* 2012;132:658-666.
2. Higgins CA, Cruickshank ME. A population-based case-control study of aetiological factors associated with vulval lichen sclerosus. *J Obstet Gynaecol.* 2012;32:271-275.
3. Halonen P, Jakobsson M, Heikinheimo O, Riska A, Gissler M, Pukkala E. Lichen sclerosus and risk of cancer. *Int J Cancer.* 2017;140:1998-2002.
4. Lee A, Bradford J, Fischer G. Long-term management of adult vulvar lichen sclerosus: a prospective cohort study of 507 women. *JAMA Dermatol.* 2015;151:1061-1067.
5. Goldstein AT, King M, Runels C, Gloth M, Pfau R. Intradermal injection of autologous platelet-rich plasma for the treatment of vulvar lichen sclerosus. *J Am Acad Dermatol.* 2017;76:158-160.
6. Behnia-Willison F, Pour NR, Mohamadi B, et al. Use of platelet-rich plasma for vulvovaginal autoimmune conditions like lichen sclerosus. *Plast Reconstr Surg Glob Open.* 2016;4: e1124.
7. Lee A, Lim A, Fischer G. Fractional carbon dioxide laser in recalcitrant vulval lichen sclerosus. *Australas J Dermatol.* 2016; 57:39-43.
8. Goldstein AT, Mitchell L, Govind V, Heller D. A randomized double-blind placebo-controlled trial of autologous platelet-rich plasma intradermal injections for the treatment of vulvar lichen sclerosus. *J Am Acad Dermatol.* 2019;80: 1788-1789.
9. Cheng H, Oakley A, Rowan D, Lamont D. Diagnostic criteria in 72 women with erosive vulvovaginal lichen planus. *Australas J Dermatol.* 2015;57:284-287.
10. Cooper SM, Wojnarowska F. Influence of treatment of erosive lichen planus of the vulva on its prognosis. *Arch Dermatol.* 2006;142:289-294.
11. Bradford J, Fischer G. Management of vulvovaginal lichen planus. *J Low Genit Tract Dis.* 2013;17:28-32.
12. Simpson RC, Littlewood SM, Cooper SM, et al. Real-life experience of managing vulval erosive lichen planus: a case-based review and U.K. multicentre case note audit. *Br J Dermatol.* 2012;167:85-91.
13. Regauer S, Reich O, Eberz B. Vulvar cancers in women with vulvar lichen planus: a clinicopathological study. *J Am Acad Dermatol.* 2014;71:698-707.
14. Virgili A, Borghi A, Minghetti S, Corazza M. Comparative study on topical immunomodulatory and anti-inflammatory treatments for plasma cell vulvitis: long-term efficacy and safety. *J Eur Acad Dermatol Venereol.* 2015;29:507-514.
15. Retamar RA, Kien MC, Chouela EN. Zoon's balanitis: presentation of 15 patients, five treated with a carbon dioxide laser. *Dermatol Surg.* 2003;42:305-307.
16. Sobel JD, Reichman O, Misra D, Yoo W. Prognosis and treatment of desquamative inflammatory vaginitis. *Obstet Gynecol.* 2011;117:850-855.
17. Lally MR, Orenstein SR, Cohen BA. Crohn's disease of the vulva in an 8-year-old girl. *Pediatr Dermatol.* 1988;5:103-106.
18. Kuloğlu Z, Kansu A, Demirçken F, et al. Crohn's disease of the vulva in a 10-year-old girl. *Turk J Pediatr.* 2008;50:197-199.
19. Duan D, Stevenson ML, Malter LB, Pomeranz MK. Cutaneous Crohn's disease of the vulva. *BMJ Case Rep.* 2014;2014.
20. Vaid RM, Cohen BA. Cutaneous Crohn's disease in the pediatric population. *Pediatr Dermatol.* 2010;27:279-281.
21. Yüksel I, Başar Ö, Ataseven H, et al. Mucocutaneous manifestations in inflammatory bowel disease. *Inflamm Bowel Dis.* 2009;15:546-550.

22. Keiler S, Tyson P, Tamburro J. Metastatic cutaneous crohn's disease in children: case report and review of the literature. *Pediatr Dermatol.* 2009;26:604-609.
23. Mun JH, Kim SH, Jung DS, Ko HC, Kim MB, Kwon KS. Unilateral, non-tender, vulvar swelling as the presenting sign of Crohn's disease: a case report and our suggestion for early diagnosis. *J Dermatol.* 2011;38:303-307.
24. Palamaras I, Pietropaolo N, Thomson P, Mann S, Robles W, Stevens HP. Metastatic Crohn's disease: a review. *J Eur Acad Dermatol Venereol.* 2008;22:1033-1043.
25. Boxhoorn L, Stoof TJ, De Meij T, et al. Clinical experience and diagnostic algorithm of vulval Crohn's disease. *Eur J Gastroenterol Hepatol.* 2017;29:838-843.
26. El-Matary W, Abej E, Deora V, Singh H, Bernstein CN. Impact of fecal calprotectin measurement on decision-making in children with inflammatory bowel disease. *Front Pediatr.* 2017;5:7.
27. Henderson P, Casey A, Lawrence SJ, et al. The diagnostic accuracy of fecal calprotectin during the investigation of suspected pediatric inflammatory bowel disease. *Pediatrics.* 2012;107:941-949.
28. Holtman GA, Leeuwen YL, Reitsma JB, Berger MY. Noninvasive tests for inflammatory bowel disease: a meta-analysis. *Pediatrics.* 2016;137:2015-2026.
29. Huppert JS, Gerber MA, Deitch HR, Mortensen JE, Staat MA, Adams Hillard PJ. Vulvar ulcers in young females: a manifestation of aphthosis. *J Pediatr Adolesc Gynecol.* 2006;19:195-204.
30. Bohl TG. Vulvar ulcers and erosions. *Clin Obstet Gynecol.* 2015; 58:492-502.
31. Vieira-Baptista P, Lima-Silva J, Beires J, Martinez-De-Oliveira J. Lipschütz ulcers: should we rethink this? An analysis of 33 cases. *Eur J Obstet Gynecol Reprod Biol.* 2016;198:149-152.
32. Lai K, Lambert E, Mercurio MG. Aphthous vulvar ulcers in adolescent girls: case report and review of the literature. *J Cutan Med Surg.* 2010;14:33-37.
33. Lehman JS, Bruce AJ, Wetter DA, Ferguson SB, Rogers RS. Reactive nonsexually related acute genital ulcers: review of cases evaluated at Mayo Clinic. *J Am Acad Dermatol.* 2010;63: 44-51.
34. Hudson LB, Perlman SE. Necrotizing genital ulcerations in a premenarcheal female with mononucleosis. *Obstet Gynecol.* 1998;92(4 pt 2):642-644.
35. Svedman C, Holst R, Johnsson A. Ulcus vulvae acutum, a rare diagnosis to keep in mind. *Eur J Obstet Gynecol Reprod Biol.* 2004;115:104-105.
36. Chanal J, Carlotti A, Laude H, Wallet-Faber N, Avril MF, Dupin N. Lipschütz genital ulceration associated with mumps. *Dermatology.* 2010;221:292-295.
37. Haidari G, MacMahon E, Tong CY, White JA. Genital ulcers: it is not always simplex.... *Int J STD AIDS.* 2015;26:72-73.
38. Sehgal VN, Pandhi D, Khurana A. Nonspecific genital ulcers. *Clin Dermatol.* 2014;32:259-274.
39. Lin CM, Wang CC, Lai CC, Fan HC, Huang WH, Cheng SN. Genital ulcers as an unusual sign of periodic fever, aphthous stomatitis, pharyngotonsillitis, cervical adenopathy syndrome: a novel symptom? *Pediatr Dermatol.* 2011;28:290-294.
40. Scattoni R, Verrotti A, Rinaldi VE, Paglino A, Carelli A, D'Alonzo R. Genital ulcer as a new clinical clue to PFAPA syndrome. *Clin Exp Dermatol.* 2015;40:286-288.
41. Brinca A, Canelas MM, Carvalho MJ, Vieira R, Figueiredo A. Lipschütz ulcer (ulcus vulvae acutum): a rare cause of genital lesion. *An Bras Dermatol.* 2012;87:622-624.
42. Delgado-García S, Palacios-Marqués A, Martínez-Escoriza JC, Martín-Bayón TA. Acute genital ulcers. *BMJ Case Rep.* 2014; 2014.
43. Rosman IS, Berk DR, Bayliss SJ, White AJ, Merritt DF. Acute genital ulcers in nonsexually active young girls: case series, review of the literature, and evaluation and management recommendations. *Pediatr Dermatol.* 2012;29:147-153.
44. Dixit S, Bradford J, Fischer G. Management of nonsexually acquired genital ulceration using oral and topical corticosteroids followed by doxycycline prophylaxis. *J Am Acad Dermatol.* 2013;68:797-802.
45. Letsinger JA, McCarty MA, Jorizzo JL. Complex aphthosis: a large case series with evaluation algorithm and therapeutic ladder from topicals to thalidomide. *J Am Acad Dermatol.* 2005;52:500-508.
46. Altenburg A, Abdel-Naser MB, Seeber H, Abdallah M, Zouboulis CC. Practical aspects of management of recurrent aphthous stomatitis. *J Eur Acad Dermatol Venereol.* 2007;21: 1019-1026.
47. Sand FL, Thomsen SF. Efficacy and safety of TNF- α inhibitors in refractory primary complex aphthosis: a patient series and overview of the literature. *J Dermatolog Treat.* 2013;24:444-446.
48. Belenguer-Guallar I, Jiménez-Soriano Y, Claramunt-Lozano A. Treatment of recurrent aphthous stomatitis. A literature review. *J Clin Exp Dent.* 2014;6:168-174.
49. Portman DJ, Gass MLS, Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause. *Menopause.* 2014;21:1063-1068.
50. Reed BD, Harlow SD, Sen A, et al. Prevalence and demographic characteristics of vulvodynia in a population-based sample. *Am J Obstet Gynecol.* 2012;206:170.e1-170.e9.
51. Harlow BL, Kunitz CG, Nguyen RHN, Rydell SA, Turner RM, MacLehose RF. Prevalence of symptoms consistent with a diagnosis of vulvodynia: population-based estimates from 2 geographic regions. *Am J Obstet Gynecol.* 2014;210:40.e1-40.e8.
52. Prendergast SA. Pelvic floor physical therapy for vulvodynia: a clinician's guide. *Obstet Gynecol Clin North Am.* 2017;44:509-522.
53. Gentilcore-Saulnier E, McLean L, Goldfinger C, Pukall CF, Chamberlain S. Pelvic floor muscle assessment outcomes in women with and without provoked vestibulodynia and the impact of a physical therapy program. *J Sex Med.* 2010;7:1003-1022.
54. Reed BD, Harlow SD, Sen A, Edwards RM, Chen D, Haefner HK. Relationship between vulvodynia and chronic comorbid pain conditions. *Obstet Gynecol.* 2012;120:145-151.
55. Chisari C, Chilcot J. The experience of pain severity and pain interference in vulvodynia patients: The role of cognitive-behavioural factors, psychological distress and fatigue. *J Psychosom Res.* 2017;93:83-89.
56. Funaro D, Lovett A, Leroux N, Powell J. A double-blind, randomized prospective study evaluating topical clobetasol propionate 0.05% versus topical tacrolimus 0.1% in patients with vulvar lichen sclerosus. *J Am Acad Dermatol.* 2014;71:84-91.
57. Bachmann G, Santen R. Treatment of genitourinary syndrome of menopause (vaginal atrophy). In: Barbieri RL, Falk SJ. UpToDate.
58. Bornstein J, Goldstein AT, Stockdale CK, et al. 2015 ISSVD, ISSWSH, and IPPS consensus terminology and classification of persistent vulvar pain and vulvodynia. *J Sex Med.* 2016;13:607-612.
59. Bergeron S, Khalifé S, Dupuis MJ, McDuff P. A randomized clinical trial comparing group cognitive-behavioral therapy and a topical steroid for women with dyspareunia. *J Consult Clin Psychol.* 2016;84:259-268.



Leprosy: Clinical aspects and diagnostic techniques

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Learning objective

After completing this learning activity, participants should be able to identify epidemiologic characteristics, disease course, and cutaneous manifestations of leprosy (Hansen's disease); recognize key clinical presentations/classifications of leprosy; and choose the most effective diagnostic modalities.

Disclosures

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Leprosy, also known as Hansen's disease, is a curable infectious disease that remains endemic in >140 countries around the world. Despite being declared "eliminated" as a global public health problem by the World Health Organization in the year 2000, approximately 200,000 new cases were reported worldwide in 2017. Widespread migration may bring leprosy to nonendemic areas, such as North America. In addition, there are areas in the United States where autochthonous (person-to-person) transmission of leprosy is being reported among Americans without a history of foreign exposure. In the first article in this continuing medical education series, we review leprosy epidemiology, transmission, classification, clinical features, and diagnostic challenges. (J Am Acad Dermatol 2020;83:1-14.)

Key words: diagnostic techniques; epidemiology; Hansen's disease; leprosy; leprosy classification; leprosy differential diagnosis; microbiology.

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Abbreviations used:

AFB:	acid-fast bacilli
BB:	mid-borderline
BI:	bacteriological index
BL:	borderline lepromatous
BT:	borderline tuberculoid
CTB:	cutaneous tuberculosis
LL:	polar lepromatous leprosy
MB:	multibacillary
NHDP:	National Hansen's Disease Program
PB:	paucibacillary
PCR:	polymerase chain reaction
SS:	skin smear
TB:	tuberculosis
TT:	polar tuberculoid
WHO:	World Health Organization



Fig 1. Nine-banded armadillo. Photograph courtesy of David Scollard, MD, PhD.

M lepromatosis has been identified in red squirrels in Scotland and British Isles.^{7,8} The mechanism of transmission is dependent on the infectivity of the host and the proximity, frequency, and duration of contact.² Upper respiratory secretions are the most common route of transmission, though skin contamination and vertical transmission have been rarely reported.^{2,9,10} The incubation period typically range from 3 to 5 years for tuberculoid leprosy and 9 to 12 years for lepromatous leprosy.¹ Most individuals exposed to the organisms do not develop clinical symptoms.

The existence of zoonotic infection with *M leprae*, and possibly with other members of the *M leprae* complex, appears to constitute a major challenge to the World Health Organization (WHO) paradigm for leprosy elimination, which is based entirely on the interruption of human- to-human transmission and does not address zoonotic transmission of any kind.¹¹

ETIOLOGY AND TRANSMISSION

Key points

- *Mycobacterium leprae* is an obligate intracellular organism that cannot be cultured in artificial media
- Upper respiratory secretions are the likely route of transmission
- Humans are primary carriers of *M leprae*, and 9-banded armadillos serve as known zoonotic reservoir

Leprosy is caused by acid-fast bacilli (AFB) of the *Mycobacterium leprae* complex, which includes *M leprae* and *Mycobacterium lepromatosis*. The rod-shaped bacterium *M leprae*, belonging to the Mycobacterium genus, was first described by the Norwegian physician Gerhard Armauer Hansen.¹ The etiologic agent is an acid-fast, slow-growing organism that shows predilection to replicate in macrophages, endothelial cells, and Schwann cells. The 1- to 8-μm bacilli may cluster together in infective tissues to form globi containing hundreds of bacilli.² *M leprae* and *M lepromatosis* are obligate intracellular organisms that replicate slowly, ideally growing in temperatures ranging from 27°C to 33°C, and cannot be cultured in artificial media.² *M lepromatosis* is a more recently described mycobacterial organism that also causes leprosy, with an indistinguishable clinical course. The DNA sequences of *M leprae* and *M lepromatosis* differ enough to distinguish them as separate species, but they share many biologic similarities.³

Humans are the primary carriers of infection with *M leprae*, apart from the Americas, where the armadillo (Fig 1) also serves as a zoonotic reservoir.⁹ Infection with *M lepromatosis* is extremely rare, but has been reported in Canada,⁴ Asia, several Mexican states,⁵ South America, and Central America.⁶

Risk factors

An individual's susceptibility to contracting leprosy is highly variable and multifactorial. These include: close contact with a recently diagnosed patient, especially patients with polar lepromatous leprosy (LL)/multibacillary leprosy (MB),^{12,13} exposure to armadillos,^{3,14} age between 5 to 15 years and >30 years at the time of exposure,¹³ immunosuppression and immunodeficiency,¹⁵⁻¹⁹ and genetic predisposition.²⁰ The risk factors involved in higher risks of developing physical disability includes male sex, LL, and the presence of leprosy immunologic reactions.²¹

EPIDEMIOLOGY

Key points

- The WHO declared leprosy eliminated in 2000; however, the global incidence of new cases remains relatively constant over the last 10 years
- India, Brazil, and Indonesia account for most new cases (80.2%)
- There were 178 new cases of leprosy diagnosed in 2015 in the United States

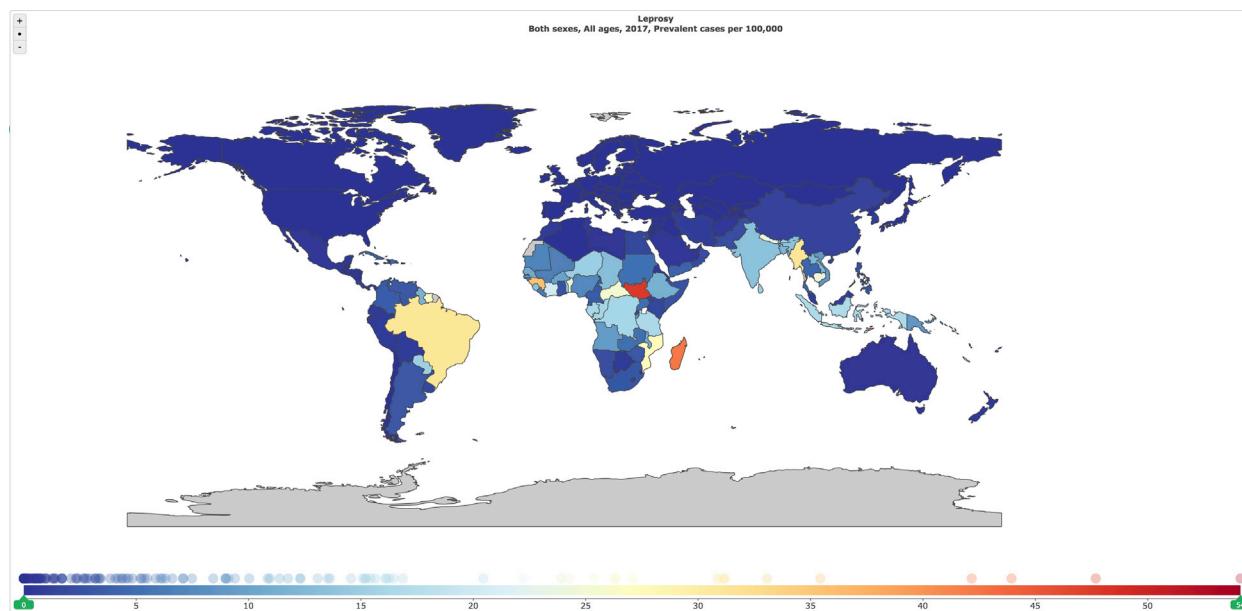


Fig 2. Leprosy prevalence map. Obtained from the Global Disease Burden website (<https://vizhub.healthdata.org/gbd-compare/>).

In the past 2 decades, nearly 16 million individuals globally have been treated with multidrug therapy. Leprosy was declared “eliminated” as an international public health problem in the year 2000 by the WHO because of a global reduction in the prevalence, defined as the number of patients on treatment at a particular point in time, to <1 case per 10,000 persons. Even though the global elimination target was reached, 12 countries including India and Brazil, took many more years to reach the national elimination target of <1 case per 10,000 persons.²²

In 2017, a total of 210,671 new cases of leprosy were reported from 150 countries, though because of underreporting in many endemic and underdeveloped regions of the world, this number may be underestimated (Fig 2).²² Active case-locating strategies and national programs rely on screening for grade 2 disabilities that rely on functional nerve impairment assessments including visible deformities.²² These grade 2 disabilities accounted for 6% of new cases globally and these clinical presentations may represent a delayed diagnosis of leprosy cases. The agenda of eliminating leprosy at the subnational level is still unfinished in many countries and therefore needs to be pursued for many more years.²³

In the United States, there were 185 new cases of leprosy diagnosed in 2018, and as in 2015, of these new cases, most occurred in 6 states: Arkansas, California, Florida,^{24,25} Hawaii, Louisiana, and New York.²⁶ Among the approximately 6500 patients with leprosy in the United States, about half currently require active medical management (Table I).²⁷

Table I. Global prevalence and incidence of leprosy in 2016

WHO region	Prevalence (% of global total)	Incidence (% of global total)
Africa	21,465 (12)	19,384 (9)
North and South America	26,365 (15)	27,356 (13)
Eastern Mediterranean	3102 (2)	2834 (1)
Southeast Asia	115,180 (67)	161,263 (75)
Western Pacific	5820 (3)	3914 (2)
Europe	16 (0)	32 (0)

WHO, World Health Organization.

Data from the Global leprosy update, 2016.²²

LEPROSY

Key points

- The Ridley-Jopling classification and the WHO classification are used to define the different forms of leprosy to guide diagnosis and management
- The Ridley-Jopling classification combines clinical manifestations, histopathologic features, and bacteriologic index
- The WHO classification is based on the bacteriologic index or the number of skin lesions

Classification

The clinical presentation of leprosy varies extensively and is dependent on the individual's immunologic response to the infection. The skin, peripheral nervous system, and reticuloendothelial system are primarily involved; however, other

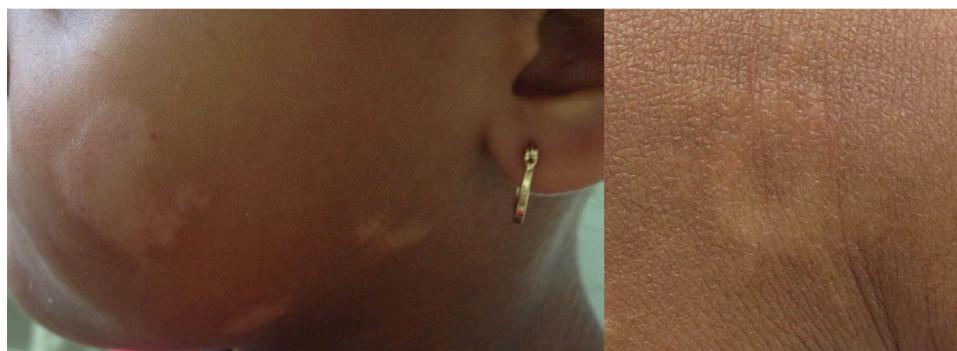


Fig 3. Polar tuberculoid leprosy. Note the hypopigmented macules and patches on the face and hand of a 3-year-old living with family members with a history of leprosy. Photograph courtesy of Gabriely L. Sacht, MD.

systems, such as the upper respiratory tract, bones and joints, eyes, testes, and adrenal glands may also be affected.²⁸ There are 2 main classification schemes used for leprosy patients: the Ridley-Jopling system²⁹ and the WHO operational classification.³⁰ The Ridley-Jopling classification system integrates clinical manifestations, histopathologic features, and bacteriologic index (BI). It aids in categorizing the different types of leprosy along a spectrum, which include polar tuberculoid leprosy (TT) (Fig 3), borderline tuberculoid leprosy (BT), mid-borderline leprosy (BB), borderline lepromatous leprosy (BL),³¹ and LL. Where affected persons fall within this classification model depends on one's cell-mediated immune response.^{32,33} Indeterminate leprosy (IL) is used to identify patients who have not yet developed a cell-mediated immune response to the organism, and can ultimately progress to either tuberculoid or lepromatous disease.

The WHO classification system is based on the BI (density of leprosy bacilli in slit-skin examination) or the number of skin lesions when a slit-skin smear (SS) is unavailable (Table II). Patients are classified as having paucibacillary leprosy (PB) when the number of skin lesions are 1 to 5 and as having MB when the number of skin lesions are >5.³⁴ However, when a SS examination is available, patients with 1 to 5 skin lesions are classified as having PB when the BI is negative at all sites examined or MB when the BI is positive at any site examined.^{35,36}

CLINICAL FEATURES

Key points

- The most common clinical findings include hypopigmented or erythematous patches with a reduced or complete loss of sensation
- Nerve damage occurs early, and assessing nerve damage is key to reducing disease comorbidity
- Ocular involvement occurs in 70% to 75% of cases

Common clinical findings

In general, patients with TT (Fig 3) have a robust cell-mediated ($T_{H}1$) response against the *M leprae* complex and therefore a less severe disease course.³⁰ TT is characterized by the presence of a single or few hypopigmented, hairless, hypo- or anesthetic, well-defined macules or plaques.^{27,31} BT is an immunologically unstable state in between TT and LL disease. This group includes BT (Fig 4), BB, and BL, with the vast majority of patients with leprosy falling within this category.^{22,37} At the end of the spectrum, patients with LL seemingly lack a cellular-immune response to the *M leprae* complex, leading to widespread disease and numerous lesions that may affect multiple organ systems, including the kidney and testes.^{32,38,39} More detailed descriptions of the clinical presentations of these variants and the rare variants of leprosy are shown in Table III.

Ocular involvement

Leprosy can lead to debilitating ocular complications, making it even more challenging for patients to care for themselves. Fortunately, they have become less frequent after the introduction of multidrug therapy for leprosy. Studies estimate that ocular involvement occurs in 70% to 75% of patients with leprosy and blindness occurs in 5% of patients.^{40,41} Ocular complications of leprosy occur as a result of 1) direct damage to ocular nerves (ophthalmic and facial) and 2) bacillary invasion of the anterior eye chamber. These can lead to significant ocular complications, the most common being diminished lid closure (lagophthalmos) (Fig 4, A), exposure keratitis (facial nerve involvement), impaired corneal sensation, cataracts, and iris atrophy (direct invasion by bacilli and its sequels).^{41,42} Patients with lepromatous leprosy (BL or LL) appear to

Table II. Classification and clinical presentation of leprosy

Cell-mediated immunity		Range from high (left) to low (right)			
Ridley-Jopling classification	TT	BT	BB	BL	LL
Lesion description	Well-defined macules and plaques	Infiltrative macules and plaques	Annular lesions with indistinct edges	Lepromas and annular lesions	Infiltrative macules, papules, and nodules
No. of lesions	Single	Single or few	Several	Numerous	Innumerable
Distribution	Localized	Asymmetric	Asymmetric	Symmetric	Symmetric
Lesion surface	Dry, scaly	Dry	Somewhat shiny	Shiny	Shiny
Hair growth in lesion	None	Diminished	Somewhat diminished	Slightly diminished	Unaffected
Sensation	Absent over plaques	Absent over plaques	Moderately diminished	Slightly diminished	Not affected early on; diffuse later in disease progression
Bacillary index/load	0/rarely 1+ (0 bacilli in 100 fields)	1-2+ (1-10 bacilli in 100 fields)	2-3+ (1-10 bacilli in 10 fields)	3-4+ (1-10 bacilli in each field)	4-6+ (100-1000 bacilli in each field)
Other findings	WHO		Paucibacillary		Multibacillary

BB, Borderline leprosy; BL, borderline lepromatous leprosy; BT, borderline tuberculoid leprosy; LL, polar lepromatous leprosy; TT, polar tuberculoid leprosy; WHO, World Health Organization.

Data from Ridley and Jopling,²⁹ the World Health Organization,³⁵ Bhat and Prakash,⁷⁶ and Talhari et al.⁷⁷



Fig 4. Borderline tuberculoid leprosy. **A**, Lagophthalmos. **B**, Multiple well-demarcated, erythematous plaques with a raised border on the torso. **C**, Bilateral contraction deformities and distal digit loss. Photograph courtesy of Barbara Stryjewska, MD.

have greater chance of developing ocular complications when compared with those classified as BB, BT, or TT.⁴³

Nasal and oral mucosal involvement

The nasal mucosa is commonly involved during lepromatous disease⁴⁴ and is often the entryway of

the *M leprae* complex. Symptoms include nasal obstruction, epistaxis, septal perforation, and saddle nose deformity, which are more often seen in patients with LL (Table IV).^{45,46} Oral mucosal lesions in leprosy are thought to be secondary to respiratory tract transmission,⁴⁷ and the prevalence varies among studies from 11.5% to 57%.^{47,48} Oral lesions

Table III. Clinical presentation of common and rare leprosy variants

Leprosy variant	Clinical presentation
Common	
TT	Single or few hypopigmented, well-defined macules or plaques ³¹ In lighter skin, lesions tend to be erythematous, whereas in darker skin lesions may have a copper to hyperpigmented appearance ²⁹ Dry and scaly (because of anhidrosis), hairless, hypo or anesthetic lesions, with very few bacilli ²⁷ ; some lesions may have elevated borders with central healing or peripheral spread ³² Pain and swelling surrounding the lesion progressing to sensory and motor loss ³³ Nerve damage may present with anesthetic areas or without any skin manifestations (PNL) ⁷⁸ Facial lesions may not have decreased sensation because the large density of facial nerves compensate for any damage ^{28,77}
BT	Asymmetric lesions similar to TT, but larger and more numerous (10-20) ⁷⁹ Satellite lesions surrounding the larger lesions are common ⁷⁷ Peripheral nerve involvement is extensive, with a high risk for severe nerve damage and disability ⁸⁰ (Fig 3)
BB	Numerous annular plaques with a well-defined inner rim and a poorly defined outer rim, giving them a "punched-out" or "Swiss cheese" appearance; lesions are asymmetric with variable nerve damage ⁸¹
BL	Numerous asymmetric macules, papules, and plaques with infiltrative borders and central healing Plaques, papules, and nodules may begin to appear similar to those seen in LL with disease progression ⁸² Multiple peripheral nerves become thickened and severe nerve damage is possible
LL	Many 20-100 widespread, symmetrical, erythematous to violaceous lesions Without treatment, lesions progress to copper-colored macules with indistinct edges, papules, and nodules (lepromas) ⁸³ (Fig 6) Lesions involve the face, scalp, fingers and toes, ¹ with warmer areas of the body being typically spared ⁸⁰ Progressive infiltration of the face can cause deepened forehead furrows, involvement of nasal mucosa (epistaxis), thickened skin (leonine facies), ⁸⁴ thickening of vocal cords (hoarseness), and loss of eyebrows (madarosis) Early nerve involvement is asymptomatic; as disease progresses, peripheral dorsal nerves become enlarged with subsequent anesthesia of the hands and feet in a "stocking and glove" pattern Diffuse LL is historically known as Lucio leprosy in Central and South America, ⁸⁵ characterized by diffuse skin infiltration of face and hands giving a smooth and erythematous appearance; thus it is also known as "lepra bonita" ("pretty leprosy") ⁸⁶ Nasal mucosa and ocular involvement may be present ⁸⁷
Rare	
Verrucous lepromatous lesions	Three clinical subtypes: finger-like projections similar to filiform warts, thick horn-like projections, and deep fissures with associated hyperkeratosis on anterior ankle ⁸⁸⁻⁹⁰
Histoid leprosy	Characterized by soft, skin-colored, subcutaneous papules to nodules, often located over bony surfaces of upper and lower extremities, buttocks, and lower back ⁹¹
PNL	Bacterial index is usually high (5+ to 6+), more commonly seen in florid LL and the BL spectrum ⁹² Peripheral nerve thickening and tenderness ⁹³ but without skin lesions and negative skin smear The rarity of this presentation makes the diagnosis of PNL extremely difficult Involved nerves include the ulnar and lateral popliteal nerves; because of the lack of skin findings, a diagnosis of PNL requires complex techniques (obtaining a nerve biopsy specimen, serology, and molecular analyses) that are not commonly available ^{78,94,95}

BB, Borderline leprosy; BL, borderline lepromatous leprosy; BT, borderline tuberculoid leprosy; LL, polar lepromatous leprosy; PNL, pure neural type leprosy; TT, polar tuberculoid leprosy.

are nonspecific, manifesting as asymptomatic, erythematous macules, papules or nodules that eventually ulcerate, involving the soft and hard palate, posterior tongue,⁴⁹ and gingivae. Oral lesions occur more often in patients with LL, yet even clinically normal oral mucosa may demonstrate histopathologic features of leprosy.^{50,51}

DIAGNOSIS

Key points

- A diagnosis of leprosy is primarily based on clinical findings, with or without a slit-skin smear examination for bacteriologic index
- Histopathologic examination is a valuable diagnostic and management tool and is performed

Table IV. Differential diagnosis of nasal leprosy

Nonleprosy conditions with nose involvement
Bacterial infections
Tuberculosis
Rhinosclerosis
Syphilis
Yaws
Deep fungal infections
Rhinophycomycosis
South American blastomycosis
Protozoal
Mucocutaneous leishmaniasis
Malignancy
Lymphoma
Basal cell carcinoma
Others
Relapsing polychondritis
Granulomatosis with polyarthritides
Sweet syndrome
Pyoderma gangrenosum

when facilities are available or for research purposes

- WHO 2018 guidelines do not recommend any additional testing other than slit-skin examination for bacteriologic index

One of the greatest challenges to diagnosing leprosy is to simply include this disease in the differential diagnosis, particularly in developed countries where leprosy has mostly been eradicated or is extremely rare.¹ Taking a thorough history, including travel to or residence in a country where leprosy is endemic, is crucial when considering a diagnosis of leprosy. Leprosy is strongly suspected when ≥ 1 of the following cardinal signs manifest⁵²:

- 1) a definitive loss of sensation in a pale (hypopigmented) or reddish skin patch; 2) a thickened or enlarged peripheral nerve, with loss of sensation and/or weakness of muscles supplied by that nerve; and 3) the presence of AFB in a SS examination.

Definitive loss of sensation in a skin lesion may be detected by touching the skin lightly using cotton wool or graded monofilaments. The patient is asked to pinpoint each place that is touched. When a patient feels the contact points in normal skin, but not in the anesthetic patches, a diagnosis of leprosy is strongly suspected.⁵²

Examination of the nerves is an important examination component in a person affected by leprosy, requiring expertise and trained staff.⁵² SS examination requires a suitably equipped laboratory with staff trained to perform and interpret this test. A

SS is not essential in the diagnosis of leprosy as the majority of TT and BL have negative smears. In some cases of early MB leprosy (Fig 5), a SS examination may be the only conclusive evidence of disease.⁵²

The presence of one cardinal sign is crucial to diagnose leprosy⁵³ and the presence of all 3 cardinal features has 97% diagnostic specificity.⁵⁴ Patients presenting with MB (≥ 6 skin lesions) are frequently misdiagnosed ($\leq 30\%$).⁵⁵ Improper or delayed diagnosis of leprosy often leads to progressive nerve sequelae and sometimes severe immunologic complications.⁵⁶

Nerve involvement in leprosy is limited to the peripheral nervous system (Fig 7). The nerves typically involved include the ulnar and common peroneal nerves (Table V).¹ However, all major peripheral nerves and multiple cutaneous nerve trunks may be affected.

DIAGNOSTIC TECHNIQUES

Key points

- Skin smear examination is a simple and widely used diagnostic tool
- Obtaining a skin biopsy specimen is useful to aid in leprosy classification and assess response to treatment
- Polymerase chain reaction testing is typically used to support a clinical diagnosis of leprosy but is limited by cost and availability of specialized equipment

Bacteriologic diagnosis

SS. A SS examination or slit-skin smear is a diagnostic tool commonly used in endemic countries outside of the United States to diagnosis and classify leprosy infections according to WHO guidelines (paucibacillary vs multibacillary).⁵⁷ SSs should be taken from lesions that appear most active or lesions that have persisted over a long period of time. If lesions are not present, specific anatomic sites corresponding to the “cooler” parts of the body are tested. Sites that have the highest probability of showing positive AFB are the earlobes, nasal mucosa, forehead, chin, the extensor surfaces of forearms and knees, and the dorsal surfaces of fingers.⁵⁸ After collection, Fite stain or modified Ziehl-Neelsen stain are used to visualize the AFB (*M leprae* is less acid-fast compared with *M tuberculosis*) and the Ridley logarithmic scale or bacterial index (BI) is used to interpret the results.² When performed correctly, the diagnostic specificity of SS is 100%;⁵⁵ however, recent studies show the SS has a 5-year average sensitivity of 34.4%.⁵⁹ As technology progresses, the use of SS at equipped facilities is slowly being replaced by molecular tests with better



Fig 5. **A**, Multibacillary leprosy. Note the ill-defined erythematous to tan macules and patches with fine scale on the chest and back. **B**, Multibacillary leprosy in a 10 year old. Well defined, erythematous plaques with infiltrative borders and some with central healing. Photograph courtesy of Gabriely L. Sacht, MD.



Fig 6. Leproma on the left upper extremity. Well-defined papules and nodules on the anterior aspect of the left arm. Photograph courtesy of Gabriely L. Sacht, MD.

sensitivity.⁶⁰ In the United States, obtaining a skin biopsy specimen and polymerase chain reaction (PCR) studies are most commonly used.

Skin biopsy and histopathologic examination. Skin biopsy specimens are taken from the leading margins of most recent and active skin lesions with the entire thickness of the dermis and at least a portion of the subcutaneous fat.⁶⁰ Tissue samples are stained with both hematoxylin–eosin and Fite tissue stains and examined for type, extent, and characteristics of the infiltrate, as well as the presence of AFB. For research purposes, biopsy specimens may be further analyzed for granuloma fraction (the proportion of dermis occupied by granuloma when visualized in low power), bacterial index of granuloma (BIG) for grading of AFB in tissue, and histopathologic index,

defined as the number of bacilli of a given tissue volume.^{2,61,62}

Histopathologic features can be extremely useful in classifying the type of leprosy and identifying the presence of a leprosy reaction. A biopsy specimen from an individual with TT typically demonstrates epithelioid granulomas, a lymphocytic infiltrate surrounding the adnexae and nerves, and very few (or absent) AFB (Fig 7).² At the lepromatous pole, there are more disorganized and diffuse histiocytic aggregates with Virchow cells (histiocytes with foamy cytoplasm) containing large numbers of AFB (Fig 8, A).² Bacilli are often clumped, forming conspicuous globi (Fig 8, B). Importantly, the presence of AFB within dermal nerves observed in a skin biopsy specimen is pathognomonic for leprosy (Fig 9). Contrary to TT, the morphology of dermal nerves in LL are well preserved early on but may become fibrotic with an onion skin appearance as the disease progresses.⁶²

The reported diagnostic specificity of skin biopsy specimens and histopathologic examination range from 70% to 72%⁵⁴ but the sensitivity remains lower, ranging from 49% to 70%.^{63,64} A recent study observed that obtaining a skin biopsy specimen confirmed the diagnosis in 71% of study patients.⁶⁵ The sensitivity and specificity of the WHO classification tested, using SS examination and skin biopsy specimen results as the gold standard, was found to be 63% and 85%, respectively.⁶⁶ Although obtaining a skin biopsy specimen is not considered a mandatory investigation by the WHO, it is a valuable adjunct tool in diagnosing and assessing treatment response.

PCR. PCR is a molecular technique used to amplify the DNA of *M leprae* and *M lepromatosis*. PCR is highly sensitive (87-100%) when patients demonstrate a positive BI or are classified as having LL; PCR sensitivity can be much lower (30-83%) in

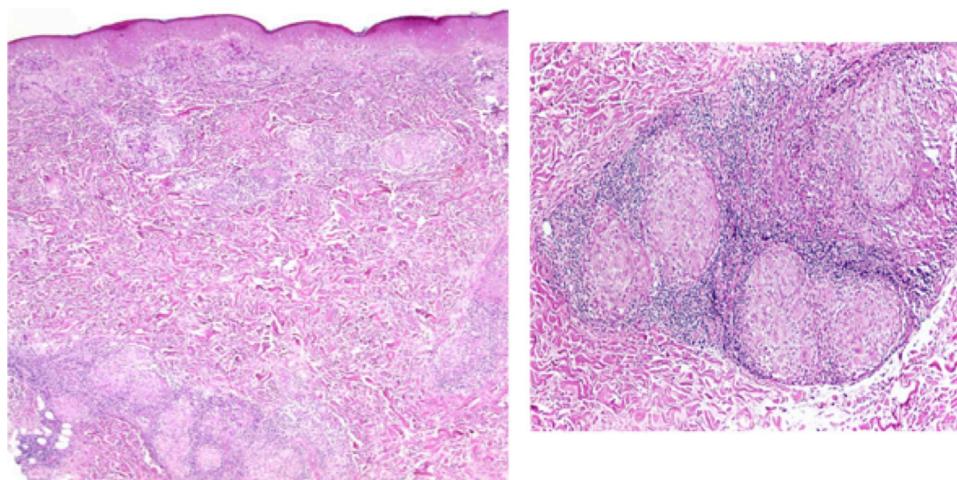


Fig 7. Histology of tuberculoid leprosy. Note the infiltrate and perineural accentuation. (Hematoxylin–eosin stain; original magnifications: $\times 4$ [left] and $\times 10$ [right].) Photographs courtesy of David Scollard, MD, PhD.

Table V. Pattern of nerve damage and differential diagnosis of leprosy neuropathy

Neuropathy type	Leprosy type	Pattern	Differential diagnosis
Micro mononeuropathy	IL	Localized (injury to terminal cutaneous nerve branches)	Surgery or trauma
Mononeuropathy or multiple mononeuropathy	BB, BL, BT, LL, or TT	Single or multiple nerve trunks	Surgery or trauma, nerve tumor, carpal tunnel syndrome, or other compression syndromes
Polyneuropathy	LL	Diffuse (stocking and glove pattern)	Hereditary sensory neuropathy (Thevenard syndrome), HIV polyneuropathy, Déjérine–Sotta disease (peripheral nerve thickening), drug- or poison-induced neurotoxicity, diabetes, amyloidosis, systemic lupus, or scleroderma

BB, Borderline leprosy; BL, borderline lepromatous leprosy; BT, borderline tuberculoid leprosy; IL, indeterminate leprosy; LL, polar lepromatous leprosy; TT, polar tuberculoid leprosy.

Data from Raicher et al.⁹⁶

patients with a negative BI or with tuberculoid leprosy.^{67–69} For these reasons, PCR is typically used to support a clinical diagnosis of leprosy, commonly in the United States, where PCR is free of charge at the National Hansen's Disease Program; however, in most endemic countries it is an expensive and labor-intensive technique and is not routinely performed.

Other diagnostic procedures

Electrophysiologic nerve tests include nerve conduction studies and needle electromyography. Both studies provide information about extent of nerve involvement, distribution of lesions, and mechanism of injury.⁷⁰ Nerve conduction studies show an 88% sensitivity in leprosy, while electromyography used in conjunction with nerve conduction studies does not increase the sensitivity.⁷¹ Obtaining a nerve biopsy specimen is

confirmatory in cases of pure neural leprosy⁵⁵ and this procedure should be performed when leprosy is suspected and skin lesions are absent.⁷² The common sensory nerves from which nerve biopsy specimens are taken in leprosy are the sural and radial cutaneous nerves.

Ultrasonography of peripheral nerves in leprosy is a low cost, noninvasive technology that has been increasingly used over the last 2 decades to measure the extent of thickening (increase in cross sectional area) of peripheral nerves. Loss and destruction of fascicular pattern is the most specific feature for neural impairment in leprosy.^{73–75} Ultrasonography of nerves is the tool for the “objective” assessment of nerve involvement in leprosy. It is most useful for the assessment of nerves that are inaccessible for clinical palpation, such as the median nerve at the wrist; however, higher sensitivity and specificity have been reported for ulnar and common fibular nerves.⁷⁵

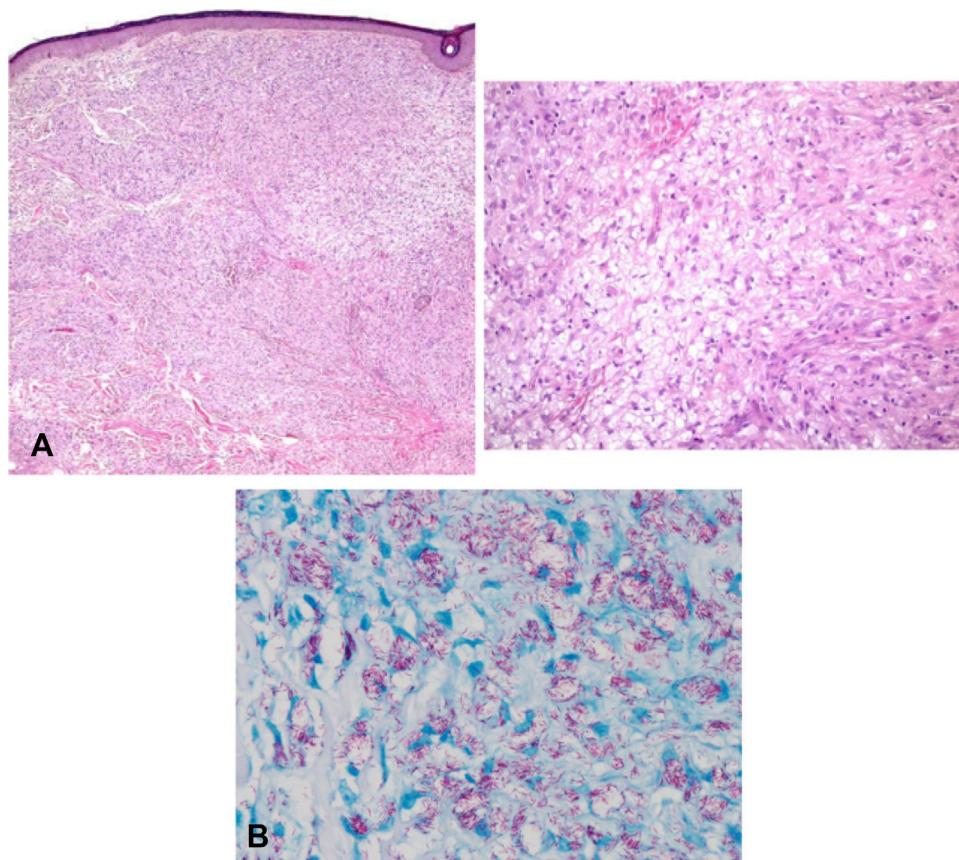


Fig 8. Histology of polar lepromatous leprosy. **A**, Diffuse and disorganized histiocytic aggregates with foamy cytoplasm. **B**, Abundant acid-fast bacilli in polar lepromatous leprosy. (**A**, Hematoxylin–eosin stain; **B**, Fite stain; original magnifications: **A**, $\times 4$ [left] and $\times 20$ [right]; **B**, Fite stain.) Photographs courtesy of David Scollard, MD, PhD.

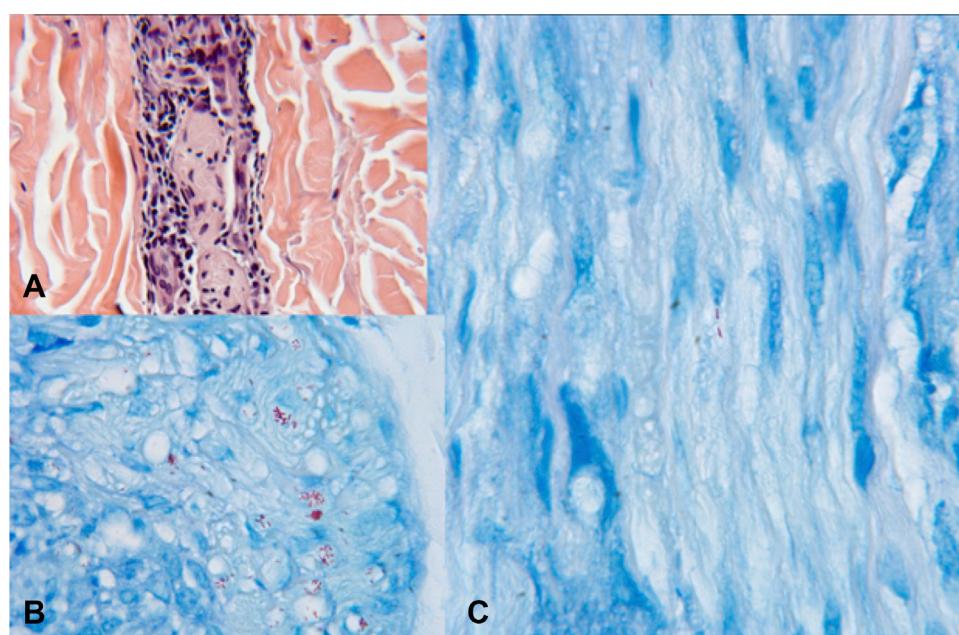


Fig 9. Perineural inflammation and acid-fast bacilli within a cutaneous nerve. **A**, Cutaneous nerve with perineurial lymphocytes and histiocytes. **B**, Numerous solitary and clustered acid-fast bacilli. **C**, Intraneuronal acid-fast bacilli. (**A** and **B**, Hematoxylin–eosin stain; **C**, Fite stain; original magnifications: **A** and **B**, $\times 20$; **C**, $\times 40$.) Photographs courtesy of David Scollard, MD, PhD.

Table VI. Cutaneous disorders that mimic leprosy

Leprosy classification	Mimickers
Indeterminate and tuberculoid	Pityriasis alba, segmental vitiligo, acquired postinflammatory hypopigmentation, nummular eczema, and tinea versicolor
Borderline tuberculoid	Granuloma annulare, disseminated granuloma annulare, sarcoidosis, tinea corporis, psoriasisiform eruptions, and erythema annulare centrifugum
Mid-borderline and borderline lepromatous	Morphea, necrobiosis lipoidica, eosinophilic granulomatosis with polyangiitis, necrobiotic xanthogranuloma, late syphilis, Sweet syndrome, mastocytosis, lichen planus, ichthyosis vulgaris, parapsoriasis, and mycosis fungoides
Polar lepromatous	Erythema elevatum diutinum, juvenile xanthogranulomatosis, steatocystoma multiplex, trichoepithelioma, leishmaniasis, blastomycosis keloidal, tuberculosis, blastomycosis, chromoblastomycosis, and verrucous lesions ⁹⁰
Pure neural	Peripheral nerve sheath tumor ^{98,99}

Adapted from Talhari et al⁷⁷ and Moschella and Garcia-Albea.⁹⁷

Table VII. Common leprosy complications based on organ system

Organ system involvement	Clinical manifestations
Endocrine ¹⁰⁰	Thyroid disease and gonadal axes abnormalities
Musculoskeletal ¹⁰¹	Lepromous osteitis of the hands and feet; loss of digits because of distal absorption ("mittens hand"); wrist and foot drop; ape thumb deformity (abducted thumb); claw hands; claw toes; plantar anesthesia; osteomyelitis
Ocular ⁹⁷	Lagophthalmos; reduced corneal sensation; corneal ulcers; uveitis/scleritis; cataract; glaucoma
Renal ³⁸	Acute and chronic glomerulonephritis; interstitial nephritis; secondary amyloidosis; pyelonephritis
Soft tissue ¹⁰¹	Plantar ulceration and secondary infection

Differential diagnosis

The differential diagnosis of leprosy is broad and varies according to the clinical classification (Table VI). The loss of pinprick or light touch sensation is helpful to distinguish leprosy from other disorders. Anesthetic lesions or neuropathy may not always be present and obtaining a skin biopsy specimen can aid in establishing the diagnosis. The common complications of leprosy are listed in Table VII.

CONCLUSION

Leprosy remains an important public health challenge, with new cases occurring worldwide, including cases in the United States. Clinicians should consider the diagnosis of leprosy in nonendemic regions when patients present with hypopigmented and hypoesthetic skin lesions, especially when associated with possible exposure through travel to endemic areas or close contact with individuals with leprosy. Early detection and appropriate management are key in limiting both the physical and emotional sequelae of leprosy.

REFERENCES

- Reibel F, Cambau E, Aubry A. Update on the epidemiology, diagnosis, and treatment of leprosy. *Med Mal Infect*. 2015;45:383-393.
- Eichelmann K, Gonzalez Gonzalez SE, Salas-Alanis JC, Ocampo-Candiani J. Leprosy. An update: definition, pathogenesis, classification, diagnosis, and treatment. *Actas Dermosifiliogr*. 2013;104:554-563.
- Truman RW, Singh P, Sharma R, et al. Probable zoonotic leprosy in the southern United States. *N Engl J Med*. 2011;364:1626-1633.
- Jessamine PG, Desjardins M, Gillis T, et al. Leprosy-like illness in a patient with *Mycobacterium lepromatosis* from Ontario, Canada. *J Drugs Dermatol*. 2012;11:229-233.
- Sotiriou MC, Stryjewska BM, Hill C. Two cases of leprosy in siblings caused by *Mycobacterium lepromatosis* and review of the literature. *Am J Trop Med Hyg*. 2016;95:522-527.
- Han XY, Aung FM, Choon SE, Werner B. Analysis of the leprosy agents *Mycobacterium leprae* and *Mycobacterium lepromatosis* in four countries. *Am J Clin Pathol*. 2014;142:524-532.
- Meredith A, Del Pozo J, Smith S, Milne E, Stevenson K, McLuckie J. Leprosy in red squirrels in Scotland. *Vet Rec*. 2014;175:285-286.
- Avanzi C, Del-Pozo J, Benjak A, et al. Red squirrels in the British Isles are infected with leprosy bacilli. *Science*. 2016;354:744-747.
- Rodrigues LC, Lockwood D. Leprosy now: epidemiology, progress, challenges, and research gaps. *Lancet Infect Dis*. 2011;11:464-470.
- Ghorpade A. Inoculation (tattoo) leprosy: a report of 31 cases. *J Eur Acad Dermatol Venereol*. 2002;16:494-499.
- Scollard DM. Infection with *Mycobacterium lepromatosis*. *Am J Trop Med Hyg*. 2016;95:500-501.
- Sales AM, Ponce de Leon A, Dupre NC, et al. Leprosy among patient contacts: a multilevel study of risk factors. *PLoS Negl Trop Dis*. 2011;5:e1013.

13. Moet FJ, Pahan D, Schuring RP, Oskam L, Richardus JH. Physical distance, genetic relationship, age, and leprosy classification are independent risk factors for leprosy in contacts of patients with leprosy. *J Infect Dis.* 2006;193:346-353.
14. da Silva MB, Portela JM, Li W, et al. Evidence of zoonotic leprosy in Para, Brazilian Amazon, and risks associated with human contact or consumption of armadillos. *PLoS Negl Trop Dis.* 2018;12:e0006532.
15. Trindade MA, Palermo ML, Pagliari C, et al. Leprosy in transplant recipients: report of a case after liver transplantation and review of the literature. *Transpl Infect Dis.* 2011;13:63-69.
16. Galtrey CM, Modarres H, Jaunmuktane Z, et al. Leprosy in a patient infected with HIV. *Pract Neurol.* 2017;17:135-139.
17. Carvalho KI, Bruno FR, Snyder-Cappione JE, et al. Lower numbers of natural killer T cells in HIV-1 and *Mycobacterium leprae* co-infected patients. *Immunology.* 2012;136:96-102.
18. Souyoul S, Saussy K, Stryjewska BM, Grieshaber E. Leprosy mimicking basal cell carcinoma in a patient on fingolimod. *JAAD Case Rep.* 2017;3:58-60.
19. Talhari C, Mira MT, Massone C, et al. Leprosy and HIV coinfection: a clinical, pathological, immunological, and therapeutic study of a cohort from a Brazilian referral center for infectious diseases. *J Infect Dis.* 2010;202:345-354.
20. Sauer ME, Salomao H, Ramos GB, et al. Genetics of leprosy: Expected-and unexpected-developments and perspectives. *Clin Dermatol.* 2016;34:96-104.
21. de Paula HL, de Souza CDF, Silva SR, et al. Risk factors for physical disability in patients with leprosy: a systematic review and meta-analysis. *JAMA Dermatol.* 2020. <https://doi.org/10.1001/jamadermatol.2019.1768>. [e-pub ahead of print].
22. Global leprosy update, 2016: accelerating reduction of disease burden. *Wkly Epidemiol Rec.* 2017;92:501-519.
23. Rao PN, Suneetha S. Current situation of leprosy in India and its future implications. *Indian Dermatol Online J.* 2018;9:83-89.
24. Anderson KL, Minni JP, Nowak MA, Karai LJ, Sanik E. A case of leprosy in central Florida. *Cutis.* 2017;100:327-329.
25. Villada G, Zarei M, Romagosa R, Forgione P, Fabbrocini G, Romanelli P. Autochthonous borderline tuberculoid leprosy in a man from Florida. *Lepr Rev.* 2016;87:101-103.
26. National Hansen's Disease Program, Health Resources and Services Administration website. National Hansen's Disease (Leprosy) Program caring and curing since 1894. Available at: <https://www.hrsa.gov/hansens-disease/index.html>. Accessed April 10, 2020.
27. Martin RD, Gomez IF, Spies LA. Burden of leprosy. *J Nurs Pract.* 2017;13:538-545.
28. Britton WJ, Lockwood DN. Leprosy. *Lancet.* 2004;363:1209-1219.
29. Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. *Int J Lepr Other Mycobact Dis.* 1966;34:255-273.
30. WHO Chemotherapy Study Group 1993. *Indian J Lepr.* 1995; 67:350-352.
31. Pin D, Guerin-Fauble V, Garreau V, et al. *Mycobacterium* species related to *M. leprae* and *M. lepromatosis* from cows with bovine nodular thelitis. *Emerg Infect Dis.* 2014;20:2111-2114.
32. Fonseca AB, Simon MD, Cazzaniga RA, et al. The influence of innate and adaptative immune responses on the differential clinical outcomes of leprosy. *Infect Dis Poverty.* 2017;6:5.
33. Modlin RL. Th1-Th2 paradigm: insights from leprosy. *J Invest Dermatol.* 1994;102:828-832.
34. WHO Expert Committee on Leprosy. *World Health Organ Tech Rep Ser.* 1998;874:1-43.
35. World Health Organization. WHO Expert Committee on Leprosy. *World Health Organ Tech Rep Ser.* 2012;1:61.
36. Walker SL, Lockwood DN. The clinical and immunological features of leprosy. *Br Med Bull.* 2006;77-78:103-121.
37. Global leprosy update, 2013; reducing disease burden. *Wkly Epidemiol Rec.* 2014;89:389-400.
38. Silva Junior GB, Daher Ede F, Pires Neto Rda J, et al. Leprosy nephropathy: a review of clinical and histopathological features. *Rev Inst Med Trop Sao Paulo.* 2015;57: 15-20.
39. Lewis WR, Lanza AP, Swersie S, Meeker HC, Schuller-Levis GB, Bardin CW. Testicular dysfunction in leprosy: relationships of FSH, LH and testosterone to disease classification, activity and duration. *Lepr Rev.* 1989;60:94-101.
40. Ffytche TJ. The prevalence of disabling ocular complications of leprosy: a global study. *Indian J Lepr.* 1998;70:49-59.
41. Malik AN, Morris RW, Ffytche TJ. The prevalence of ocular complications in leprosy patients seen in the United Kingdom over a period of 21 years. *Eye (Lond).* 2011;25:740-745.
42. Citirik M, Batman C, Aslan O, Adabag A, Ozalp S, Zilelioglu O. Lepromatous iridocyclitis. *Ocul Immunol Inflamm.* 2005;13:95-99.
43. Daniel E, Koshy S, Joseph GA, Rao PS. Ocular complications in incident relapsed borderline lepromatous and lepromatous leprosy patients in south India. *Indian J Ophthalmol.* 2003;51: 155-159.
44. Martins AC, Castro Jde C, Moreira JS. A ten-year historic study of paranasal cavity endoscopy in patients with Leprosy. *Braz J Otorhinolaryngol.* 2005;71:609-615.
45. Menger DJ, Fokkens WJ, Lohuis PJ, Ingels KJ, Nolst Trenite GJ. Reconstructive surgery of the leprosy nose: a new approach. *J Plast Reconstr Aesthet Surg.* 2007;60:152-162.
46. Walker SL, Lockwood DN. Leprosy. *Clin Dermatol.* 2007;25: 165-172.
47. de Abreu MA, Michalany NS, Weckx LL, Neto Pimentel DR, Hirata CH, de Avelar Alchorne MM. The oral mucosa in leprosy: a clinical and histopathological study. *Braz J Otorhinolaryngol.* 2006;72:312-316.
48. Taheri JB, Mortazavi H, Moshfeghi M, et al. Oro-facial manifestations of 100 leprosy patients. *Med Oral Patol Oral Cir Bucal.* 2012;17:e728-e732.
49. Morgado de Abreu MA, Roselino AM, Enokihara M, et al. *Mycobacterium leprae* is identified in the oral mucosa from paucibacillary and multibacillary leprosy patients. *Clin Microbiol Infect.* 2014;20:59-64.
50. Rodrigues GA, Qualio NP, de Macedo LD, et al. The oral cavity in leprosy: what clinicians need to know. *Oral Dis.* 2017;23: 749-756.
51. Pallagatti S, Sheikh S, Kaur A, Aggarwal A, Singh R. Oral cavity and leprosy. *Indian Dermatol Online J.* 2012;3:101-104.
52. Pannikar V. Enhanced global strategy for further reducing the disease burden due to leprosy: 2011-2015. *Lepr Rev.* 2009;80: 353-354.
53. Central Leprosy Division of the Directorate General of Health Services. National Leprosy Eradication Programme, India. National Action Plan for 2006-07. *Indian J Lepr.* 2006;78: 48-50.
54. Report of the International Leprosy Association Technical Forum. Paris, France, 25-28 February 2002. *Indian J Lepr.* 2002;74(suppl):1-93.
55. Moschella SL. An update on the diagnosis and treatment of leprosy. *J Am Acad Dermatol.* 2004;51:417-426.

56. Leon KE, Jacob JT, Franco-Paredes C, Kozarsky PE, Wu HM, Fairley JK. Delayed diagnosis, leprosy reactions, and nerve injury among individuals with Hansen's disease seen at a United States clinic. *Open Forum Infect Dis.* 2016;3:ofw063.
57. Ooi WW, Moschella SL. Update on leprosy in immigrants in the United States: status in the year 2000. *Clin Infect Dis.* 2001;32:930-937.
58. Mahajan VK. Slit-skin smear in leprosy: lest we forget it! *Indian J Lepr.* 2013;85:177-183.
59. Soneja S, Malhotra A, Devi P, Malhotra S, Singh B. Sensitivity of slit skin smear examination in suspected leprosy cases in a tertiary care centre: rising trends. *Int J Scin Res.* 2017;69:34-35.
60. Banerjee S, Biswas N, Kanti Das N, et al. Diagnosing leprosy: revisiting the role of the slit-skin smear with critical analysis of the applicability of polymerase chain reaction in diagnosis. *Int J Dermatol.* 2011;50:1522-1527.
61. Ridley D. Skin biopsy in leprosy. Histological interpretation and clinical application. 1977. Basel, Switzerland.
62. Singh A, Weng X, Nath I. Skin biopsy in leprosy. In: Khopkar U, ed. *Skin Biopsy- Perspectives.* London: IntechOpen; 2011:74-86.
63. Lockwood DN, Nicholls P, Smith WC, et al. Comparing the clinical and histological diagnosis of leprosy and leprosy reactions in the INFIR cohort of Indian patients with multibacillary leprosy. *PLoS Negl Trop Dis.* 2012;6:e1702.
64. Groenen G, Saha NG, Rashid MA, Hamid MA, Pattyn SR. Classification of leprosy cases under field conditions in Bangladesh. II. Reliability of clinical criteria. *Lepr Rev.* 1995; 66:134-143.
65. Naveed T, Shaikh Z, Anwar M. Diagnostic accuracy of slit skin smears in leprosy. *Pak Armed Forces Med J.* 2015;65:649-652.
66. Gupta R, Kar HK, Bharadwaj M. Revalidation of various clinical criteria for the classification of leprosy—a clinic-pathological study. *Lepr Rev.* 2012;83:354-362.
67. Torres P, Camarena JJ, Gomez JR, et al. Comparison of PCR mediated amplification of DNA and the classical methods for detection of *Mycobacterium leprae* in different types of clinical samples in leprosy patients and contacts. *Lepr Rev.* 2003;74:18-30.
68. Martinez AN, Talhari C, Moraes MO, Talhari S. PCR-based techniques for leprosy diagnosis: from the laboratory to the clinic. *PLoS Negl Trop Dis.* 2014;8:e2655.
69. Santos AR, De Miranda AB, Sarno EN, Suffys PN, Degrave WM. Use of PCR-mediated amplification of *Mycobacterium leprae* DNA in different types of clinical samples for the diagnosis of leprosy. *J Med Microbiol.* 1993;39:298-304.
70. Wein TH, Albers JW. Electrodiagnostic approach to the patient with suspected peripheral polyneuropathy. *Neuro Clin.* 2002;20:503-526.
71. Khambati FA, Shetty VP, Ghate SD, Capadia GD. Sensitivity and specificity of nerve palpation, monofilament testing and voluntary muscle testing in detecting peripheral nerve abnormality, using nerve conduction studies as gold standard; a study in 357 patients. *Lepr Rev.* 2009;80:34-50.
72. de Freitas MR, Nascimento OJ, Drago MJ, de Freitas AR, Hahn MD. Ulnar nerve palsy in leprosy without skin changes: biopsy of the superficial branch of the ulnar nerve in the hand [in Portuguese]. *Arq Neuropsiquiatr.* 1998;56:585-594.
73. Rao PN, Jain S. Newer management options in leprosy. *Indian J Dermatol.* 2013;58:6-11.
74. Garbino JA, Heise CO, Marques W Jr. Assessing nerves in leprosy. *Clin Dermatol.* 2016;34:51-58.
75. Frade MA, Nogueira-Barbosa MH, Lugao HB, Furini RB, Marques Junior W, Foss NT. New sonographic measures of peripheral nerves: a tool for the diagnosis of peripheral nerve involvement in leprosy. *Mem Inst Oswaldo Cruz.* 2013;108.
76. Bhat RM, Prakash C. Leprosy: an overview of pathophysiology. *Interdiscip Perspect Infect Dis.* 2012;2012:181089.
77. Talhari C, Talhari S, Penna GO. Clinical aspects of leprosy. *Clin Dermatol.* 2015;33:26-37.
78. Jardim MR, Antunes SL, Santos AR, et al. Criteria for diagnosis of pure neural leprosy. *J Neurol.* 2003;250:806-809.
79. Pimentel MI, Sampaio EP, Nery JA, et al. Borderline--tuberculoid leprosy: clinical and immunological heterogeneity. *Lepr Rev.* 1996;67:287-296.
80. Sehgal VN. Reactions in leprosy. Clinical aspects. *Int J Dermatol.* 1987;26:278-285.
81. Gaschignard J, Grant AV, Thuc NV, et al. Pauci- and multibacillary leprosy: two distinct, genetically neglected diseases. *PLoS Negl Trop Dis.* 2016;10:e0004345.
82. Nunzi E, Noto S. Observing the skin: papules and nodules in leprosy. *Lepr Rev.* 2008;79:118.
83. Alvarez-Ruiz SB, Delgado-Jimenez Y, Aragues M, Fraga J, Garcia-Diez A. Subcutaneous lepromas as leprosy-type presentation. *J Eur Acad Dermatol Venereol.* 2006;20:344-345.
84. Salgado CG, Barreto JG. Images in clinical medicine. Leonine facies: lepromatous leprosy. *N Engl J Med.* 2012;366:1433.
85. Nunzie E, Ortega Cabrera LV, Macanchi Moncayo FM, Ortega Espinosa PF, Clapasson A, Massone C. Lucio leprosy with Lucio's phenomenon, digital gangrene and anticardiolipin antibodies. *Lepr Rev.* 2014;85:194-200.
86. Rea TH, Jerskey RS. Clinical and histologic variations among thirty patients with Lucio's phenomenon and pure and primitive diffuse lepromatosis (Latapi's lepromatosis). *Int J Lepr Other Mycobact Dis.* 2005;73:169-188.
87. Jurado F, Rodriguez O, Novales J, Navarrete G, Rodriguez M. Lucio's leprosy: a clinical and therapeutic challenge. *Clin Dermatol.* 2015;33:66-78.
88. Richard EB, Williamson EA, Jackson SM, Stryjewska BM. A rare form of Hansen's disease presenting as filiform verrucous papules on the feet. *JAAD Case Rep.* 2016;2:105-107.
89. Medeiros MZ, Hans Filho G, Takita LC, Vicari CF, Barbosa AB, Couto DV. Verrucous lepromatous leprosy: a rare form of presentation—report on two cases. *An Bras Dermatol.* 2014; 89:481-484.
90. Yuchua-Guillen A, Dofitas BL. Atypical Hansen's disease presenting as florid verrucous plaques on the lower extremities: a case report. *Int J Dermatol.* 2012;51:697-701.
91. Gupta SK. Histoid leprosy: review of the literature. *Int J Dermatol.* 2015;54:1283-1288.
92. Kaur I, Dogra S, De D, Saikia UN. Histoid leprosy: a retrospective study of 40 cases from India. *Br J Dermatol.* 2009;160:305-310.
93. Sehgal VN, Tuli SM, Dube B. Leprotic nerve abscesses in northern India. *Int J Lepr Other Mycobact Dis.* 1967;35:60-64.
94. Chemouilli P, Woods S, Said G, Cole ST. Detection of *Mycobacterium leprae* in nerve lesions by the polymerase chain reaction. *Int J Lepr Other Mycobact Dis.* 1996;64:1-5.
95. Garbino JA, Marques W Jr, Barreto JA, et al. Primary neural leprosy: systematic review. *Arq Neuropsiquiatr.* 2013;71:397-404.
96. Raicher I, Stump PR, Baccarelli R, et al. Neuropathic pain in leprosy. *Clin Dermatol.* 2016;34:59-65.
97. Moschella SL, Garcia-Albea V. Differential diagnosis of leprosy. In: Scollard DM, Gillis TP, eds. International Textbook of Leprosy. Available at: <https://www.internationaltextbookofleprosy.org/>. Accessed April 10, 2020.
98. Gupta V, Dev T, Das CJ, Khanna N. Nerve abscess in pure neural leprosy mistaken for peripheral nerve sheath tumour

- with disastrous consequence: what can we learn? *BMJ Case Rep.* 2017;2017.
99. Lima CM, Da Costa PC, Carneiro L, De Oliveira ML. Schwannoma and nerve abscess of leprosy: differential diagnosis. *Lepr Rev.* 2013;84:141-144.
100. Singh RK, Bhasin R, Bisht YS, Kumar KV. Endocrine dysfunction in patients of leprosy. *Indian J Endocrinol Metab.* 2015;19: 369-372.
101. Moonot P, Ashwood N, Lockwood D. Orthopaedic complications of leprosy. *J Bone Joint Surg Br.* 2005;87:1328-1332.



Leprosy: Treatment and management of complications

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Learning objective

After completing this learning activity, participants should be able to discuss treatment options for uncomplicated leprosy (Hansen's disease) including multi-drug therapy; review the clinical presentations and management of immunologic reactions associated with leprosy (Type 1 and Type 2 reactions); and review the concept of relapse and how drug resistance plays a role in management.

Disclosures

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In the second article in this continuing medical education series, we review the treatment of leprosy, its immunologic reactions, and important concepts, including disease relapse and drug resistance. A fundamental understanding of the treatment options and management of neuropathic sequelae are essential to reduce disease burden and improve patients' quality of life. (J Am Acad Dermatol 2020;83:17-30.)

Key words: chemoprophylaxis; disease burden; disease relapse; drug resistance; Hansen's disease; immunoprophylaxis; leprosy; leprosy treatment; Lucio phenomenon; National Hansen's Disease Program; prevention; type 1 leprosy reaction; type 2 leprosy reaction.

Before the introduction of antibiotics, chaulmoogra oil was used to treat leprosy with some success.¹ In the 1940s, sulfone therapy

was considered a miracle cure for leprosy; however, the limited efficacy and side effect profile of sulfone prompted the use of dapsone in the late 1940s until

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Abbreviations used:

BB:	mid-borderline leprosy
BCG:	Bacillus Calmette-Guérin
BL:	borderline lepromatous leprosy
BT:	borderline tuberculoid leprosy
ENL:	erythema nodosum leprosum
LL:	lepromatous leprosy
MB:	multibacillary leprosy
NHDP:	National Hansen's Disease Program
PB:	paucibacillary leprosy
T1R:	type 1 reaction
T2R:	type 2 reaction
TT:	tuberculoid leprosy
WHO:	World Health Organization

antibiotic resistance was noted.¹ In the 1980s, the World Health Organization (WHO) began to recommend multidrug therapy (MDT) for the treatment of leprosy. The success of this therapy led to WHO de-emphasizing leprosy as a public health problem.¹ However, despite significant advances in the treatment of leprosy, gaps in knowledge regarding disease transmission, management, and antibiotic resistance present continuing challenges.¹

TREATMENT

Key points

- The 2018 WHO guidelines recommend treatment with rifampicin, dapsone, and clofazimine for paucibacillary leprosy and multibacillary leprosy for 6 and 12 months, respectively
- The National Hansen's Disease Program recommends longer treatment duration and excludes clofazimine in paucibacillary leprosy treatment
- Endemic leprosy drug resistance has reached a rate of 8%

Standard therapy

MDT is the mainstay of treatment for leprosy and includes rifampicin, dapsone, and clofazimine. MDT prevents dapsone resistance, induces a rapid decline in infectivity, and decreases the rate of recurrence.² As part of centralized strategies for leprosy management by the WHO, recommendations from 2018 include uniform MDT for both multibacillary leprosy (MB) and paucibacillary leprosy (PB; Table I).³ This is in contrast to WHO MDT recommendations that were in existence from 1998, wherein 2 drugs (dapsone and rifampicin) were recommended for 6 months for PB, while 3 drugs (dapsone, clofazimine, and rifampicin) were recommended for MB for 12 months. Better clinical outcomes were reported with a 3-drug regimen for PB, though increased pharmacovigilance was deemed necessary.³⁻⁶ Side effects and mechanisms

of action of recommended treatment regimens and alternative agents are listed in Table II.⁷⁻¹⁵

In the United States, the recommended regimen by the National Hansen's Disease Program (NHDP) involves a longer duration of treatment because of fewer cost restrictions and excludes clofazimine in PB treatment.¹⁶ The relapse rate for this regimen is extremely low.¹⁷ Alternate regimens suggested by the NHDP may include minocycline (100 mg/day) as a substitute for dapsone, clarithromycin (500 mg/day) as a substitute for any of the medications, or ofloxacin (400 mg) in place of clofazimine (Table III; level of evidence IIA).^{16,18,19} Recommended laboratory monitoring includes baseline laboratory values in addition to trending blood counts and liver function tests.¹⁹

Leprosy treatment in pregnancy

During pregnancy there is a reduction in cell-mediated immunity, increasing the risk of acquiring leprosy,²⁰ the spread of disease, and the development of leprosy reactions. Type 1 reaction (T1R) is more commonly observed during the postpartum period, while type 2 reaction (T2R) is more likely to occur during pregnancy.²¹ Because of the risk of permanent nerve injury and sequelae, pregnant woman should be adequately treated. MDT is safe during pregnancy, and the treatment of leprosy reactions during pregnancy is similar to treatment in nonpregnant women. Dapsone is not recommended by the WHO during breastfeeding; however, the American Academy of Pediatrics recommends that the decision to discontinue or limit breastfeeding should be made on an individual basis.²²

Drug resistance

Antimicrobial resistance is an important consideration in the management of leprosy; however, the inability to culture *Mycobacterium leprae* in vitro limits efficient testing for resistance.²³ Resistance studies are now performed in highly specialized laboratories using genotypic molecular techniques.²³ Recently, a prospective survey obtaining data from endemic countries described a global resistance rate of 8% from the years 2009 to 2015 among nearly 2000 reported cases.²⁴ Among these cases, 74 showed resistance to rifampicin, 87 to dapsone, and 21 to ofloxacin.²⁴ Multidrug resistance was noted in 20 patients to both rifampicin and dapsone²⁵ and in 4 patients to both ofloxacin and dapsone in Brazil, India, and Indonesia.²⁴ There were no reported cases of resistance to all 3 drugs within the collection period; however, the study highlights the need for increased vigilance to antimicrobial resistance.²⁴

Table I. Recommended treatment regimen from the World Health Organization

Diagnosis	Population	Medication	Dose	Duration
Paucibacillary leprosy	Adults	Rifampicin Clofazimine Dapsone	600 mg/month 300 mg/month + 50 mg/day 100 mg/day	6 months
	Children	Rifampicin Clofazimine Dapsone	450 mg/month 150 mg/month + 50 mg/day 50 mg/day	6 months
	Adults	Rifampicin Clofazimine Dapsone	600 mg/month 300 mg/month + 50 mg/day 100 mg/day	12 months
	Children	Rifampicin Clofazimine Dapsone	450 mg/month 150 mg/month + 50 mg/day 50 mg/day	12 months
Multibacillary leprosy				

Data from the World Health Organization.³

Table II. Mechanism of action and side effects of recommended treatment regimen and alternative agents

Drug	Mechanism of action	Side effects
Rifampicin	Inhibits bacterial DNA-dependent RNA polymerase; bactericidal ⁷	Hepatotoxicity with intrahepatic cholestasis, especially with alcohol use; thrombocytopenia; renal failure; gastrointestinal symptoms; red-orange discoloration of body fluids ⁸
Clofazimine	Unclear mechanism, but aminophenazone dye shown to bind to mycobacterial DNA; bactericidal ⁷	Red-brown hyperpigmentation of skin; xerosis; gastrointestinal symptoms caused by crystal accumulation ⁸
Dapsone	Inhibitor of dihydropteroate synthase needed for folate synthesis; bactericidal ⁷	Dose-dependent hemolytic anemia, more severe in glucose-6-phosphate dehydrogenase deficiency; agranulocytosis; gastrointestinal symptoms; headaches; delayed hypersensitivity reactions ^{7,8}
Ofloxacin	Quinolone antibiotic inhibiting bacterial DNA gyrase; bactericidal ⁸	Gastrointestinal symptoms; headaches; dizziness; insomnia; induces cytochrome P450 microenzymes; tendon rupture, especially in conjunction with steroids ⁷
Clarithromycin	Macrolide antibiotic inhibiting bacterial protein synthesis by binding to 50S ribosomal subunits; bactericidal ⁸	Gastrointestinal symptoms ⁷
Minocycline	Tetracycline antibiotic inhibiting bacterial protein synthesis by binding to 30S ribosomal subunits; bactericidal ⁹	Gastrointestinal symptoms; photosensitivity; blue-gray discoloration of the skin ⁸
Corticosteroids	Antiinflammatory action through inhibition of phospholipase A2 ¹⁰	Bruising; muscle weakness; skin atrophy; sleep disturbance; glaucoma, cataract, pathologic fractures; mood disorders; insulin resistance; excess mineralocorticoid activity ^{10,11}
Thalidomide	Antiinflammatory effect through modulation of tumor necrosis factor- α ¹²	Teratogen; drowsiness; pruritic, erythematous macular rash over trunk; peripheral neuropathy; constipation, ¹² deep vein thrombosis
Thioamides (ethionamide and protonamide)	Disrupts synthesis of mycolic acid; bactericidal ¹³	Frequent hepatotoxicity ⁸
Cyclosporine	Inhibition of T-cell activation by transcription reduction of interleukin-2 ¹⁴	Acute renal failure; hypertension; headaches; tremor; parasthesias; gastrointestinal symptoms; gingival hyperplasia; hypertrichosis ¹⁵

Table III. Recommended treatment regimen from the National Hansen's Disease Program and the United States Health Resources and Services Administration

Diagnosis	Population	Medication	Dose	Duration
Paucibacillary leprosy	Adults	Rifampicin	600 mg/day	12 months
	Children	Dapsone	100 mg/day	
Multibacillary leprosy	Adults	Rifampicin	10-20 mg/kg/day (<600 mg)	12 months
	Children	Clofazimine	1 mg/kg/day	
	Adults	Dapsone	600 mg/day	24 months
	Children	Rifampicin	50 mg/day	
	Adults	Dapsone	100 mg/day	
	Children	Clofazimine	10-20 mg/kg/day (<600 mg)	24 months
	Adults	Dapsone	1 mg/kg/day	
	Children	Dapsone	1 mg/kg/day	

Data taken from National Hansen's Disease Program.¹⁶**Table IV.** Recommended treatment regimens for drug-resistant leprosy from the World Health Organization

Resistance type	Treatment for first 6 months	Dose	Treatment for next 18 months	Dose
Rifampicin	Ofloxacin	400 mg/day	Ofloxacin	400 mg/day
	Minocycline	100 mg/day	OR	100 mg/day
	Clofazimine	50 mg/day	minocycline + clofazimine	50 mg/day
	Ofloxacin	400 mg/day	Ofloxacin	400 mg/day
Rifampicin and ofloxacin	Clarithromycin	500 mg/day	Clofazimine	50 mg/day
	Clofazimine	50 mg/day		
	Clarithromycin	500 mg/day	Clarithromycin	500 mg/day
Rifampicin and ofloxacin	Minocycline	100 mg/day	OR	100 mg/day
	Clofazimine	50 mg/day	minocycline + clofazimine	50 mg/day

Data from the World Health Organization.³

Regardless of clinical outcome, the WHO recommends that patients beginning MDT who are found to have resistance to rifampicin alone or in conjunction with dapsone should restart a course of second-line therapy (Table IV).³

Measuring response to treatment and long-term monitoring

During therapy, flattened nodules, plaques, and papules are expected, in addition to improved neural function.²⁶ A physical examination is required at each visit, focusing on skin, nerve palpation for tenderness, and a simple eye examination to check for symmetrical eye lid closure, irritation, or redness of sclera. Any abnormalities should prompt a referral for eye evaluation.^{26,27} Obtaining skin biopsy specimens annually from active lesions is also suggested to monitor inflammation; however, this may not be feasible in developing countries.²⁶ After completion of treatment, patients are advised to return annually for 5 years in the case of PB and annually for 10 years in cases of MB.²⁶ Treatment efficacy is directly correlated to both health care delivery and patient adherence. For personal or medical reasons, many

patients are noncompliant with multidrug therapy.²⁸ New strategies that address the social determinants of health are needed to improve patient compliance and encourage adherence (Table V).

RECOGNITION AND TREATMENT OF LEPROSY IMMUNOLOGIC REACTIONS

Key points

- There are 3 types of leprosy reactions: T1R, T2R or erythema nodosum leprosum, and a rare form known as Lucio phenomenon
- Leprosy reactions are medical emergencies
- The recognition of clinical manifestations and timely treatment is essential for limiting disease morbidity

T1R

Leprosy T1R is characterized by subacute to acute inflammation of the skin and nerves caused by an increase in cell-mediated immunity and delayed-type hypersensitivity to antigens of *M leprae* and *Mycobacterium lepromatosis* (*M leprae* complex).^{29,30} T1R may occur at any time during the leprosy disease course (Table VI).³¹⁻³⁹ There are

Table V. Recommendations to improve compliance and treatment adherence

Factors	Specific measures
Low health literacy, poverty, and low socioeconomic status	Provide educational material in an easy-to-understand format
Complexity of treatment regimen, long duration of treatment	Provide treatment instructions that are easy to follow and noncomplicated Provide additional information for treatment regimens that are longer Schedule follow-up appointments at appropriate intervals to decrease risk of relapse
Misconceptions, beliefs, and stigma related to disease	Provide information to patients about risk or spread and prevention Educate others on possible risks Build patient-provider relationship

Table VI. Clinical and histologic characteristics of leprosy immunologic reactions

Types of immunologic reactions	Leprosy classification	Skin manifestations	Histology	Associated symptoms
Type I reversal reaction	Borderline (BT, BB, and BL) and less often LL ³¹	Preexisting skin lesions become red and edematous ³¹	Tuberculoid granulomas that may coalesce and present with central fibrinoid necrosis; inflammatory lymphocytic infiltrate and multinucleated giant cells ³² (Fig 2)	Hand and feet edema, neuritis, and nerve function loss, weakness, and anesthesia ³³
Type II reversal reaction (ENL)	BL and LL	New, painful, erythematous nodules on the face, trunk, upper and lower extremities, often with a bilateral and symmetrical distribution ³⁴	Lobular panniculitis, chronic inflammatory infiltrate with predominance of neutrophils, macrophages with abundant <i>Mycobacterium leprae</i> bacterial load, and vasculitis may not always be present ^{30,31,35} (Fig 4)	Fever; malaise; arthralgia; arrhythmias; neuritis; dactylitis; iritis/ uveitis; orchitis; adenitis; glomerulonephritis; tibial periostitis ^{36,37}
Lucio leprosy/Lucio phenomenon	LL	Diffuse skin edema with myxedema-like appearance ³⁸ ; painful, erythematous to dark purple, irregularly shaped lesions that eventually form a central blister and ulcerate; atrophic scars	Vasculitis, epidermal necrosis, and plenty of acid-fast bacilli aggregates in endothelial cells ^{31,38} (Fig 5)	Fever; anemia; hepatosplenomegaly; lymphadenopathy ³⁸

BB, Mid-borderline leprosy; BL, borderline lepromatous leprosy; BT, borderline tuberculoid leprosy; ENL, erythema nodosum leprosum; LL, lepromatous leprosy.



Fig 1. Type 1 (reversal) reaction. Note the well-defined erythematous plaques on anterior and posterior trunk, some with a gyrate appearance. Photograph courtesy of Gabriely L. Sacht, MD.

even reports of reversal reactions occurring years after successful treatment completion and cure, highlighting the importance of follow-up.³¹ Regardless of the leprosy reaction type, 30% to 50% of patients will develop this complication.^{23,31,40} It is commonly seen in borderline tuberculoid (BT), mid-borderline (BB), and borderline lepromatous (BL) cases.³¹ Existing skin lesions may become red and edematous, and new lesions may appear (Fig 1). Associated edema of the extremities and the face is common.³¹ T1R is the main cause of nerve damage leading to nerve function impairment and disability.^{31,33,41} In addition, nerve involvement is more evident in T1R presenting as neuritis, paresthesia, and sudden motor loss resulting in wrist drop, foot drop, and facial palsy. The risk factors involved in developing T1R are not fully understood. Some possible triggers include immune status,⁴² advanced age, treatment or lack of treatment, pregnancy or postpartum period,²⁰ clinical type of leprosy,⁴³ positive bacterial index,⁴⁴ presence of positive anti-phenolic glycolipid-1 antibodies,⁴³ and nerve function impairment.⁴⁵ Leprosy reactions are challenging to diagnose. Although many promising serologic markers have been tested,⁴⁶⁻⁴⁸ to date there are no recommended laboratory tests to detect leprosy reactions.³⁰

Diagnosis of a T1R is a clinical diagnosis and requires a high degree of suspicion because this reaction may be the initial presentation of leprosy.³⁹ The histopathologic examination of an obtained skin biopsy specimen may reveal an increase in epithelioid granulomas, multinucleated giant cells, dermal edema, and a brisk lymphocytic infiltrate (Fig 2). However, no definitive histologic criteria exist for T1R, and clinical correlation is required. Corticosteroids are the standard treatment for T1R with nerve damage, and there is no consensus on optimal dose and duration. The WHO

recommendation is 40 to 60 mg daily (maximum 1 mg/kg) for 12 weeks. A 2016 Cochrane review on steroids for treating nerve damage in leprosy reported no superior effect of corticosteroids when compared with placebo for the treatment of mild and longstanding nerve injury.⁴⁹ However, a recent large, randomized controlled trial demonstrated that longer courses of steroids were effective, and that a treatment course of 20 weeks has similar effectiveness as 32 weeks (level of evidence IB).⁵⁰ In the NHDP, during the course of prednisone, rifampin dose is reduced from 600 mg daily to 600 mg once a month because of a drug-drug interaction and the rapid clearance of steroids via cytochrome P450.³⁰ Cyclosporine may be used as an alternative treatment in corticosteroid non-responding patients, and those with important side effects (level of evidence IB).¹⁴ MDT should be continued and patient counseling assuring that this is not a medication reaction is recommended.³⁰

T2R or erythema nodosum leprosum

T2R, also known as erythema nodosum leprosum (ENL), is characterized by crops of superficial and deep, painful nodules that may ulcerate and discharge purulent contents.^{30,51} Lesions often occur on the face, trunk, and upper and lower extremities, and may resolve with hyperpigmentation and scarring (Fig 3).³¹ Although considered an immune-mediated disorder, its pathogenesis is not fully understood.³⁵ It may affect 5% to 10% of patients with BL and ≤50% of those with LL, and its onset is more common within the first year of MDT.^{35,51} The diagnosis of T2R is also clinical, and histopathologic review of an obtained skin biopsy specimen within 24 to 72 hours may show a neutrophilic infiltrate, helping to confirm the diagnosis of ENL (Table VI). Histopathologic examination reveals histiocytes with large numbers

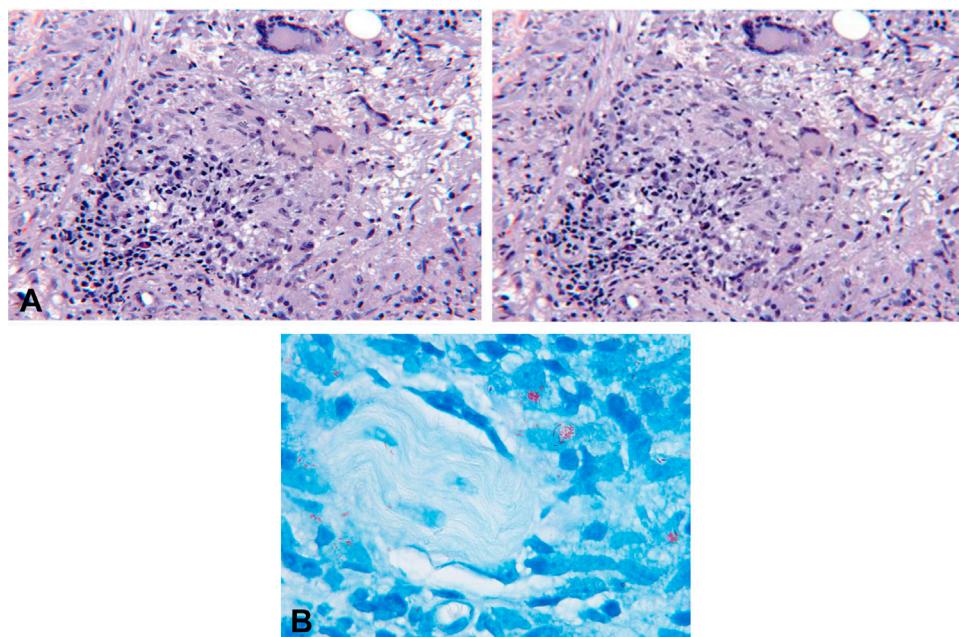


Fig 2. Histopathology of type 1 reaction (reversal reaction). **A**, Diffuse granulomatous infiltrate with scattered multinucleated giant cells. **B**, Acid-fast bacilli within histiocytes and cutaneous nerves. (**A**, Hematoxylin–eosin stain; **B**, Fite stain; original magnification: **A**, $\times 20$; **B**, $\times 100$.)



Fig 3. Erythema nodosum leprosum (type 2 reaction) in a man leading to gynecomastia related to testicular involvement. **A**, Multiple erythematous nodules and ulcerations on trunk and upper extremities with breast enlargement. **B**, Well-defined, punched out ulcer with central necrosis. Photograph courtesy of Gabriely L. Sacht, MD.

of acid-fast bacilli, an acute and chronic inflammatory infiltrate with neutrophils, and often a lobular panniculitis. Vasculitis may or may not be present (Fig 4).^{30,31,35} Unlike T1R, skin nodules are associated with systemic symptoms, including fever, malaise, arthralgia, neuritis, dactylitis, iritis, orchitis, lymphadenitis, glomerulonephritis, and tibial

periostitis.^{36,37} Laboratory work-up may reveal anemia, leukocytosis, elevated C-reactive protein, amyloid A protein, and alpha 1-antitrypsin.³¹ The course of each episode of ENL is from 1-3 weeks, and recurrences are common.²³ Severe ENL can also manifest as recurrent or chronic episodes. Chronic ENL is defined as the persistence of ENL for > 6

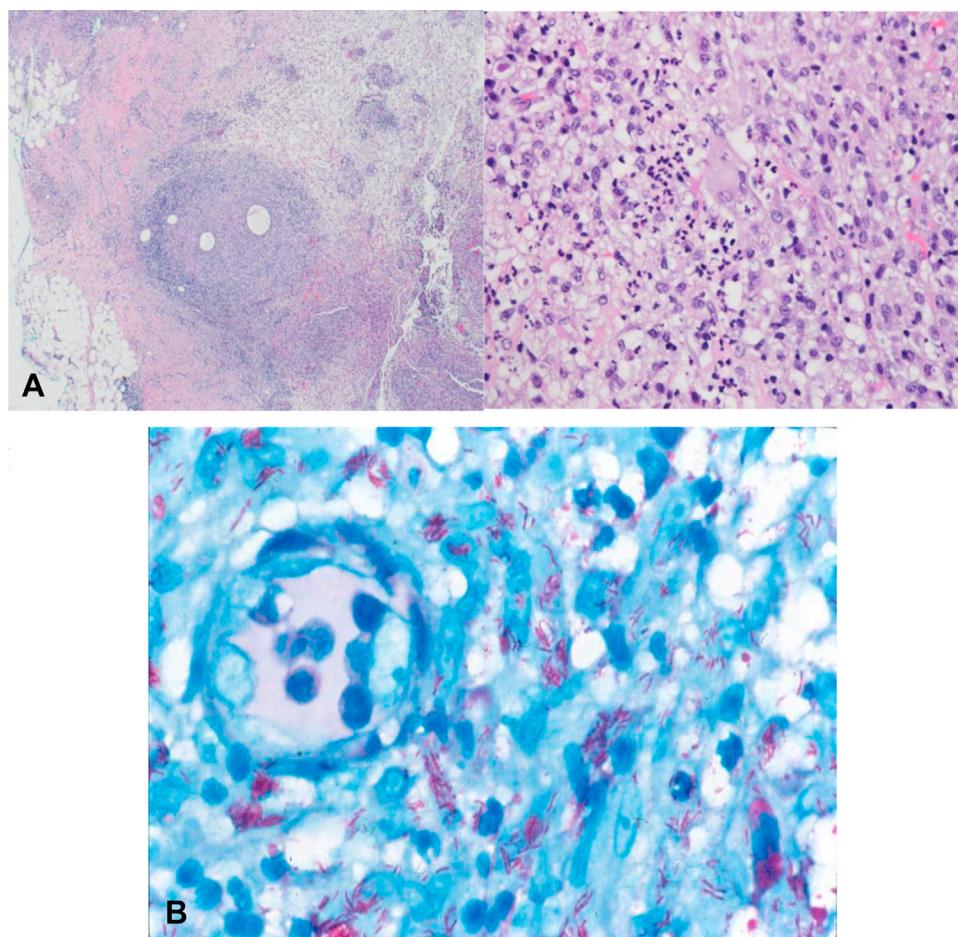


Fig 4. Histopathology of a type 2 reaction (erythema nodosum leprosum). **A**, Disorganized granulomatous infiltrate with foamy histiocytes and interspersed neutrophils. **B**, Abundant acid-fast bacilli within histiocytes. (**A**, Hematoxylin–eosin stain; **B**, Fite stain; original magnification: **A**, $\times 4$ and $\times 20$; **B**, $\times 100$.)

months despite adequate treatment.⁵² The main risk factor is high bacillary index, and hormonal changes during puberty, pregnancy, puerperium, and menopause seem to also play a role.⁵¹

The ENLIST ENL severity scale is a helpful tool to guide clinicians on appropriate management.⁵³ Mild cases may only require supportive treatment with nonsteroidal antiinflammatory drugs. If neuritis is present, initial treatment and steroid-sparing drugs should be initiated early to prevent steroid dependency; however, corticosteroids may often be needed.^{30,31} There is no optimal dosage, and the standard corticosteroid dose of 40 to 60 mg per day is used for a 5-month period and appears to be more beneficial than shorter regimens (level of evidence IA).⁴⁹ Of note, there are reports of increased mortality caused by corticosteroid side effects.⁵⁴ Thalidomide is the drug of choice in the treatment of T2R in many countries.^{55,56} The usual initial dose is 300 to 400 mg per day to control

acute symptoms for the first 2 days, and dosage should be reduced to 100 mg per day. Maintenance doses may be required for years in some patients.³⁰ The main adverse effects of thalidomide are teratogenesis, peripheral neuropathy, and sedation.⁵⁶ When thalidomide is combined with steroids, there is an increased risk of developing deep vein thrombosis and pulmonary embolism.⁵⁷ In the United States, thalidomide is available through the Risk Evaluation and Mitigation Strategy program, and only enrolled prescribers and pharmacists have authorization to prescribe and dispense thalidomide.⁵⁸ If patients develop symmetrical painful paresthesia of the hands and feet and sensory loss in lower extremities, thalidomide should be immediately discontinued.^{26,34} Clofazimine has been used in the management of T2R, and although it does not prevent T2R, it may have an effect on reducing disease severity (level of evidence III).

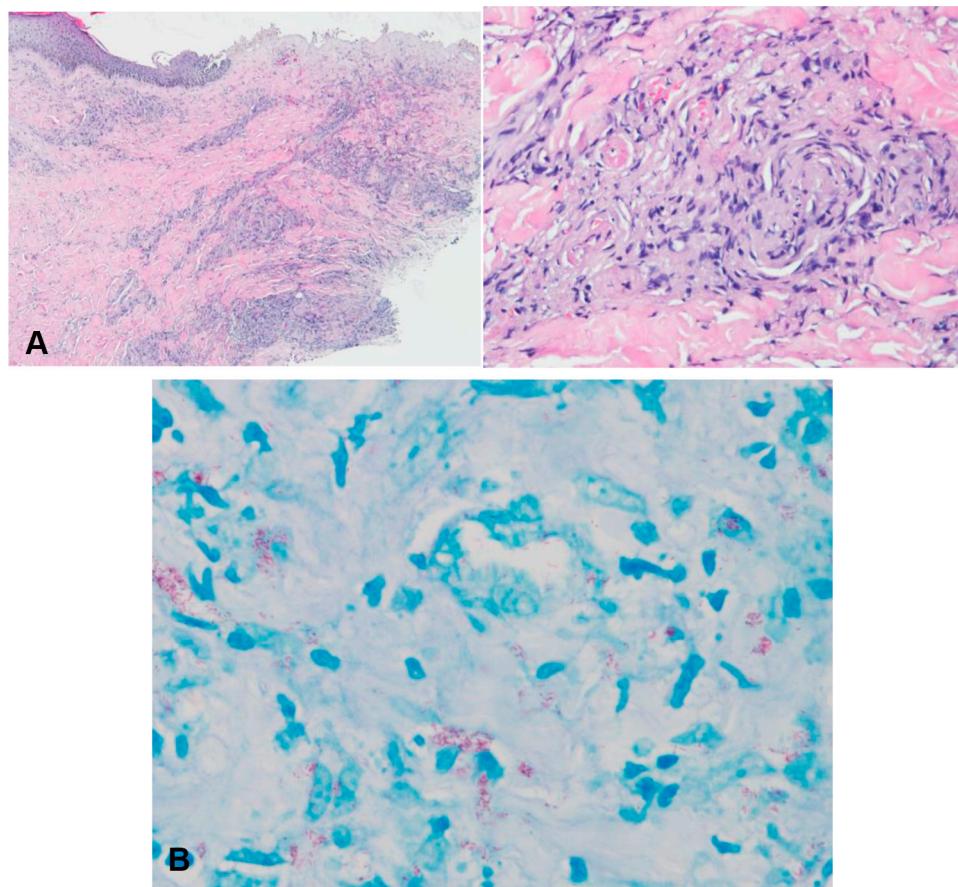


Fig 5. Histopathology of Lucio phenomenon. **A**, Granulomatous infiltrate with epidermal ulceration and fibrin thrombi. **B**, Abundant acid-fast bacilli within histiocytes and endothelial cells. (**A**, Hematoxylin–eosin stain; **B**, Fite stain; original magnification: **A**, $\times 4$ and $\times 20$; **B**, $\times 40$.)

Diffuse lepromatous leprosy and Lucio phenomenon

Diffuse lepromatous leprosy is a nonnodular form of lepromatous leprosy characterized by diffuse skin infiltration. The resultant edema and induration soften the wrinkles giving the impression of a healthy look, thus it is also known as “lepra bonita” (“pretty leprosy”).⁵⁹ Associated edema of the ear lobes, hands, legs, and feet are common, and confer a myxedema-like appearance, and as it progresses, the skin becomes atrophic, dry, and scaly (Table VI).⁶⁰ Lucio phenomenon (LPh) is a distinct leprosy reaction that may occur in patients with the 2 clinical forms of diffuse lepromatous leprosy: the pure and primitive diffuse leprosy (presence of nodules and diffuse infiltration) and secondary pure diffuse leprosy.^{38,60,61} The majority of case reports of LPh are from Central America and Mexico, with fewer reports from North America, South America, Africa, and Europe.^{38,62}

LPh is a thrombotic reaction characterized by painful, erythematous to dark purple, irregularly shaped lesions that eventually form a central blister resulting in an atrophic scar.^{38,60} Lesions are often located on lower extremities, forearms, and buttocks.³⁸ Systemic symptoms include fever, anemia, hepatosplenomegaly, lymphadenopathy, and upper respiratory tract involvement resulting in epistaxis and nasal bone destruction.³⁸ Obtaining a skin biopsy specimen is helpful to differentiate LPh lesions from lepromatous leprosy ulcerative lesions. The histopathologic review of biopsy specimens obtained from LPh lesions reveals necrotizing vasculitis, epidermal necrosis, intravascular fibrin thrombi, and acid-fast bacilli aggregates within endothelial cells (Fig 5).^{31,38} Treatment includes MDT if not already started, corticosteroids, and aggressive wound care.⁶¹ The differential diagnosis of leprosy immunologic reactions is broad and can be found in Table VII.^{27,63}

Table VII. Differential diagnosis of leprosy immunologic reactions

Type 1 reaction (reversal reaction)	Urticaria; angioedema; gyrate erythema; Well's syndrome; drug eruption; erysipelas; erythema multiforme
Type 2 reaction (erythema nodosum leprosum)	Systemic lupus erythematosus-like ⁶³ ; acute systemic lupus erythematosus; basal cell carcinoma ²⁷ ; discoid lupus erythematosus; tumid lupus; Sweet syndrome; subcorneal pustular dermatosis; sarcoidosis; systemic infections: tuberculosis, coccidiomycosis, histoplasmosis, blastomycosis; erythema nodosum, induratum; vasculitis ⁶³ ; lymphoproliferative disorders
Lucio phenomenon	Leukocytoclastic vasculitis; cryoglobulinemia; calciphylaxis; coumadin necrosis; cholesterol emboli; pyoderma gangrenosum; factitial dermatitis

Adapted from the International Textbook of Leprosy (<https://www.internationaltextbookofleprosy.org/chapter/differential-diagnosis-leprosy>).

Table VIII. Brief list of online resources for clinicians and patients

Resource	Website
American Leprosy Missions	https://www.leprosy.org/leprosy
International Textbook of Leprosy	https://internationaltextbookofleprosy.org
International Leprosy Association	http://www.leprosy-ila.org/do.php/Home
The Leprosy Mission International	https://www.leprosymission.org
National Hansen's Disease Program	https://www.hrsa.gov/hansens-disease/index.html
Global Partnership for Zero Leprosy	https://zeroleprosy.org
International Federation of Anti-Leprosy Associations	https://www.ilepfederation.org/
National Leprosy Eradication Program (India)	http://www.nlep.nic.in
Pacific Leprosy Foundation	https://www.leprosy.org.nz
Sasakawa-India Leprosy Foundation	https://silf.in
Effect: Hope The Leprosy Mission Canada	https://effecthope.org/
Novartis Foundation	https://www.novartisfoundation.org/
Lepra	https://www.lepra.org.uk

DISEASE RELAPSE

Key points

- Relapse is defined as the resurgence of signs and symptoms of disease after a complete course of multidrug therapy
- The WHO estimates the rate of relapse after multidrug therapy at 0.77% for multibacillary leprosy and 1.07% for paucibacillary leprosy 9 years after treatment
- Predisposing factors for relapse include inadequate therapy, irregular therapy, and monotherapy, and it has been linked to low health literacy, socioeconomic status, and gender

The WHO guide to leprosy control defines relapse as the resurgence of signs and symptoms of disease after a complete course of MDT.^{64,65} Studies report leprosy relapse occurring ≤ 20 years after MDT treatment, representing the maximum incubation period of *M leprae*.⁶⁴ MB is characterized by new lesions, new activity in previously existing lesions, and a 2+ increase in the bacteriologic index at any single site.⁶⁶ Compared with MB, relapse in patients with PB may occur 2 years after treatment and PB is

typically more difficult to distinguish from reversal reactions presenting as new lesions, the extension of existing lesions, and nerve pain.⁶⁷ The WHO estimates the rate of relapse after MDT as 0.77% for MB and 1.07% for PB 9 years after treatment.⁶⁸ Other studies estimate the relapse rate at 0.6% to 3.0% for PB and 0.21% to 0.8% for MB.⁶⁹⁻⁷¹ The relapse rate for PB and MB in the United States is extremely low.⁷² The relapse rate for both PB and MB after MDT is 10 times lower than dapsone therapy alone.⁷² Some studies link an increase in relapse risk to a high bacterial load before MDT,⁶⁴ while others show a high number of skin and nerve lesions indicate an increased relapse risk.⁷¹ Persisting organisms able to survive therapy can lead to relapse. It has been reported that >14% of slit-skin smear-positive patients with BL/lepromatous leprosy have viable leprosy bacilli 12 months after MDT.¹¹ In addition, reinfection as a cause of relapse must be considered, especially for late relapse extending beyond 10 years posttreatment.⁵ Other predisposing factors for relapse include inadequate therapy, irregular therapy, and monotherapy.^{72,73} Inadequate or

irregular therapy may be caused by patients defaulting MDT and can be related to educational status, socioeconomic status, and gender.⁷⁴ Some recommendations presented by the WHO to combat noncompliance include increased health education and literacy, the removal of myths and misconceptions, improved facilities, and patient-provider rapport.⁷⁵

DISEASE BURDEN

Key points

- Southeast Asia has the largest number of registered leprosy cases and new cases each year
- The global disability-adjusted life years for leprosy was 31,512 in 2017

After the implementation of MDT, the global prevalence of leprosy decreased from >5 million cases in the 1980s to <200,000 cases in 2017.⁶⁵ Because of leprosy's long incubation period and delay in diagnosis, the incidence of leprosy is difficult to determine.⁷⁶ According to the WHO, in 2017, Southeast Asia had the largest number of registered leprosy cases and new cases, followed by North and South America, Africa, Western Pacific, Eastern Mediterranean, and Europe.⁴ Between individual countries, India had the highest number of new cases of leprosy in 2017 (126,164), followed by Brazil (26,875) and Indonesia (15,910).⁴ In 2016, the WHO launched a 5-year global leprosy strategy to reduce the burden of disease that included 3 main goals: 1) strengthen government ownership, coordination, and partnership; 2) stop leprosy and its complications; and 3) stop discrimination and promote inclusion.⁷⁷ This initiative focuses on decreasing disabilities among pediatric patients and decreasing the number of patients with grade 2 disabilities, those with visible deformities.⁷⁷ There has been a reduction in the proportion of new childhood cases of leprosy (in patients <15 years of age) from 8.6% in 2016 to 7.5% in 2017,⁴ and a steady decrease in the total number of new grade 2 disability cases from 2013 (13,289) to 2017 (12,189).⁴ An important measure in determining burden of disease is disability-adjusted life years (DALYs). This measure is determined by the sum of years of life lost and years lost because of disability.⁷⁸ Mortality from leprosy is low, and therefore DALYs are mostly derived from years lost because of disability, which captures the prevalence of disease and the health loss accounting for severity of disease.⁷⁹ The global DALYs for leprosy was 31,512 in 2017 and 31,922 10 years earlier. Of note, this number did not significantly change over time, indicating that disability associated with leprosy remains high and

continues to represent a crucial issue in caring for those affected by this chronic disease.

PREVENTION

Key points

- Early detection of active cases, patient education, and annual evaluation of household contacts are key to leprosy prevention
- The WHO recently recommended chemoprophylaxis is single-dose rifampicin for close contacts
- Immunoprophylaxis with *Bacillus Calmette-Guérin* offers variable protection and the WHO vaccination is recommended if there is a high incidence of tuberculosis, leprosy burden, and Buruli ulcers

Chemoprophylaxis

The Chemoprophylaxis of Leprosy Trial conducted from 2002 to 2003 reported that a single dose of rifampin (SDR) provides a 57% reduction in incidence of all types of leprosy for 2 years.⁸⁰ The effectiveness of SDR appears to be higher when the mycobacterial load is low and decreases with time.^{80,81} The WHO guideline currently recommends SDR as the preventative measure for adults and children (≥ 2 years of age) who are in contact with patients with leprosy.^{82,83} Concerns regarding cost effectiveness, leprosy status confidentiality, and the possibility of drug resistance have been raised.⁸⁴ Dapsone (weekly dose for 2-3 years) and acedapsone (every 10 weeks for 7 months) were both studied previously and were favored compared with placebo but are not recommended at present.^{85,86}

Immunoprophylaxis

Bacillus Calmette-Guérin (BCG) vaccination provides variable protection against leprosy ranging from 20% to 90%.⁸⁷ Higher protection is observed in the younger population and wanes over time.⁸⁸⁻⁹⁰ Protection is greater after 2 vaccine doses and provides better protection against MB than PB.^{91,92} BCG efficacy was higher in observational studies than clinical trials (60% vs 41%) and among leprosy contacts compared with the general population (68% vs 53%).^{92,93} The 2018 WHO and Strategic Advisory Group of Experts on Immunization BCG working group recommends that the BCG vaccine be given in countries with high leprosy burden.⁹⁴ Moreover, BCG vaccine at birth may potentiate the effects of SDR. LepVax, a new subunit vaccine, is currently under study for pre- and postexposure leprosy prophylaxis.⁹⁵

Leprosy resources

Access to appropriate resources and medications vary according to individual countries. A brief list of resources is available in Table VIII.

In conclusion, early detection and proper treatment of leprosy are key to reducing transmission and lifelong disabilities. Cutaneous manifestations are observed in almost all leprosy types, and therefore dermatologists play an important role in early diagnosis. Management of leprosy and its reactions may be quite challenging even for experienced dermatologists. Comprehensive treatment for these patients requires coordination of care with other health care professionals to address the multiple sequelae of leprosy (dermatologic, neurologic, physical/occupational rehabilitation, and psychosocial).

REFERENCES

1. Bennett BH, Parker DL, Robson M. Leprosy: steps along the journey of eradication. *Public Health Rep.* 2008;123:198-205.
2. Eichelmann K, González González SE, Salas-Alanis JC, Ocampo-Candiani J. Leprosy. An update: definition, pathogenesis, classification, diagnosis, and treatment. *Actas Dermosifiliogr.* 2013;104:554-563.
3. World Health Organization. Guidelines for the diagnosis, treatment and prevention of leprosy. Available at: <https://apps.who.int/iris/bitstream/handle/10665/274127/9789290226383-eng.pdf?ua=1>. Accessed April 13, 2020.
4. Mondiale de la Santé O, World Health Organization. Global leprosy update, 2017: reducing the disease burden due to leprosy. Available at: <https://apps.who.int/iris/handle/10665/274290>. Accessed April 13, 2020.
5. Global Leprosy Strategy. Strategy 2016–2020: accelerating towards a leprosy free-world. Available at: <https://www.who.int/lep/resources/9789290225256/en/>. Accessed April 13, 2020.
6. Penna GO, Bührer-Sékula S, Kerr LRS, et al. Uniform multidrug therapy for leprosy patients in Brazil (U-MDT/CT-BR): results of an open label, randomized and controlled clinical trial, among multibacillary patients. *PLoS Negl Trop Dis.* 2017;11:e0005725.
7. Talhari S, Ameen M. *Drugs in leprosy*. Springer; 2012: 281-286.
8. Fischer M. Leprosy – an overview of clinical features, diagnosis, and treatment. *J Dtsch Dermatol Ges.* 2017;15:801-827.
9. Garrido-Mesa N, Zarzuelo A, Gálvez J. Minocycline: far beyond an antibiotic. *Br J Pharmacol.* 2013;169:337-352.
10. Ericson-Nielsen W, Kaye AD. Steroids: pharmacology, complications, and practice delivery issues. *Ochsner J.* 2014;14:203-207.
11. Shetty VP, Khambati FA, Ghate SD, Capadia GD, Pai VV, Ganapati R. The effect of corticosteroids usage on bacterial killing, clearance and nerve damage in leprosy; part 3—Study of two comparable groups of 100 multibacillary (MB) patients each, treated with MDT + steroids vs. MDT alone, assessed at 6 months post-release from 12 months MDT. *Lepr Rev.* 2010; 81:41-58.
12. Teo SK, Resztak KE, Scheffler MA, et al. Thalidomide in the treatment of leprosy. *Microbes Infect.* 2002;4:1193-1202.
13. Quémard A, Lanéelle G, Lacave C. Mycolic acid synthesis: a target for ethionamide in mycobacteria? *Antimicrob Agents Chemother.* 1992;36:1316-1321.
14. Lambert SM, Alemba DT, Nigusse SD, Yamuah LK, Walker SL, Lockwood DN. A randomized controlled double blind trial of ciclosporin versus prednisolone in the management of leprosy patients with new type 1 reaction, in Ethiopia. *PLoS Negl Trop Dis.* 2016;10:e0004502.
15. Ryan C, Amor KT, Menter A. The use of cyclosporine in dermatology: part II. *J Am Acad Dermatol.* 2010;63:949-972.
16. National Hansen's Disease Program, Health Resources and Services Administration. Recommended treatment regimens. Available at: <https://www.hrsa.gov/hansens-disease/diagnosis/recommended-treatment.html>. Accessed April 13, 2020.
17. Dacso MM, Jacobson RR, Scollard DM, Stryjewska BM, Prestigiacomo JF. Evaluation of multi-drug therapy for leprosy in the United States using daily rifampin. *South Med J.* 2011; 104:689-694.
18. Worobec SM. Current approaches and future directions in the treatment of leprosy. *Res Rep Trop Med.* 2012;3:79-91.
19. Singh B, Schoeb TR, Bajpai P, Slominski A, Singh KK. Reversing wrinkled skin and hair loss in mice by restoring mitochondrial function. *Cell Death Dis.* 2018;9:735.
20. Lockwood DN, Sinha HH. Pregnancy and leprosy: a comprehensive literature review. *Int J Lepr Other Mycobact Dis.* 1999; 67:6-12.
21. Maurus JN. Hansen's disease in pregnancy. *Obstet Gynecol.* 1978;52:22-25.
22. Ozturk Z, Tatliparmak A. Leprosy treatment during pregnancy and breastfeeding: a case report and brief review of literature. *Dermatol Ther.* 2017. <https://doi.org/10.1111/dth.12414>. [e-pub ahead of print].
23. Scollard DM, Adams LB, Gillis TP, Krahenbuhl JL, Truman RW, Williams DL. The continuing challenges of leprosy. *Clin Microbiol Rev.* 2006;19:338-381.
24. Cambau E, Saunderson P, Matsuoka M, et al. Antimicrobial resistance in leprosy: results of the first prospective open survey conducted by a WHO surveillance network for the period 2009-15. *Clin Microbiol Infect.* 2018;24:1305-1310.
25. Williams DL, Araujo S, Stryjewska BM, Scollard D. Dapsone resistance in leprosy patients originally from American Samoa, United States, 2010-2012. *Emerg Infect Dis.* 2018;24:1584-1585.
26. Scollard D, Stryjewska B, Dacso M. Leprosy: treatment and prevention. In: Baron EL, ed. UpToDate. Waltham, MA: UpToDate; 2020 Available at: <https://www.uptodate.com/contents/leprosy-treatment-and-prevention>. Accessed April 13, 2020.
27. Malik AN, Morris RW, Ffytche TJ. The prevalence of ocular complications in leprosy patients seen in the United Kingdom over a period of 21 years. *Eye (Lond).* 2011;25:740-745.
28. Girão RJS, Soares NLR, Pinheiro JV, et al. Leprosy treatment dropout: a systematic review. *Int Arch Med.* 2013;6:34.
29. Raffe SF, Thapa M, Khadge S, Tamang K, Hagge D, Lockwood DN. Diagnosis and treatment of leprosy reactions in integrated services—the patients' perspective in Nepal. *PLoS Negl Trop Dis.* 2013;7:e2089.
30. Scollard D, Stryjewska B, Dacso M. Leprosy: epidemiology, microbiology, clinical manifestations, and diagnosis. In: Baron EL, ed. UpToDate. Waltham, MA: UpToDate; 2020.
31. Kamath S, Vaccaro SA, Rea TH, Ochoa MT. Recognizing and managing the immunologic reactions in leprosy. *J Am Acad Dermatol.* 2014;71:795-803.
32. Scollard DM, Joyce MP, Gillis TP. Development of leprosy and type 1 leprosy reactions after treatment with infliximab: a report of 2 cases. *Clin Infect Dis.* 2006;43:e19-e22.
33. Croft RP, Nicholls PG, Steyerberg EW, Richardus JH, Cairns W, Smith S. A clinical prediction rule for nerve-function impairment in leprosy patients. *Lancet.* 2000;355:1603-1606.
34. Costa P, Fraga LR, Kowalski TW, Daxbacher ELR, Schuler-Faccini L, Vianna FSL. Erythema nodosum leprosum: update and challenges on the treatment of a neglected condition. *Acta Trop.* 2018;183:134-141.

35. Polycarpou A, Walker SL, Lockwood DN. A systematic review of immunological studies of erythema nodosum leprosum. *Front Immunol.* 2017;8:233.
36. Lastoria JC, Abreu MA. Leprosy: review of the epidemiological, clinical, and etiopathogenic aspects - part 1. *An Bras Dermatol.* 2014;89:205-218.
37. Kliozé AM, Ramos-Caro FA. Visceral leprosy. *Int J Dermatol.* 2000;39:641-658.
38. Sehgal VN. Lucio's phenomenon/erythema necroticans. *Int J Dermatol.* 2005;44:602-605.
39. Naafs B, van Hees CL. Leprosy type 1 reaction (formerly reversal reaction). *Clin Dermatol.* 2016;34:37-50.
40. Lockwood DN, Lucas SB, Desikan KV, Ebenezer G, Suneetha S, Nicholls P. The histological diagnosis of leprosy type 1 reactions: identification of key variables and an analysis of the process of histological diagnosis. *J Clin Pathol.* 2008;61:595-600.
41. Andrade PR, Pinheiro RO, Sales AM, et al. Type 1 reaction in leprosy: a model for a better understanding of tissue immunity under an immunopathological condition. *Expert Rev Clin Immunol.* 2015;11:391-407.
42. Saunderson P, Gebre S, Byass P. Reversal reactions in the skin lesions of AMFES patients: incidence and risk factors. *Lepr Rev.* 2000;71:309-317.
43. Roche PW, Le Master J, Butlin CR. Risk factors for type 1 reactions in leprosy. *Int J Lepr Other Mycobact Dis.* 1997;65:450-455.
44. Antunes DE, Araujo S, Ferreira GP, et al. Identification of clinical, epidemiological and laboratory risk factors for leprosy reactions during and after multidrug therapy. *Mem Inst Oswaldo Cruz.* 2013;108:901-908.
45. Croft RP, Nicholls PG, Steyerberg EW, Richardus JH, Withington SG, Smith WC. A clinical prediction rule for nerve function impairment in leprosy patients-revisited after 5 years of follow-up. *Lepr Rev.* 2003;74:35-41.
46. Devides AC, Rosa PS, de Faria Fernandes Belone A, Coelho NMB, Ura S, Silva EA. Can anti-PGL-1 and anti-NDO-LID-1 antibody titers be used to predict the risk of reactions in leprosy patients? *Diagn Microbiol Infect Dis.* 2018;91:260-265.
47. Fabri Ada C, Carvalho AP, Vieira NF, et al. Integrative literature review of the reported uses of serological tests in leprosy management. *Rev Soc Bras Med Trop.* 2016;49:158-164.
48. Hungria EM, Buhrer-Sekula S, de Oliveira RM, et al. Leprosy reactions: the predictive value of *Mycobacterium leprae*-specific serology evaluated in a Brazilian cohort of leprosy patients (U-MDT/CT-BR). *PLoS Negl Trop Dis.* 2017;11:e0005396.
49. Van Veen NH, Nicholls PG, Smith WC, Richardus JH. Corticosteroids for treating nerve damage in leprosy. *Cochrane Database Syst Rev.* 2016;CD005491.
50. Wagenaar I, Post E, Brandsma W, et al. Effectiveness of 32 versus 20 weeks of prednisolone in leprosy patients with recent nerve function impairment: a randomized controlled trial. *PLoS Negl Trop Dis.* 2017;11:e0005952.
51. Voorend CG, Post EB. A systematic review on the epidemiological data of erythema nodosum leprosum, a type 2 leprosy reaction. *PLoS Negl Trop Dis.* 2013;7:e2440.
52. Wankhade VH, Debnath P, Singh RP, et al. A retrospective study of the severe and uncommon variants of erythema nodosum leprosum at a tertiary health center in central India. *Int J Mycobacteriol.* 2019;8:29-34.
53. Walker SL, Sales AM, Butlin CR, et al. A leprosy clinical severity scale for erythema nodosum leprosum: an international, multicentre validation study of the ENLIST ENL Severity Scale. *PLoS Negl Trop Dis.* 2017;11:e0005716.
54. Walker SL, Lebas E, Doni SN, Lockwood DN, Lambert SM. The mortality associated with erythema nodosum leprosum in Ethiopia: a retrospective hospital-based study. *PLoS Negl Trop Dis.* 2014;8:e2690.
55. Ishii N, Ishida Y, Okano Y, et al. Japanese guideline on thalidomide usage in the management of erythema nodosum leprosum [in Japanese]. *Nihon Hansenbyo Gakkai Zasshi.* 2011;80:275-285.
56. Walker SL, Waters MF, Lockwood DN. The role of thalidomide in the management of erythema nodosum leprosum. *Lepr Rev.* 2007;78:197-215.
57. Hebe Petit-Martin G, Villar-Buill M, de la Hera I, et al. Deep vein thrombosis in a patient with lepromatous leprosy receiving thalidomide to treat leprosy reaction. *Actas Dermosifiliogr.* 2013;104:67-70.
58. US Food and Drug Administration website. Risk Evaluation and Mitigation Strategy for Thalomid. Summit, NJ: Celgene Corp. Available at: <https://www.fda.gov/media/79047/download>. Accessed April 13, 2020.
59. Nunzie E, Ortega Cabrera LV, Macanchi Moncayo FM, Ortega Espinosa PF, Clapasson A, Massone C. Lucio leprosy with Lucio's phenomenon, digital gangrene and anticardiolipin antibodies. *Lepr Rev.* 2014;85:194-200.
60. Jurado F, Rodriguez O, Novales J, Navarrete G, Rodriguez M. Lucio's leprosy: a clinical and therapeutic challenge. *Clin Dermatol.* 2015;33:66-78.
61. Rea TH, Jerskey RS. Clinical and histologic variations among thirty patients with Lucio's phenomenon and pure and primitive diffuse lepromatosis (Latapi's lepromatosis). *Int J Lepr Other Mycobact Dis.* 2005;73:169-188.
62. Han XY, Sizer KC, Tan HH. Identification of the leprosy agent *Mycobacterium lepromatosis* in Singapore. *J Drugs Dermatol.* 2012;11:168-172.
63. Gupta L, Zanwar A, Wakhlu A, Agarwal V. Leprosy in the rheumatology clinic: an update on this great mimic. *Int J Rheum Dis.* 2016;19:941-945.
64. Poojabylaiah M, Marne RB, Varikkodan R, Bala N, Dandakeri S, Martis J. Relapses in multibacillary leprosy patients after multidrug therapy. *Lepr Rev.* 2008;79:320-324.
65. World Health Organization. Global leprosy update, 2015: time for action, accountability and inclusion. *Wkly Epidemiol Rec.* 2016;91:405-420.
66. Becx-Bleumink M. Relapses among leprosy patients treated with multidrug therapy: experience in the leprosy control program of the All Africa Leprosy and Rehabilitation Training Center (ALERT) in Ethiopia; practical difficulties with diagnosing relapses; operational procedures and criteria for diagnosing relapses. *Int J Lepr Other Mycobact Dis.* 1992;60:421-435.
67. Boerriger G, Ponnighaus JM, Fine PE, Wilson RJ. Four-year follow-up results of a WHO-recommended multiple-drug regimen in paucibacillary leprosy patients in Malawi. *Int J Lepr Other Mycobact Dis.* 1991;59:255-261.
68. Risk of relapse in leprosy. The Leprosy Unit, WHO. *Indian J Lepr.* 1995;67:13-26.
69. Shen J, Yan L, Sun P. Clinical features of relapse after multidrug therapy for leprosy in China. *Lepr Rev.* 2015;86:165-169.
70. Shen J, Liu M, Zhang J, Su W, Ding G. Relapse in MB leprosy patients treated with 24 months of MDT in south west China: a short report. *Lepr Rev.* 2006;77:219-224.
71. Ali MK, Thorat DM, Subramanian M, Parthasarathy G, Selvaraj U, Prabhakar V. A study on trend of relapse in leprosy and factors influencing relapse. *Indian J Lepr.* 2005;77:105-115.
72. Kaimal S, Thappa DM. Relapse in leprosy. *Indian J Dermatol Venereol Leprol.* 2009;75:126-135.
73. Rodrigues LC, Lockwood D. Leprosy now: epidemiology, progress, challenges, and research gaps. *Lancet Infect Dis.* 2011;11:464-470.

74. Lira KB, Leite JJ, Maia DC, Freitas Rde M, Feijao AR. Knowledge of the patients regarding leprosy and adherence to treatment. *Braz J Infect Dis.* 2012;16:472-475.
75. Kar S, Pal R, Bharati DR. Understanding non-compliance with WHO-multidrug therapy among leprosy patients in Assam, India. *J Neurosci Rural Pract.* 2010;1:9-13.
76. Naaz F, Mohanty PS, Bansal AK, Kumar D, Gupta UD. Challenges beyond elimination in leprosy. *Int J Mycobacteriol.* 2017;6:222-228.
77. Rao PN. Global leprosy strategy 2016-2020: issues and concerns. *Indian J Dermatol Venereol Leprol.* 2017;83:4-6.
78. Richardus JH. Leprosy remains an important public health challenge in India. *Indian J Med Res.* 2013;137:878-879.
79. Mathers CD, Ezzati M, Lopez AD. Measuring the burden of neglected tropical diseases: the global burden of disease framework. *PLoS Negl Trop Dis.* 2007;1:e114.
80. Moet FJ, Pahan D, Oskam L, Richardus JH, COLEP Study Group. Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. *BMJ.* 2008;336:761-764.
81. Idema WJ, Majer IM, Pahan D, Oskam L, Polinder S, Richardus JH. Cost-effectiveness of a chemoprophylactic intervention with single dose rifampicin in contacts of new leprosy patients. *PLoS Negl Trop Dis.* 2010;4:e874.
82. Feenstra SG, Pahan D, Moet FJ, Oskam L, Richardus JH. Patient-related factors predicting the effectiveness of rifampicin chemoprophylaxis in contacts: 6 year follow up of the COLEP cohort in Bangladesh. *Lepr Rev.* 2012;83:292-304.
83. Moet FJ, Pahan D, Oskam L, Richardus JH. Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. *BMJ.* 2008;336:761-764.
84. Lockwood DNJ, Krishnamurthy P, Kumar B, Penna G. Single-dose rifampicin chemoprophylaxis protects those who need it least and is not a cost-effective intervention. *PLoS Negl Trop Dis.* 2018;12:e0006403.
85. Neelan P, Noordeen S, Sivaprasad N. Chemoprophylaxis against leprosy with acedapsone. *Indian J Med Res.* 1983;78:307-313.
86. Neelan PN, Sirumban P, Sivaprasad N. Limited duration acedapsone prophylaxis in leprosy. *Indian J Lepr.* 1986;58:251-256.
87. Richardus JH, Oskam L. Protecting people against leprosy: chemoprophylaxis and immunoprophylaxis. *Clin Dermatol.* 2015;33:19-25.
88. Zodpey S, Ambadekar N, Thakur A. Effectiveness of Bacillus Calmette-Guérin (BCG) vaccination in the prevention of leprosy: a population-based case-control study in Yavatmal District, India. *Public Health.* 2005;119:209-216.
89. Zodpey S, Bansod B, Shrikhande S, Maldhere B, Kulkarni S. Protective effect of Bacillus Calmette Guerin (BCG) against leprosy: a population-based case-control study in Nagpur, India. *Lepr Rev.* 1999;70:287-294.
90. Rodrigues LC, Kerr-Pontes LRS, Frietas MVC, Barreto ML. Long lasting BCG protection against leprosy. *Vaccine.* 2007;25:6842-6844.
91. Setia MS, Steinmaus C, Ho CS, Rutherford GW. The role of BCG in prevention of leprosy: a meta-analysis. *Lancet Infect Dis.* 2006;6:162-170.
92. Merle CS, Cunha SS, Rodrigues LC. BCG vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control. *Expert Rev Vaccines.* 2010;9:209-222.
93. Richardus JH, Oskam L. Protecting people against leprosy: chemoprophylaxis and immunoprophylaxis. *Clin Dermatol.* 2015;33:19-25.
94. World Health Organization. BCG vaccine: WHO position paper, February 2018 - Recommendations. *Vaccine.* 2018;36:3408-3410.
95. Duthie MS, Pena MT, Ebenezer GJ, et al. LepVax, a defined subunit vaccine that provides effective pre-exposure and post-exposure prophylaxis of *M. leprae* infection. *NPJ Vaccines.* 2018;3:12.



Cosmetic treatment in patients with autoimmune connective tissue diseases

Best practices for patients with morphea/systemic sclerosis

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Learning objectives

After completing this learning objective, the reader will be able to better discuss cutaneous manifestations of chronic cutaneous lupus erythematosus, specifically discoid, panniculitis, profundus and tumidus and review the physiological and psychological burden of these diseases; identify and compare different laser treatments, injectables, and surgical options for cutaneous deficits attributable to these diseases; and recognize how to minimize side effects when performing cosmetic procedures on this special patient population.

Disclosures

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Morphea and systemic sclerosis are inflammatory, sclerosing disorders. Morphea primarily affects the dermis and subcutaneous fat, while systemic sclerosis typically involves the skin and internal organs. Functional impairment and cosmetic disfigurement are common in both diseases. Treatment options to mitigate disease progression remain limited. Both functional impairment and cosmetic deficits negatively impact quality of life and psychological well-being in this patient population. While the number of cosmetic procedures performed in the United States continues to rise each year, limited data exist regarding best practices for correcting aesthetic deficits caused by autoimmune conditions. There is scarce information to guide safety decisions regarding laser parameters, soft tissue augmentation, treatment intervals, and the concurrent use of immune-modifying or immune-suppressing medications. Given the fears of disease reactivation and exacerbation from postprocedural inflammation along with limited data, it is difficult for clinicians to provide evidence-based cosmetic treatment with realistic expectations with regard to short- and long-term outcomes. In the first article in this continuing medical education series, we attempt to address this practice gap. (J Am Acad Dermatol 2020;83:315-41.)

Key words: calcium hydroxyapatite; fat transfer; hyaluronic acid; injectables; intense pulsed light; mental health; morphea; poly-L-lactic acid; polymethylmethacrylate; pulsed dye laser; quality of life; systemic sclerosis.

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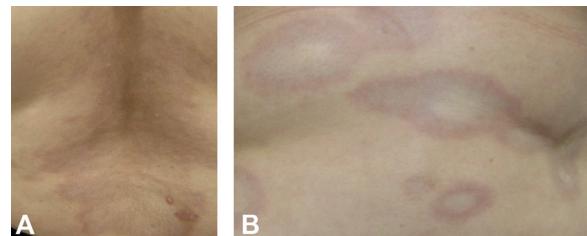
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Abbreviations used:

ECDS:	en coup de sabre
HA:	hyaluronic acid
IPL:	intense pulsed light
MDD:	major depressive disorder
MHSS:	Mouth Handicap in Systemic Sclerosis
PDL:	pulsed dye laser
PRS:	Parry–Romberg syndrome
QoL:	quality of life
SSc:	systemic sclerosis

**Fig 1.** Plaque type morphea.**EPIDEMIOLOGY AND OVERVIEW OF MORPHEA/SYSTEMIC SCLEROSIS SUBTYPES****Key points**

- Clinical findings of morphea include sclerotic plaques and possible involvement of fat and bone
- Cutaneous findings of systemic sclerosis include taut skin, sclerodactyly, microstomia, dyspigmentation, telangiectasia, calcinosis cutis, and cutaneous ulcers

Morphea and systemic sclerosis are inflammatory, sclerosing disorders. Morphea primarily affects the dermis and subcutaneous fat, while systemic sclerosis (SSc) typically involves the skin and internal organs. Functional impairment and cosmetic disfigurement are common in both diseases. Treatment options to mitigate disease progression remain limited.^{1,2} Both functional impairment and cosmetic deficits negatively impact quality of life and psychological well-being in this patient population.

Morphea

Morphea is divided into several subtypes and typically evolves from an early inflammatory phase to skin sclerosis and subsequent atrophy.^{3–6} Between 1960 and 1993, the annual incidence of morphea was 2.7 per 100,000 people, with 56%, 20%, 13%, and 11% having plaque-type, linear, generalized, and deep morphea, respectively.⁷

Plaque (or circumscribed) morphea. Plaque (or circumscribed) morphea is the most common variant of morphea and typically presents as an erythematous or hyperpigmented plaque. With time, the plaque center becomes sclerotic and centrifugally expands⁶ (Fig 1).

Linear morphea and Parry–Romberg syndrome. Linear morphea is characterized by sclerotic plaques in a linear distribution. Morphea en coup de sabre (ECDS) is a type of linear morphea that involves the head and scalp. Some include Parry–Romberg syndrome (PRS) or progressive hemifacial atrophy, a condition characterized by unilateral atrophy of the skin, soft tissues, and

**Fig 2.** Scleroderma-associated dyspigmentation. **A**, Leukoderma (or “salt and pepper” pigmentation) of scleroderma on lateral neck of patient with Fitzpatrick skin phototype V to VI. **B**, Close-up of leukoderma of scleroderma of patient with Fitzpatrick skin phototype V to VI skin.

underlying structures, as a variant of linear morphea.⁶

Generalized morphea. The generalized morphea subtype is defined as ≥ 4 morphea plaques occurring over ≥ 2 anatomic sites. Generalized morphea can be distinguished from SSc due to lack of

Table I. Pulsed dye laser for morphea and systemic sclerosis

Authors/ Study type	N	Disease	Age/ skin type	Treatment/ location	Settings	Cooling/ postoperatively	Sessions/ interval	Perioperative medication	Results	Follow-up	Side effects
Eisen and Alster ⁹² case report	1	Plaque type morphea	41	Long pulse PDL to submandibular area	Wavelength: 585 nm, power/ fluence: 5 J/cm ² , pulse size: 1.5 ms, spot size: 10 mm	Dynamic epidermal cooling	4 at 2- month intervals	NR	Subjective improvement after each session with improved pliability and skin coloration	6 months	None
Ciatti et al ⁹³ case series	8	Scleroderma telangiectasia	36-71, disease duration of 3-20 years	PDL of face and neck	Wavelength: 585 nm, power/ fluence: 5-7 J/cm ² , pulse size: 0.45 ms, spot size: 5 mm	NR	1-4 sessions, NR interval NR	NR	Subjective efficacy, no evidence of adverse effect on disease progression	6 months- 2 years	Purpura lasting 7-10 days
Dinsdale et al ²⁵ RCT	19	SSc (limited n = 17, diffuse n = 2)	49-72, disease duration 2-31 years (mean 14)	PDL and IPL on face and upper limbs	PDL settings wavelength: 595 nm, power/ fluence: 9 J, pulse: 1.5 ms, spot size: 7 mm	Integrated cooling spray, 30 ms duration, 20-ms delay for pulse	3 (plus 1 spot test), 4-week interval	NR	PDL had greater improvement than IPL at week 16 for photographs and dermoscopy; no difference in red or green laser Doppler imaging between PDL/IPL at any time; more patients preferred PDL	8 weeks - 7 months from last session	Transient bruising
Halachmi et al ²⁶ retrospective case control study	16	Scleroderma or CREST (n = 16), control group (n = 20)	21-67 (mean 37.4 years) Fitzpatrick skin phototypes II-IV	PDL on nose, neck, chest, and cheeks	Wavelength: 585 nm, power/ fluence: 5.5-7 J/cm ² , single pulse of 0.45 ms,	External cooling device	1-8, interval NR	NR	1.92 sessions needed for control group, 3.24 sessions needed for experimental group; all	NR	NR

Continued

Authors/ Study type	N	Disease	Age/ skin type	Treatment/ location	Cooling/ postoperatively	Sessions/ interval	Perioperative medication	Results	Follow-up	Side effects	
				spot size: 5-7 mm				patients had 95% clearance; no significant association between outcome, energy fluence, anatomic site, age, or gender; lesion size was significant for no. of treatments needed			

CREST, Calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; PDL, pulsed dye laser; IPL, intense pulsed light; NR, not reported; SSc systemic sclerosis, RCT, randomized controlled trial.

hand involvement, absence of the Raynaud phenomenon, and early truncal lesions.⁶

Uncommon variants of morphea. Uncommon morphea variants include guttate morphea, atrophoderma of Pasini and Pierini, deep morphea, and keloidal morphea.⁶

Systemic sclerosis (limited and diffuse)

The annual incidence and prevalence of SSc in the United States is approximately 20 and 275 cases per million, respectively.³ The differentiation between limited and diffuse SSc depends upon the degree of skin involvement. Limited SSc involves the distal extremities and the face, while diffuse SSc involves both distal and proximal extremities, the trunk, and the face.⁸ Both subtypes may involve internal organs, most frequently the lungs, joints, and gastrointestinal tract. Cutaneous involvement typically begins with an edematous phase followed by sclerosis and then gradual atrophy. Other cutaneous features of both include microstomia, dyspigmentation (Fig 2), and telangiectasia. End-stage SSc of the fingers can result in contracted fingers, often with distal ulcerations and autoamputations and occasionally calcinosis.⁴ According to the 2013 American College of Rheumatology Classification Criteria for SSc, thickening of the skin on the fingers of both hands extending proximal to the metacarpophalangeal joints is sufficient for a patient to be classified as having SSc irrespective of truncal lesions.⁹

IMPACT ON QUALITY OF LIFE AND PSYCHOLOGICAL WELL-BEING

Key points

- Systemic sclerosis/morphea may have a mild to severe impact on quality of life
- Major depressive disorder is common in patients with SSc and the prevalence varies among studies

Mental health

Both SSc and morphea may impact quality of life (QoL) in several ways, including physical symptoms, such as pain, pruritus, sensation of skin tightening, fatigue, myalgias, and arthralgias. Mobility limitations, cosmetic appearance, sleep disturbances, and impaired sexual function may also occur, leading to social and emotional distress.¹⁰⁻¹² There are limited data in the published literature, however, related to the specific impact of cosmetic disfigurement on QoL in these patients.

Of the instruments used to measure QoL in patients with morphea, both the Dermatology Quality of Life Index and Skindex-29¹³ are examples

Table II. Intense pulsed light therapy for morphea and systemic sclerosis

Authors/ study type	N	Disease	Age/ skin type	Treatment/ location	Settings	Cooling/ postoperative	Sessions/ interval	Perioperative medication	Results	Follow-up	Side effects
Comstedt et al, ³⁰ 2012 case series	4	SSc with microstomia	37-61, diagnosed 10-17 years earlier	IPL to perioral and cheeks	Wavelength: 530-570 nm? power/ fluence: 11-14 J/cm ² ; pulse size: 10-14 pulse durations	NR	3-6 at 4-week intervals	None	Oral opening increased 1 mm per treatment; patients described subjective softening of skin and easier speaking, eating, and tooth brushing	4 months	Transient moderate erythema and edema
Onesti et al, ²⁷ 2009 case report	1	PRS	40, disease duration 19 years	Customized PLLA filler, lipofilling, and IPL to face	NR		3, interval NR	NR	Subjective improvement of hyperpigmentation, flattening of skin lesions, patient satisfied	12 months	NR
Dinsdale et al, ²⁵ 2014 randomized within- subject trial	19	SSc (limited n = 17, diffuse duration n = 2)	49-72, disease duration 2-31 years (mean 14)	PDL and IPL on face and upper limbs	IPL settings: wavelength: 550-1100 nm; power/ fluence: 28-30 J/cm ² ; each pulse had 2 shots with 20-ms delay	Delivered through US gel, postoperative cooling with water	3 (plus 1 spot test), 4-week interval	NR	PDL had greater improvement than IPL at week 16 for photographs and dermoscopy; no difference in red or green LDI between PDL/IPL at any time, and more patients preferred PDL	8 weeks-7 months from last session	None
Murray et al, ²⁸ 2012 open study	17	SSc limited and diffuse	37-69 (median 58) Fitzpatrick types: I (n = 12), II (n = 7)	IPL to cheek, forehead, upper arm, and hand	Wavelength: 550-1100 nm, peak of 585 nm; power/ fluence: 24-36 J/cm ² depending on skin type; pulse size:	Ice water before and after treatment for 5 min, IPL delivered through US gel	3 (plus 1 spot test), 1 month interval	NR	6-month images graded “no change” (n = 4), “improved” (n = 8), or “much improved” (n = 4); significant decrease in perfusion measured with LDI compared	6-12 months after last session	Facial edema, transient hyperpigmentation in Fitzpatrick IV patient (withdrew from study), blistering on dorsal surface of hand after

Continued

Table II. Cont'd

Authors/ study type	N	Disease	Age/ skin type	Treatment/ location	Settings	Cooling/ postoperative interval	Sessions/ medication	Results	Follow-up	Side effects
					2–6 ms duration, 10–30 ms delay	with baseline at 1- and 6-month follow-ups, but not at 12 months; improvement not maintained in all patients, suggesting need for further treatments		with baseline at third session (n = 1)		

IPL, Intense pulsed light; LDI, laser Doppler imaging; NR, not reported; PDL, pulsed dye laser; PLLA, poly-L-lactic acid; PRS, Parry–Romberg syndrome; RCT, randomized controlled trial; SSc, systemic sclerosis; US, ultrasound.

of skin-specific health-related QoL questionnaires. The short-form health survey is an instrument used to measure general health-related QoL.¹⁴ The Localized Scleroderma Assessment Tool is a morphea-specific questionnaire comprised of 2 domains, a modified localized skin severity index and the localized scleroderma damage index.¹⁵ Both tools are commonly used to measure disease severity. Factors demonstrated to have the greatest impact on QoL include disease severity, female sex, adult patients,¹⁶ generalized disease,¹³ being on systemic therapy, and hand and foot involvement.¹⁰ Although patients with linear morphea reported a mild effect on QoL, about one-third of patients reported physical limitations that might not have been captured by the QoL tool used.¹⁷ A retrospective study evaluating the QoL in a small cohort of adolescents with PRS reported a negative impact on QoL, especially within the appearance and emotional subscales. After surgical intervention, 80% of patients were extremely to somewhat satisfied with the surgical outcome and would consider another intervention or recommend surgery to those with a similar condition.¹⁸

The prevalence of major depressive disorder (MDD) in patients with SSc varies with the population studied, the questionnaire score used, and disease duration, ranging from 4% to 65%,^{19,20} and appears to be higher in patients who are hospitalized.²¹ A Russian study reported a much higher prevalence (83%) of mental disorders among patients with SSc, including MDD (67.3%), dysthymia (30%), and recurrent depressive disorder (31%).²² While most patients are diagnosed with mild MDD and have episodes of low mood that may not require treatment, active monitoring is recommended.²³ Moreover, the unpredictable course of SSc and fear of disease progression may generate anxiety disorders.¹¹ Access to and management of health care resources may be an additional source of stress for patients with SSc because of diagnosis delays, multiple referrals, insurance coverage, and treatment cost.²⁴

USE OF LASER AND LIGHT-BASED THERAPY

Key points

- Pulsed dye laser and intense pulsed light have been used to treat telangiectasias of morphea and systemic sclerosis, which may require more treatment sessions compared with nondisease telangiectasias
- Objective functional improvements have been reported after treatment with IPL and CO₂ laser for microstomia and joint contractures

Table III. Ablative and nonablative laser treatment for morphea and systemic sclerosis

Authors/ study type	N	Disease	Age/skin type	Treatment/ location	Settings	Cooling/ postoperative	Sessions/ interval	Perioperative medication	Results	Follow-up	Side effects
Kineston et al, ³³ 2011 case study	1	Generalized morphea	27	CO ₂ laser on leg	Wavelength: 10.6 μm; density: 5%; power/fluence: 50 mJ pulse; single pulse; pass/overlap: single pass, no overlap	Forced cooling system/dilute vinegar compresses BID and petrolatum TID	1	MTX 20 mg/week, topical calcipotriene 0.005% BID, introlesional triamcinolone acetone, UVA1 phototherapy	Regained full plantar flexion of foot, decreased pain	1 year	None
Bottomley et al, ³⁶ 1996 case series	6	Digital calcinosis of SSc	36-78, disease duration of 4-10 years	CO ₂ laser on fingers	Power/fluence: 7.5-10 W; continuous wave mode; spot size: 1 mm	NR	1	None	Improvement seen 8-16 weeks postoperatively. Of 21 calcinoses treated, complete resolution in 12, partial improvement in pain in 5, no improvement of pain in 2. Calcinosis recurred within 3-4 months in 2 lesions. Overall, 3 patients had good response, 2 moderate, and 1 had no response	Median: 20 months	Postoperative infection in 2 patients 2 weeks after, treated with erythromycin (moderate results in both patients); mean healing time 4- 10 weeks. 4 lesions had residual hyperkeratosis, remaining 17 had good cosmetic result
Chamberlain and Walker, ³⁷ 2003 case report	1	Limited scleroderma	40	CO ₂ laser on fingers	Power/fluence: 13-16 W, 3 mm scan; paint mode; spot size: 125 mm	NR	6 sessions over 5 years	NR	Subjective significant remission	3 years	6-week healing time
Apfelberg et al, ³⁸ 1998 case series	3	Generalized systemic scleroderma	60-66, disease duration 5-30 years	CO ₂ laser on perioral rhytides	Power/fluence: 300 mJ/60 W; pass/overlap: 3 full passes + 2 passes over raised "shoulders," 30% overlap	Dilute vinegar soaks 5-6 times/ day starting postoperative day 3	1	Prophylactic antiviral agents 2 days before treatment, continued until epithelialization complete	Subjective satisfactory wound healing with cosmetic improvement	12-18 months	None; epithelialization complete in 7- 10 days, erythema for 8-10 weeks
Bennani et al, ³² 2016 case series	4	Diffuse SSc (n = 2), sclero-myositis (n = 1), CREST (n = 1)	43-63, sclerosis present for ≥5 years	Pulsed CO ₂ Laser on peri- oral area	125 mm hand piece Power/Fluence: 7W Pulse: 0.39 ms Spot size: 5 mm Pass/overlap: 2-3 passes until contraction of dermis, no overlapping	2% sodium fusidate ointment and petroleum jelly TID without dressing	1-3 sessions, 8- to 12-month intervals	Hydroxychloroquine 200 mg/day (n = 1), CCBs, PPIs, and pulmonary HPTN drugs for other symptoms	Mean interincisor distance gain: 8.5 mm (37% improvement, range 7-10 mm), mean MHSIS decrease: 14 points (11-17); no change in modified Rodnan skin score	12 months	Transient erythema (15 days resolved) and dyschromia (90 days resolved)

Continued

Table III. Cont'd

Authors/ study type	N	Disease	Age/skin type	Treatment/ location	Settings	Cooling/ postoperative	Sessions/ interval	Perioperative medication	Results	Follow-up	Side effects
St Surin-Lord and Obagi, ⁹⁴ 2011 case report	1	Scleroderma, polymyositis and lupus	35	High peak power Nd:YAG on hand ulcers from Raynaud's	Wavelength: 1064 nm; power/fluence: 10-15 J/cm ² ; pulse size: 0.3 ms pulse width at 10 Hz; spot size: 5 mm; 5k-7k pulses/session	No cooling	11 sessions, 2-week intervals	NR	Patient reported satisfaction, ability to close hand, fewer Raynaud's attacks, and improved nail growth	NR	NR
Shalaby et al, ³⁵ 2016 RCT intraindividual parallel study	21	Plaque (n = 12) and linear (n = 3) morphea, ECDS (n = 2)	7-47 years with disease duration 6-96 months, active disease in n = 7, Fitzpatrick type: III (n = 10) and IV (n = 7)	CO ₂ laser vs. UVA1 phototherapy (each patient had ≥2 similar lesions that were randomized to 1 of the 2 treatments)	Power: 25 W; stack 2 dwelling time: 500 msec; spacing: 500 μm	NR	3 sessions with 1-month interval	None	Significantly improved LoSCAT score in CO ₂ arm (2.65) compared with UVA1 arm (4.24), significantly higher patient satisfaction score in CO ₂ arm (2.24) compared to UVA1 arm (1.12), significantly better collagen homogenization scores on histopathologic examination in CO ₂ arm	Hyperpigmentation (n = 1), persistent erythema (n = 1), mild-moderate (n = 17) and marked (n = 10) pain	
Chodkiewicz et al, ⁹⁵ 2018 case report	1	Diffuse systemic scleroderma	42	Nd:YAG endovascular ablation to leg ulcer followed by sclerotherapy	Wavelength: 1320 nm; power: 6 W; frequency: 50 Hz	20-30 mm Hg compression stockings all day for 3 days, waking hours for following 7 days	1 session	NR	Resolution of ulcer	12 months	None

BID, Bis in die; CCB, calcium channel blocker; CREST, calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; ECDS, en coup de sabre; HPTN, hypertension; LDI, laser Doppler imaging; LoSCAT, Localized Scleroderma Assessment Tool; MHISS, Mouth Handicap in Systemic Sclerosis; MTX, methotrexate; Nd:YAG, neodymium-doped yttrium aluminum garnet; NR, not reported; PPI, proton pump inhibitor; RCT, randomized controlled trial; SSc, systemic sclerosis; TID, ter in die; US, ultrasound; UVA1, ultraviolet A1 light phototherapy.

Table IV. Strength of recommendations for laser treatment for morphea and systemic sclerosis

Recommendation	Recommendation no.	Level of evidence	Studies
Treatment of telangiectasias in this patient population may require more treatment sessions compared with nondisease telangiectasias	1.1	IIB	Halachmi et al ²⁶
For treatment of telangiectasias in patients with systemic sclerosis, patients may prefer the outcomes of PDL compared with IPL	1.2	IIB	Dinsdale et al ²⁵
IPL can be used to treat morphea- or systemic sclerosis –associated microstomia	1.3	III	Comstedt et al ³⁰
CO ₂ laser can be used to treat morphea-related Heel contractures	1.4	III	Kineston et al ³³
Digital calcinoses	1.5	III	Bottomley et al ³⁶ and Chamberlain and Walker ³⁷
Perioral rhytids and microstomia	1.6	III	Bennani et al ³² and Apfelberg et al ³⁸
Plaque, linear, and ECDS morphea	1.7	IB	Shalaby et al ³⁵

Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥ 1 randomized controlled trial; level IIA evidence includes evidence from ≥ 1 controlled study without randomization; level IIB evidence includes evidence from ≥ 1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

ECDS, En coup de sabre; IPL, intense pulsed light; PDL, pulsed dye laser.

Pulsed dye laser (PDL), via its targeted photothermolysis of hemoglobin, is an effective treatment for vascular lesions like port wine stains, hemangiomas, and telangiectasias, with potential side effects including pain, bruising, edema, hypopigmentation, and scarring.²⁵ The telangiectasias of SSc have been described as treatment resistant, perhaps because of the thicker capillary walls associated with collagen vascular diseases.²⁶ This theory is supported by a small-scale retrospective study showing that, regardless of size, 1.92 (range 1-5) PDL sessions were needed to treat the control group's telangiectasias compared with 3.24 (range 1-8) sessions that were needed to treat telangiectasias in patients with SSc.²⁶

In addition to PDL, intense pulsed light (IPL) therapy can be used to treat telangiectasias via broad spectrum light that induces vessel coagulation through evenly distributed heat energy to capillary walls (Tables I and II).^{25,27,28} A randomized split-face trial comparing PDL and IPL for treatment of telangiectasias in patients with SSc found that 50% of patients ($n = 8$) preferred the results of PDL treatment at 16 weeks of follow-up compared with 25% ($n = 4$) that preferred IPL results.²⁵

In addition to telangiectasia treatment, IPL can induce collagen formation, which has been used in the treatment of microstomia.²⁹ Treatment of the perioral region with IPL has led to objective improvement in oral opening and subjective improvement in ease of speaking, eating, and tooth brushing.³⁰

Microstomia can also be improved with mouth opening and elongation exercises; however, improvement is typically lost upon discontinuation of these exercises.³¹

Fractional³² and fully ablative lasers can be used to treat skin fibrosis associated with morphea and SSc (Table III). It has been postulated that immediate improvement after treatment is related to mechanical loosening of sclerotic tissue,³³ with delayed improvements arising from tissue response and upregulation of growth factors and cytokines that modulate healing.^{34,35} CO₂ laser has been used to treat morphea-related heel contractures,³³ digital calcinoses,^{36,37} and perioral rhytids^{32,38} with good improvement. A randomized study showed CO₂ laser to be superior to phototherapy for various morphea types, including active disease.³⁵ A summary of treatment recommendations is provided in Table IV.

INJECTABLES

Key points

- Skin fibrosis in morphea and systemic sclerosis can create difficulty with initial injections but appears to improve over subsequent sessions
- Although there are no documented cases of disease reactivation of stable morphea after injectable treatment, caution should still be taken because most patients described in the published literature had reportedly inactive disease

Table V. Fat transfer for morphea and systemic sclerosis

Authors/ study type	N	Age	Disease	Treatment	Location/amount	Sessions/ interval	Perioperative medication	Result	Side effects	Follow- up	
Zanelato et al, ⁹⁶ 2013 case report	4	17-26	PRS	Fat transfer	Chin/NR	1 session	NR	Immediate subjective improvement	No one experienced hematomas	>1 year	
Roh et al, ⁸¹ 2008 retrospective review	20	Age at procedure: 10-55 (mean: 26.3), disease duration: 1-15 (mean: 6.8 years), all disease was clinically inactive	LS	Fat transfer	Forehead, chin, infraorbital, nose; injected in multiple planes until slight over correction	2-11 (mean 4.2) with 3-month intervals	NR	51-75% subjective improvement of forehead, <25% improvement chin, fair correction infraorbital, poor correction nose; no changes in hyper- or hypopigmentation or telangiectasias	Minimal bruising, pain, edema, and erythema for <72 hours	12-94 months (age 43)	
Oh et al, ⁹⁷ 2003 case report	1	21 at procedure, 6-year disease history, 2 years stable	Trilinear scleroderma ECDS	Autologous "tissue cocktail"	Forehead, overcorrected until convex	1 session	NR	Excellent cosmetic results; almost level with surrounding tissue, hyperpigmentation disappeared	None	14 months	
Sautereau et al, ⁵⁹ 2016 longitudinal open label study	14	Mean age 53.8 at procedure, mean disease duration 9.4 years	SSc, 6 limited, 8 diffuse	Microfat grafting	Face, mouth; mean: 16.3 mL, median was 17 mL	1 session	Steroids <10 mg/day (n = 3), mycophenolae mofetil (n = 1), mycophenolae mofetil + steroid <10 mg/day (n = 1), methotrexate (n = 1), methotrexate + steroid <10 mg/day (n = 1)	Improvement in mouth pain, oral opening, and sicca; 75% of patients satisfied or very satisfied; mean 34.6% MHSS improvement from baseline at 6 months; 79.5% and 65.3% improvement of skin sclerosis at 3 and 6 months, respectively; no correlation between improvement and amount of injected fat	Harvest site bruising (n = 8)	6 months, and pain (n = 3); injection site bruising (n = 3), pain (n = 3), perioral sensitive manifestation (n = 1), and trigeminal neuralgia (n = 1), all mild and spontaneously resolved in a few days	1 patient refused, 1 died of unrelated cause
Gheisari et al, ⁴⁵ 2018 open label study	16	29-54 at procedure, disease duration 4-10 years	SSc, 6 limited, 10 diffuse	Autologous fat transfer; Coleman technique but gravity separation	Face, mouth: 15-40 mL	NR	Taking prednisolone >10 mg/d was exclusion criteria	62.5% patients very satisfied, 12.5% somewhat satisfied, 18.75% unsatisfied due to total resorption at 3 months but maintained improvements in mouth opening and function; improvements on MHSS (-6.12) and Rodnan (-0.5) scores; no significant change in Cutaneous Resonance Running Time value	Bruising at harvest site reported by 10 patients, spontaneously resolved within 2 weeks	3 months	
Del Papa et al, ⁹⁸ 2015 prospective study	20	Median age 36.5 years and median 8 years of disease duration	Diffuse SSc	Autologous fat transfer; Coleman technique	8 different perioral areas; 2 mL per site, mean 16 mL total	1 session	None for 3 months prior	Increased inter-incisal distance (mean increase 2.63 mm at 3 months), oral perimeter (9.2 mm at 3 months), and neovascularization; 80% very satisfied, 20% rather satisfied; partial restoration of skin structure based off	Small ecchymosis that resolved in 2 weeks	3 months	

Lauzer et al. ⁹⁹ 2011 retrospective cohort	2	Mean age 38	PRS	Coleman technique fat graft	NR	Mean 1.6 sessions, interval NR	NR	14 months					
Hammer-Hansen et al. ¹⁰⁰ 2015 case report	1	9	LS	Fat transfer, Coleman technique	Face, 14, 22, 36 mL per session respectively	3, interval NR	NR	22 months	Partial necrosis of tip of nose, unclear if this occurred in either of the PRS patients				
Hunstad et al. ¹⁰¹ 2011 case report	1	9, disease active stage	PRS	Coleman technique microfat grafting	Malar, mandible, chin: 13 mL total	1 session	NR	4 years	Patient underwent a growth spurt with significant weight gain and grafted areas became very hypertrophic and had to be reduced by liposuction				
Lauzer et al. ¹⁰² 2010 case report	1	15	PRS	Structural fat grafting with PLLA revision	Cheek, chin: 30-75 mL per session	5 sessions over 3-year period	NR	3 years from first procedure	Stable results at 2-month follow-up except parasympathetic prejowl region which was going to require additional treatments; disease process halted after treatment	NR			
Avelar et al. ¹⁰³ 2010 case report	1	42 at procedure, PRS started at 23, inactive since 30	PRS	Autologous fat transplant + auricular cartilage graft to chin	First session: 30 mL buccal, 20 mL zygomatic, 15 mL preauricular, 10 mL oral rim, 10 mL mentum; second session: 35 mL buccal, 15 mL zygomatic, 10 mL preauricular expected small degree of resorption	2- with 6-month interval	NR	18 months since first procedure	After first procedure, gradual atrophy recurrence over frontal bone; complete patient satisfaction 15 months after second procedure	Subjective facial symmetry after second procedure	NR		
Suárez-Rodríguez et al. ¹⁰⁴ 2007 case series	4	20-40	PRS	Lipoinjection	Face, 10-60 mL per session	1-4 sessions with 6- to 12-month intervals	NR	6 months- 8 years	Subjective excellent aesthetic improvement	NR			
Sterodims et al. ¹⁰⁵ 2009 case report	1	26 at procedure, disease stable for 8 years	PRS	Autologous fat transfer	Zygomatic, pre-auricular, buccal, mandible, mentum: 155 mL	1 session	NR	13 months	Subjective symmetry, some absorption noted at 13 months; patient declined additional procedure	Swelling resolved in 1 week	None		
Jiang et al. ¹⁰⁶ 2016 case series	27	16-31 at procedure, mean age of onset: 10.1, mean duration of atrophy: 7.2	PRS	Fat transfer	Face: mean total: 133.61 mm ³ ; did not overcorrect to avoid oil cysts and necrosis	2-5 sessions (mean 3.1), interval NR	NR	12-15 months (mean 13.6)	Mean satisfaction score: immediate postoperatively = 4.3, 3 months postoperatively = 4.1, 12 months postoperatively = 4.0; mean fat absorption ratio was 72.9%				

Continued

Table V. Cont'd

Authors/ study type	N	Age	Disease	Treatment	Location/amount	Sessions/ interval	Perioperative medication	Result	Side effects	Follow- up
Jiang et al, ⁴² 2016 retrospective study	13	Mean 33	PRS	3L3M fat transfer	Face: means: 30.3 mL first session, 23.2 mL second session	2 sessions, 6-month (n = 12) or 1 year (n = 1) intervals	NR	measured by 3D laser technology Significant increase in patient (3.8-4.6) and surgeon satisfaction scores after second treatment compared with first; with 3D laser scan, first graft survival 43.3%, second graft survival 75.1%, despite no significant difference in injected volume	None	3 months
Alencar et al, ¹⁰⁴ 2011 case report	1	38 at procedure with active disease, 15 at disease presentation	PRS	Autologous fat graft	Face, 50 mL per session	2 with 2-month interval	NR	High subjective patient satisfaction	NR	6 months
Consorti et al, ¹⁰⁵ 2012 case report	1	34	ECDS	Autologous fat graft	Forehead: session amounts: first: 39 mL, second: 30 mL, third: 40 mL	3, interval NR	NR	Subjective improvement in frontoorbital symmetry, morphology, and tissue atrophy and texture	NR	2 years
Magalon et al, ⁵⁰ 2015 case report	1	57	SSc	Autologous fat graft	Perioral: 19.8 mL	1 session	Low-dose steroids, methotrexate, folic acid, nifedipine, bosentan, and esomeprazole and emollient creams BID	MHIS: 36 to 23; xerostomia inventory index 52 to 44; sugar test 4:00 to 2:54; mouth opening 25 to 35 mm	None	6 months
Ho-Asjoe et al, ¹⁰⁶ 1996 case report	1	41	SSc	Autologous fat graft + free dermal graft	Fat graft: naso-labial fold; dermal graft: vermillion border; amount NR	1 session	NR	Subjective patient satisfaction	NR	6 weeks
Palmero et al, ¹⁸ 2010 retrospective chart review	17	Mean 15 at procedure, mean 6.14 years from diagnosis	12 ECDS, 5 PRS	Fat injection (ECDS 9, PRS 5), poly-ethylene implant (ECDS 6, PRS 2), bone paste cranioplasty (ECDS 2, PRS 2), scar revision (ECDS 3, PRS 1), groin flap (ECDS 2), rhinoplasty (ECDS 1, PRS 1), canthoplasty (PRS 2)	NR	1-4, interval NR	Calcipotriol (n = 3), MTX (n = 6), pulse steroids (n = 1), oral steroids (n = 3), topical steroids (n = 1), topical Vitamin A (n = 2), mycofenolate (n = 1), IVIG (n = 1)	1/10 "Extremely satisfied," 4/10 "very satisfied," 3/10 "somewhat satisfied," 1/10 "not too satisfied," 1/10 "not at all satisfied"	Fat necrosis (1, ECDS)	1-9 years
Longobardi et al, ¹⁰⁷ 2011 case report	1	Presented at 23, remission at 41, procedure at 50	PRS	Autologous fat graft + facial rejuvenation (rhytidectomy)	40 mL total, 5 mL buccal, 10 mL zygomatic, 10 mL preauricular, 5 mL orbital rim, 10 mL mental	1 session	NR	Excellent subjective results with no additional transplant necessary	NR	4 years
Slack et al, ⁶² 2013 retrospective controlled study	42	NR	PRS	Autologous fat transfer (most patients had received additional surgical interventions)	Face: mean volume was 48 ± 3.3 mL per session; and a mean total volume was	Means: mild disease 1.8, moderate: 3.4, severe: 5.2, overall:	NR	3D photogrammetry system showed fat preservation after 1 year was 19.5 ± 2.0 mL (40%) in PRS patients, 81% in	6% complication rate, which included bleeding, wound infection, diplopia, eyelid ptosis, hardware failure, corneal	5.3-28.8 years (mean 8.5)

155 ± 5.1 mL (after mean 3.3 procedures)	3.2. Mean treatment span was 4.2 years			control group. Mean symmetry score of 68% preoperatively and 94% postop. Skin color and texture scores improved from 2.4 ± 0.06 to 3.4 ± 0.09	abrasion, and delayed wound healing, though unclear what procedures led to these complications; no donor-site morbidity
Rodby et al, ¹⁰⁸ 2016 case report	1 15, stable for 2 years	PRS	Coleman technique autologous fat transfer	Malar, nasolabial fold, lips, buccal, mental, mandible; first session: 30 mL, second: 45 mL, goal was 10-15% overcorrection	2 with 2-month interval NR 2 years
Agrawal et al, ⁹⁰ 2015 case report	1 19 at surgery 6 when disease started, stable since 17	PRS w/ECDS, type 3 per Guenero Santos classification	Autologous fat graft + cartilage graft into sub periosteal space in forehead	First session: 15 mL forehead, 1.5 mL supraorbital rim, 5 mL temple, 5 mL zygoma, 10 mL mandible, 5 mL chin; second session: 5 mL zygoma, 1.5 mL supraorbital, 2 mL infrabital	2 with 6-month interval NR Stable and satisfactory result up to 15 months since second procedure
Van der Cruyssen et al, ¹⁰⁹ 2018 retrospective	1 21 with 8 years disease duration	Localized scleroderma	Fat graft	Forehead, cheek: amount NR	Minimal hairline scar from cartilage graft NR 3 years
Contese et al, ¹¹⁰ 2000 case series	2 NR	PRS, 1 severe, 1 moderate	Autologous fat graft (severe patient had primary temporal bone & muscle flap and zygomatic augmentation procedures)	Cheek, zygomatic bridge: used 20% overcorrection in session 1, based overcorrection for next sessions on amount resorbed in first	Stable results with perioral muscular strength regained NR 6 months
Lee et al, ⁶⁶ 2017 case report	1 34 at procedure, disease started at 16 and stable since 24.	PRS	Fat transfer	Forehead, cheek: amount NR	Minor postoperative scarring NR 2 years
Moscoso et al, ¹¹¹ 1989 case report				Face, 100 mL in 1st session. 4 with 4- to 6-week intervals	Marked edema that resolved in 14 days from last injection NR 3 months

Table V. Cont'd

Authors/ study type	N	Age	Disease	Treatment	Location/amount	Sessions/ interval	Perioperative medication	Result	Side effects	Follow- up
Xie et al, ¹¹² 2007 case series	31	19-28 (mean 23.5), disease stable for at least 1 year	PRS	Autologous fat transfer	3-14 mL mandibular, 5- 25 mL buccal, 2-10 mL zygomatic, goal was 20- 30% overcorrection	1 (n = 15), 2 (n = 13, all moderate disease), 3 (n = 3, all severe disease). 3- to 6-month intervals	NR	At 6 months, >65% of patients assessed as satisfactory by all 3 groups (patient, surgeon, layperson), 10- 30% mostly satisfactory, <7% unsatisfactory; most volume on postoperative day 7, reduced continuously until 3 months, then stable in long term; hyperpigmentation was noticeably improved; direct correlation between the severity of hemi facial atrophy and the requirement for multiple treatments	None	Mean after last injection, 2.06 years
Roddi et al, ¹¹³ 1994 case series	6	16-41 (mean 25.7) at surgery, 12-40 years stable (mean 21)	PRS	Microfat lipofilling	Face: 20-60 mL total, 1 mL amounts, 1 layer only subcutaneously	NR	NR	Subjective satisfactory results	NR	NR
Chajchir and Benzaquen, ¹¹⁴ 1989 case series	9	20-70	Scleroderma (n = 3), PRS (n = 6)	Fat graft injection	Parieto, temporal, mandibular areas: 50- 120 mL, 30-50% overcorrection	5 for PRS, 4 for SSC, interval NR	NR	Unable to assess	Edema, hematoma	NR
Denadai et al, ⁴³ 2018 prospective randomized study without control	53	Mean 27.1	PRS	Coleman technique autologous fat graft	Forehead, chin, and cheek. Mean 13.8 mL initial procedure, mean 12.4 mL repeat procedures	2 sessions, interval at 3, 6, or 12 months by random assortment	NR	Significant decrease of injected volume during initial 3 months, stable volume following 3 months; no significant difference in intergroup (second fat graft performed at 3 vs. 6 vs. 12 months after initial graft) secondary graft retention; significantly higher graft retention rate for second procedure across all 3 groups at 3, 6, and 12 months postoperatively	Self-resolving swelling and bruising	12 months
Harp et al, ¹¹⁵ 2018 case report	1	28	PRS	Autologous fat injection	Right hemiface: session 1: 12.5 mL, session 2: 20 mL, session 3: 46 mL	3 sessions at 4- to 5-month intervals	NR	Patient satisfied	NR	NR
Mura et al, ⁴⁰ 2018 case report	1	40	Linear morphea	Autologous fat transfer	Upper limb	3 sessions at 6-month intervals	None	Patient reported immediate improvement of paresthesia, eventual improvement of tissue consistency and flexibility	None	NR

BID, Bis in die; ECDS, en coup de sabre; IVIG, intravenous immunoglobulin; LS, linear scleroderma; MHISS, Mouth Handicap in Systemic Sclerosis; MTX, methotrexate; NR, not reported; PLLA, poly-L-lactic acid; PRS, Parry-Romberg syndrome; SSC, systemic sclerosis.

Table VI. Cell-assisted injectables for morphea and systemic sclerosis

Author/study type	N	Age	Disease	Treatment	Location/amount	Sessions/interval	Perioperative medication	Results	Side effects	Follow-up
Blezién et al, ⁴⁶ 2017 prospective study	7	31-65, mean = 46.3; mean disease duration was 10 years	SSc	Microfat graft with PRP	Lips, 3 mL total with no overcorrection	NR	NR	Mean 0.6-cm increase in oral opening; 11.94% increase lower lip and 8.47% upper lip increased thickness; mean 5.28 decrease in MHS score; focal reduction in dermal fibrosis in 5/7 patients	Graft area edema (3%), harvesting site ecchymosis (5%), and postoperative pain >3 days (11%)	12 months
Scuderi et al, ¹¹⁶ 2013 prospective trial	6	Age: 18-41; age of onset: 4-12; no active disease for ≥6 months	Generalized morphea with psoriasis (n = 1), linear scleroderma (n = 2), ECDS (n = 1), linear and plaque scleroderma (n = 2, 1 of which also had SLE)	8 × 10 ⁵ ASCs per 1 mL of HA filler	Face, arm, upper limb: <10 mL total	1	No immune-modifying drugs within 4 weeks; no topical meds within 2 weeks except emollients	Arrest of disease progression (n = 6), regression of dyschromia (n = 4), erythema reduction (n = 1), skin softening (n = 5), better subjective skin sensitivity (n = 4); patients extremely satisfied (n = 4), moderately (n = 1), and satisfied (n = 1)	Small ecchymosis	12 months
Virzi et al, ¹¹⁷ 2017 prospective study	6	Age: 41-63; disease duration 3-20 years	Diffuse cutaneous SSc	ADMSCs + PRP	Perioral	NR	No immune-modifying drugs	Elasticity increased 16.64% for lip, 17.80% for cheek; marked improvement in opening and extension of labial rhyme; increased capillary density (n = 4) and decreased vascular ectasia (n = 2)	NR	3 months
Onesti et al, ¹¹⁸ 2016 controlled trial	10	Age: 23-48; disease duration 3-18 years; stable for 1-16 years	Diffuse cutaneous scleroderma	Fat transfer (n = 5) vs ADMSCs with HA (n = 5)	6 perioral areas, 2 mL per site, 16 mL total	2 sessions with 3-month interval	No immune modifying drugs within 4 weeks; no topicals within 2 weeks except emollients	Significant improvement in mouth opening and Italian version MHS score within each group, insignificant difference between groups; patient satisfaction in fat transfer group, 80% rather satisfied, 20% very satisfied; in ADMSC group, 80% very satisfied, 20% rather satisfied	NR	12 months
Cervelli and Gentile, ⁴⁷ 2009 case report	2	Age: 25, 50; disease duration 12, 38 years	PRS	Autologous fat lipostructure + PRP	Zygomatic region: 20-55 mL, cheek: 5-35 mL, buccal rime: 10-25 mL, upper eye-lid: 3-5 mL, temporal area: 5-45 mL, supraorbital area: 3-13 mL	1-2 sessions with 4-month interval	NR	Obtained desired thickening of skin, but not facial contour filling	NR	NR
Koh et al, ⁴⁹ 2012 RCT	10	Mean age: 28	PRS	Microfat graft vs microfat graft with 1 × 10 ⁷ ADMSC	9.3-22.5 mL session 1, 3.2-7.4 mL session 2, 30% overcorrection	2 sessions with 14-day interval	NR	Measurements with 3D camera and CT showed 20.59% resorption in stem cell group, 46.81% resorption in graft alone group; mean patient satisfaction was higher in experimental group than in control group	Exaggerated volume loss on treated hemiface in 1 patient after intentional 15-kg weight loss	Mean follow-up 15 months
Karaaltin et al, ⁵⁰ 2012 case report	1	19 year old, 4 year disease duration	ECDS	Autologous fat graft + ADMSC	Forehead, amount NR	2 sessions, 1-year interval	NR	Result at 1 year was satisfactory for the patient but required an additional session	None	1 year

Continued

Table VI. Cont'd

Author/study type	N	Age	Disease	Treatment	Location/amount	Sessions/interval	Perioperative medication	Results	Side effects	Follow-up
Ortega and Sastogue, ⁴⁸ 2015 case report	1	12-year-old, disease started at 5, previous free flap surgery at 8	PRS	Integra filler + fat transfer with PRP + realignment of latissimus dorsi flap	Face, amount NR	1 session	NR	Symmetry maintained as determined by CT imaging; histopathologic examination showed integra filler had integrated into soft tissues; patient satisfied	None	2 years
Chang et al, ⁵¹ 2013 controlled trial	20	Mean age 27.5; stable disease for ≥1 year	PRS	Fat graft vs fat graft + stromal vascular fraction	Mandibular: 5-20 mL per session; buccal: 4-30 mL per session; zygomatic: 3-12 mL per session; 0.5 mL per injection site, goal was 10-20% overcorrection	1-3 sessions with 6-month intervals	NR	At 6 months, fat survival was 68.3% in SVF group vs 58.5% in fat alone group; facial volumes increased until postoperative days 10-14, then reduced until 3 months postoperatively, after which volume remained stable; subjective improvement of skin color at injection site	None	At least 1.5 years after the first injection, and 1 year after last injection
Castro-Govea et al, ⁵² 2012 case report	1	35 years old, 10-year disease history, 5 years stable disease	PRS	Fat transfer with ADMSC	15 mL temporal, 25 mL cheek, 3 mL lips, 15 mL malar, 35 mL mandible/base of neck	1 session	NR	Subjective improvement in volume, skin quality, texture, and elasticity	NR	1 and 12 months
Jianhui et al, ⁵⁵ 2014 controlled trial	36	Fat only group: age 18-38; MSC group: 20-35; all in stable phase for ≥1 year	PRS	Fat graft (n = 26) vs fat graft with bone marrow MSCs (n = 10)	Face, 4-32 mL per session, goal was 2-30% overcorrection	1-3 sessions with 6-month intervals	NR	In fat only group, satisfactory symmetry obtained after 1 session (n = 12), 2 sessions (n = 8), and 3 sessions (n = 4); 1 patient had unsatisfactory result; in MSC group, symmetry after 1 session (n = 10); most volume on postoperative day 7; volume decreased until 3 months postoperatively and then remained stable	1 patient from fat only group had to undergo liposuction to correct overcorrection	Mean follow-up after last session was 14 months
Yoshimura et al, ⁵³ 2008 prospective study	1	Age: 35	PRS	CAL	110 mL total into the face	NR	None	Excellent subjective improvement (80% improvement or better)	Subcutaneous bleeding that resolved in 1-2 weeks; swelling resolved in 4 weeks	13 months
Chen et al, ⁴⁴ 2018 case series	11	18-29, disease duration 3-15 years	Scleroderma	CAL	Forehead (4-30 mL), cheek (10-45 mL), lip (4-20 mL), chin (2-15 mL)	1 (n = 4), 2 (n = 3), 3 (n = 3), 4 (n = 1), previous flap surgery (n = 3), interval 5-29 months	Chronic systemic corticosteroids (n = 5) for 3-10 years	Patient satisfaction VAS (1-10) at 6 months postoperatively, nonsteroid cohort: 5, 7, 8, 8, 8, 9; steroid cohort 6, 6, 6, 7, 9; also compared ADMSCs from patients and n = 10 healthy control liposuction patients; significant cell growth delay and decrease in total cell number in corticosteroid cohort compared with healthy controls and	None	6 months

Almadori et al. ^{5,6} 2019 case series		SSc (diffuse n = 26, limited n = 36)	Lipotransfer with added ADMSC	Nose, cheeks, chin, nasolabial folds, lips	Mean 3 sessions (range 1-10)	MMF (n = 14), MTX (n = 6), other nonspecified immune- suppressing medication (n = 11), none (n = 31)	Bruising, swelling, tenderness resolving in 14 days; 1 case of recipient site infection treated with oral antibiotics	Mean 12.4 months (range 6-53 months)
62	Mean: 56; mean disease duration 15 years; all with stable disease for ≥ 2 years							

ADMSC, Adipose-derived mesenchymal stem cell; ASC, adipose stem cell; BFD/ES, Brief Fear of Negative Evaluation Scale; CAL, cell-assisted lipotransfer; CT, computed tomography; DAS24, Derriofd Appearance Scale; ECDS, en coup de sabre; HA, hyaluronic acid; HADS-D, Hospital Anxiety and Depression Scale-Depression; LS, linear sclerodema; MHISS, Mouth Handicap in Systemic Sclerosis; MMF, mycophenolate mofetil; MSC, mesenchymal stem cell; MTX, methotrexate; NR, not reported; PLA, poly-L-lactic acid; PRP, platelet-rich plasma; PSS, Parry-Romberg syndrome; RCT, randomized controlled trial; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; SVF, stromal vascular fraction; VAS, visual analog scale.

ADMSC, Adipose-derived mesenchymal stem cell; ASC, adipose stem cell; BFD/ES, Brief Fear of Negative Evaluation Scale; CAL, cell-assisted lipotransfer; CT, computed tomography; DAS24, Derriofd Appearance Scale; ECDS, en coup de sabre; HA, hyaluronic acid; HADS-D, Hospital Anxiety and Depression Scale-Depression; LS, linear sclerodema; MHISS, Mouth Handicap in Systemic Sclerosis; MMF, mycophenolate mofetil; MSC, mesenchymal stem cell; MTX, methotrexate; NR, not reported; PLA, poly-L-lactic acid; PRP, platelet-rich plasma; PSS, Parry-Romberg syndrome; RCT, randomized controlled trial; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; SVF, stromal vascular fraction; VAS, visual analog scale.

Reconstructive treatment with the use of fillers and injectables has become an increasingly common method of restoring the postinflammatory contour changes associated with morphea. Despite the theoretical risk of disease reactivation because of trauma from injection, to our knowledge there are no reports of disease reactivation after injectable use in this patient population. The majority of patients with documented morphea who underwent cosmetic injectable treatment had inactive disease at the time of injection and were not taking immune-modifying medications (Tables V-VIII). In addition, we did not find any reports of vascular compromise or skin necrosis among 488 cases of injectable use in patients with morphea or SSc.

Fat transfer

Autologous fat transfer has long been a preferred method for facial volume augmentation given that fat is easily accessible, versatile, and biocompatible.^{39,40} However, it has been hypothesized that the combination of chronic inflammation,⁴¹ poor environment at the recipient site,^{42,43} and corticosteroid use⁴⁴ makes fat transfer in patients with morphea and SSc more subject to degradation. While some studies have shown this hypothesis to be true, fat transfer still represents an important treatment modality. Functional oral improvements appear to persist even in patients in whom transferred fat has been completely resorbed.⁴⁵ Some authors have attempted to improve unpredictable fat survival by augmenting traditional fat transfers with added cellular cultures including platelet-rich plasma,⁴⁶⁻⁴⁸ adipose-derived mesenchymal stem cells,^{44,49-54} or bone marrow-derived mesenchymal stem cells.⁵⁵ Mesenchymal stem cells are multipotent progenitor cells that are capable of differentiating into mesenchymal tissue⁴⁹ and that are hypothesized to have angiogenic and immunomodulatory effects.^{46,56,57}

Although the majority of the published literature on fat transfer in the autoimmune patient population is based on subjective outcome measures, few studies have also demonstrated objective improvement after fat transfer by using the Mouth Handicap in Systemic Sclerosis (MHISS) scale,^{45,46,54,58-60} computed tomography, and 3-dimensional (3D) imaging (Table V).^{42,54,61,62} The MHISS Scale is a reliable and validated scale for assessing mouth opening impairment, sicca symptoms, and aesthetic concerns in SSc patients, with higher scores (maximum score 48) correlating with more severe symptoms.⁵⁸

CT, ultrasound,⁴³ 3D photogrammetry, and 3D laser imaging have been used to evaluate the percentage of fat transfer “take,” meaning the amount of

Table VII. Poly-L-lactic acid filler for morphea and systemic sclerosis

Authors/ study type	N	Disease	Treatment	Processing	Amount	Postprocedure	Sessions/interval	Result	Side effects	Follow up
Onesti et al, ⁶⁵ 2009 case series	6	PRS (n = 2), LS (n = 4) all inactive disease	PLLA	Dilution ratio with sterile water ranged from 1:5-1:8	1-6 mL total per session, 0.1-0.2 mL per infiltration spaced 0.5 cm apart via 25-26 G needles, 30-40° angles, tunneling technique for lower face, depot technique for upper face	Ice compress before and after treatment, facial massage postoperatively to prevent subcutaneous nodules, patient at-home massage BID for 14 days	3-5 sessions at 4-week intervals	Subjective improvements in volume, symmetry, skin quality, hyperpigmentation (PRS only); all patients satisfied	Edema (n = 4), erythema (n = 4), submucous nodule (n = 1, due to infiltration error, removed surgically), postinjection bleeding (n = 1), pain (n = 1), palpable but not visible nodule (n = 1)	18 months
Clauser et al, ⁶⁶ 2010 case report	1	PRS	Structural fat grafting with PLLA revision	NR	NR	NR	5 sessions total over 3-year span, last 2 with PLLA	Subjective good aesthetic outcome with complete patient satisfaction	NR	15 months after second session
Grimaldi et al, ⁶⁸ 2008 case report	1	Inactive PRS	Poly-G-lactic acid + autologous fat transfer	Diluted in 8 mL sterile saline for superficial planes, in 3 mL for deeper planes	NR	NR	3 sessions, interval not reported other than 8 months between last poly-G-lactic acid treatment and fat transfer	Obtained desired thickening of skin but not filling effects (thus pursued fat transfer); patient satisfied but future fat transfers planned	NR	NR
Onesti et al, ²⁷ 2009 case report	1	PRS	PLLA + lipofilling + IPL laser therapy	Diluted in 6 mL sterile water	Amount not reported, used 27G needle into deep derma or superficial hypoderm	Massaged PLLA after every 3 infiltrations	4 sessions at 4-week intervals	Stable result at follow-up; patient satisfied with volume, contours, and resolution of sclerosis and hyperpigmentation	No recurrences or complications	1 year

BID, Bis in die; IPL, intense pulsed light; LS, linear scleroderma; NR, not reported; PRS, Parry-Romberg syndrome; PLLA, poly-L-lactic acid.

Table VIII. Hyaluronic acid filler for morphea

Authors/study type	N	Disease	Treatment	Processing	Amount	Postprocedure	Sessions/interval	Result	Side effects	Follow-up
Choksi and Orringer, ⁷¹ 2011 case report	1	Inactive ECDS	UVA phototherapy followed by HA filler	NR	1 mL in linear threading technique	NR	2 sessions at 5-month intervals	Subjective >90% improvement of original defect; patient pleased	NR	NR
Thareja et al, ¹⁹ 2013 case report	1	Inactive ECDS	HA filler	NR	2 vials per session intradermal	NR	2 sessions at 6-month intervals	Patient satisfied; areas of scar tethered to underlying structures did not respond	None	7 months from first session
Sivek and Emer, ⁷² 2014 case report	1	ECDS	24 mg/mL HA filler premixed with anesthetic	23 G cannula made entry point for 25 G blunt-tipped microcannula, retrograde linear threading into preperiosteal plane	<1 mL	Light massage then ice packs	1 session	Patient satisfied with immediate results, declined future treatments	NR	9 months
Arsiwala, ¹²⁰ 2015 case report	1	Focal scleroderma (circumscribed morphea) inactive for 5 years	20 mg/mL 1000 μm particle size HA filler	30 G needle, bolus injection technique	1 mL	Ice compresses and hand molding	1 session	Patient satisfied	None	9 months
Watchmaker et al, ⁷³ 2019 case report	1	Bilateral PRS	HA filler, methotrexate 10 mg weekly	NR	NR	NR	NR	Subjective significant improvement	No apparent disease progression	2 months

ECDS, En coup de sabre; HA, hyaluronic acid; NR, not reported; PRS, Parry–Romberg syndrome; UVA, ultraviolet A light phototherapy.



Fig 3. Parry–Romberg syndrome (**A**) before and (**B**) after hyaluronic acid injection to the cheek and midface. The patient underwent serial injections spaced 4 to 12 weeks apart. **C**, Patient with Parry–Romberg syndrome before treatment with hyaluronic acid. **D**, Patient with Parry–Romberg syndrome immediately after treatment with hyaluronic acid filler to the left temple.

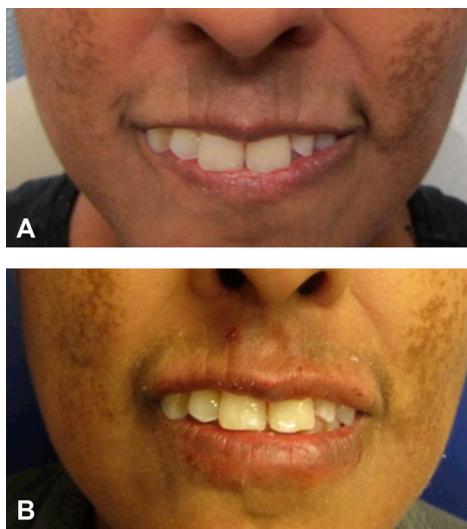


Fig 4. Lips of a patient with systemic sclerosis (**A**) before and (**B**) immediately after hyaluronic acid injection.

injected fat that successfully incorporates with surrounding tissue and persists at long-term follow-up.^{42,61,62} One study using 3D photogrammetry found that “final fat take” at 1-year follow-up was 40% in patients with PRS compared with 81% in the control

group. They recommended more treatment sessions with greater overcorrection margins when performing fat transfer for PRS (level of evidence IIA).⁶²

It has been hypothesized that progressive improvement in skin elasticity with repeated fat transfer decreases tension and improves fat graft survival. This theory is supported by a study that showed increase in fat graft survival rate based on 3D laser imaging on repeated fat injection (43.3% and 75.1% fat survival after the first and second procedures, respectively).⁴² A recent case series of patients with diffuse ($n = 26$) and limited ($n = 36$) SSc found significant differences in improvements in MHISS and multiple patient-reported outcome measures based on the number of fat transfer sessions, further supporting the hypothesis that multiple sessions of fat transfer could provide cumulative benefit (level of evidence III).⁵⁴

Poly-L-lactic acid

Poly-L-lactic acid (PLLA) is a biocompatible, immunologically inert synthetic polymer that stimulates fibroblast proliferation⁶³ and thus collagen formation^{27,64} improving both skin quality and

Table IX. Calcium hydroxyapatite or polymethyl methacrylate filler for morphea

Authors/study type	N	Disease	Treatment	Processing	Amount	Postprocedure	Sessions/interval	Result	Side effects	Follow-up
Franco et al, ⁷⁶ 2016 case report	1	Stable ECDS	PMMA 10-30% filler	Thin cannula with 10% PMMA for forehead, injected retrograde crossed in X; thicker cannula with 30% PMMA for scalp	NR	NR	3 sessions with 3-month intervals	Patient satisfied, partial hair regrowth at site of previous disease related alopecia	NR	NR
Cox and Soderberg, ⁷⁷ 2010 case report	1	Inactive PRS	CaHA and HA filler	Serial fanning with retrograde injection in the subcutaneous plane	2.6-3.9 mL CaHA to right hemiface, 1 mL HA infraorbital	NR	5 sessions at 4-week intervals for CaHA, 1 session HA	10% resorption at follow-up but patient remained satisfied	None	6 months

CaHA, Calcium hydroxyapatite; ECDS, en coup de sabre; HA, hyaluronic acid; NR, not reported; PMMA, polymethyl methacrylate; PRS, Parry–Romberg syndrome; UVA, ultraviolet A light phototherapy.

thickness.⁶⁵ Eventual material resorption limits long-term results to <2 years.⁶³ PLLA has been used in patients with PRS and facial linear scleroderma (LS)⁶⁵ with subjective improvement in aesthetic deficits (Table VII). Authors who used PLLA in patients with morphea and SSc noted that the tough, fibrosed skin created injection difficulties with the first 2 sessions, subsequently improving with following sessions, and limited injection volumes to 1 to 1.5 mL per session. PLLA has also been used as adjuvant treatment⁶⁶ combined with structural fat grafting⁶⁷ in patients with PRS as a skin-thickening agent before eventual fat transfer,⁶⁸ and for small volumetric deficits in a combined PLLA/fat transfer/IPL treatment regimen.²⁷

Hyaluronic acid

Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan found in tissue extracellular matrix that provides volumizing effects via keratinocyte proliferation, water binding,⁶³ and de novo type I collagen production.⁶⁹ These properties have made bacterial derived cross-linked HA fillers among the most widely used, with results persisting for as long as 18 months after 1 treatment.⁷⁰ Choksi et al⁷¹ first reported on its use in a patient with ECDS to reduce enduring volume loss after the disease was made inactive by ultraviolet A1 light phototherapy. The authors made particular note of the financial constraints that will undoubtedly prevent many patients with morphea from pursuing reconstructive procedures but recommended large-particle HA fillers as an ideal option to maximize volume changes per amount of filler used (level of evidence III). Further studies also reported positive response to treatment of ECDS with HA filler, and specifically recommended the use of blunt-tipped cannulas to reduce trauma and prevent complications such as pain, bruising, swelling, or potential tissue necrosis caused by vascular damage.⁷² In general, the technique to use blunt-tipped cannulas is similar among all patients. A thicker sharp cannula or needle is used to create an entry point for a thinner blunt-tipped cannula used for injection.⁷² This technique can be enhanced with subcision and expansion of underlying tissue with normal saline to help prevent nodularity after the procedure. Although no cases of vascular compromise have been reported, some recommend injection volumes of 1 to 1.5 mL to prevent vascular compression leading to similar necrosis (level of evidence III).^{65,72} We have used HA filler successfully to treat facial cosmetic deficits in a patient with bilateral PRS (Fig 3), for lip augmentation in patients with SSc and microstomia (Fig 4), and in patients with localized scleroderma on

Table X. Strength of recommendations for injectable treatment for morphea and systemic sclerosis

Recommendation	Recommendation no.	Level of evidence	Studies
When performing fat transfer for Parry–Romberg syndrome, more treatment sessions with greater overcorrection margins may be necessary	2.1	IIA	Slack et al ⁶²
Repeat fat injections can show improved survival compared with the initial graft and cumulative improvements in functional and patient-reported outcomes	2.2	III	Jiang et al ⁴² and Almadori et al ⁵⁴
The following injectable fillers can be used in patients with morphea and systemic sclerosis if disease is inactive and stable, without the need to restart disease-modifying medications			
Poly-L-lactic acid	2.3	III	Onesti et al ²⁷ Onesti et al, ⁶⁵ Clauser et al, ⁶⁶ and Grimaldi et al ⁶⁸
Calcium hydroxyapatite	2.4	III	Cox and Soderberg ⁷⁷
Polymethylmethacrylate	2.5	III	Franco et al ⁷⁶
Hyaluronic acid	2.6	III	Choski and Orringer, ⁷¹ Sivek and Emer, ⁷² Watchmaker, ⁷³ Thareja et al, ¹¹⁹ and Arsiwala ¹²⁰
Large-particle hyaluronic acid filler can serve as an ideal option when financial constraints require maximum volume correction with minimal treatment	2.7	IV	Choski and Orringer ⁷¹
The use of blunt-tipped cannulas can reduce trauma and prevent complications, such as pain, bruising, swelling, or potential tissue necrosis caused by vascular damage	2.8	III	Sivek and Emer ⁷²
For filler injection, injection volumes of 1–1.5 mL are recommended to prevent vascular compression and subsequent necrosis	2.9	III	Onesti et al ⁶⁵ and Sivek and Emer ⁷²

Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥ 1 randomized controlled trial; level IIA evidence includes evidence from ≥ 1 controlled study without randomization; level IIB evidence includes evidence from ≥ 1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

the face (ECDS) and truncal/extremity lesions.⁷³ Recently, a case of scleroderma-induced microstomia treated with serial hyaluronidase injections led to subjective improvement of mouth closure and eating.⁷⁴ The second article in this continuing medical education series includes more detailed information with regard to side effects and types of filler recommendations.

Calcium hydroxylapatite and polymethyl methacrylate

Calcium hydroxylapatite microspheres within carboxymethyl cellulose carrier gel serve as dermal filler that facilitates fibroblast growth. The volume-enhancing effects are evident at the time of treatment and persist for ≤ 18 months.⁶³ Polymethyl methacrylate microspheres dispersed in magnesium-carboxygluconate-hydrolactic gel is a permanent injectable filler option. Modern variations have improved

consistency in electrostatic charge and particle shape and size that have improved long-term stability and biocompatibility.⁷⁵ Two case reports on the use of these filler types in patients with inactive morphea are summarized in Table IX.^{76,77} We were unable to find any reported cases of methacrylate hypersensitivity among this population.

In summary, based on the available data, multiple modalities appear to be cosmetic injectable treatment options for patients with inactive disease (level of evidence III). Physicians should expect the initial injections to be difficult because of increased dermal resistance with improvement of resistance over subsequent sessions. This often requires the use of multiple needle changes during injections and the use of more volume than needed for patients without these autoimmune conditions. In addition, more volume for fat transfer than typically required and counseling of patients on the likelihood of multiple

Table XI. Surgical treatment options for Parry–Romberg syndrome and en coup de sabre scleroderma

Single surgical procedures	Facial reconstruction	Lipofilling ¹⁰⁸
	Flaps and grafts	Polyethylene implants ¹²¹ Medpor implant ¹⁸ Cell-assisted lipotransfer Myocutaneous flap ¹²² Omental flaps Free vascular parascapular graft ⁷⁸ Thoracodorsal flaps Vascularized serratus anterior muscle flap Free groin flaps Composite galeal frontalis flap Perforator-based anterior muscle flap Autologous fat transplantation ¹²³ Fat transfer + modified Kligman formula ¹²⁴ Soft tissue expansion + artificial bone graft ¹²⁵ AlloDerm tissue matrix ¹²⁶
	Volume restoration	
	Tissue expansion	
	Acellular dermal matrices	
Combined surgical procedures		
Cheek implants + fat grafts + platelet-rich plasma ⁴⁸		
Three –dimensional + free anterolateral thigh ¹²⁷		
Poly-L-lactic + lipofilling + intense pulsed light ²⁷		
Superficial temporal fascial flap + lipofilling		
Revascularized free flap + dermal graft		
Revascularized free flap + lipoinjection ⁷⁸		
Revascularized free flap + Medpor implant		
Revascularized free flap + genioplasty		
Revascularized free flap + liposuction		
Coleman lipoinjection + polyglactic acid		
Coleman lipoinjection + blood platelet gel		
Lipoinjection+ galeal flap + free dermal graft + bone and cartilage graft		

sessions are usually needed (level of evidence IIA). Treatment recommendations are summarized in Table X.

SURGICAL INTERVENTIONS

Key points

- Surgical procedures are often considered in patients with ECDS and PRS to improve volume, symmetry, and contour
- There are many techniques for facial reconstruction and often a combination of treatments and multidisciplinary care are required⁷⁸

Surgical treatment options

Management of patients with morphea and SSc is mostly geared toward controlling the underlying inflammatory disease via a combination of topical agents, systemic therapies, and phototherapy.^{79,80} Although these may be effective in mitigating disease progression, they do not address the resulting atrophy and dyspigmentation.⁸¹ Surgical procedures are often considered in patients with ECDS and PRS to improve cosmetic appearance. While the timing of surgical treatment remains controversial,⁷⁸ there is

often a delay until disease is inactive to reduce the risk of reactivation and multiple surgeries.^{79,82-84} Many surgical modalities may be used in the treatment of ECDS and PRS, and it is important to preevaluate defect shape, size, and underlying bone deformity in order to choose the ideal surgical option for each individual. Table XI lists the surgical treatment options. Please see the second article in this continuing medical education series for the American College of Rheumatology (ACR) consensus guidelines for the perioperative management of patients with rheumatic diseases.

Dermal fat grafting. Dermal fat grafting techniques are usually indicated in patients with type 3 facial tissue atrophy, defined as thin soft tissue and bony structures, and type 4, characterized by severe facial depressions, where the skin is very close to bone.⁸⁵ The donor site is often the inguinal region and needs to be slightly larger than the defect size.⁸⁵ The reported complications are hematoma, undercorrection, edema, induration,⁸⁵ partial flap loss, and cellulitis.⁷⁸ An algorithm proposed by Lee et al⁸⁶ suggests that linear lesions <1 cm can be treated with resection and local flat or Z-plasty, and

oval/round lesions with length <5 cm, width <1 cm, and depth <2 cm are good candidates for free fat graft, dermal fat graft, or artificial dermis.⁸⁶ Dermal fat grafting seems to be an effective treatment for ECDS, with few complications and lasting results.^{87,88} Dermal fat grafts can also be used in conjunction with porous polyethylene implants⁸⁹ (level of evidence III).

Bone and cartilage grafts. The use of bone and cartilage grafts to restore contour of the frontal bone are commonly indicated for patients with PRS with more severe defects in combination with soft tissue augmentation.^{83,90} There are many techniques for facial reconstruction, and often a combination of treatments and a multidisciplinary team are required to treat facial tissue depressions.⁸³ Recently, a computer-assisted technique combining autologous outer cortex graft with fat grafting demonstrated good outcomes in patients with PRS.⁹¹ Table XI details more surgical treatment options for PRS and ECDS.

REFERENCES

- Zwischenberger BA, Jacobe HT. A systematic review of morphea treatments and therapeutic algorithm. *J Am Acad Dermatol.* 2011;65:925-941.
- El Sawy N, Suliman I, Nouh M, Naguib A. Hand function in systemic sclerosis: a clinical and ultrasongraphic study. *The Egyptian Rheumatologist.* 2012;34:167-178.
- Mayes MD, Lacey JV Jr, Beebe-Dimmer J, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum.* 2003;48: 2246-2255.
- Bologna J, Schaffer JV, Duncan KO, Ko CJ. *Dermatology Essentials.* Oxford: Saunders/Elsevier; 2014.
- Firestein GS, Gabriel SE, McInnes IB, O'Dell JR. *Kelley and Firestein's Textbook of Rheumatology.* 10th ed. Philadelphia, PA: Elsevier; 2017.
- Fett N, Werth VP. Update on morphea: part I. Epidemiology, clinical presentation, and pathogenesis. *J Am Acad Dermatol.* 2011;64:217-228.
- Peterson LS, Nelson AM, Su WP, Mason T, O'Fallon WM, Gabriel SE. The epidemiology of morphea (localized scleroderma) in Olmsted County 1960-1993. *J Rheumatol.* 1997;24:73-80.
- Firestein GS, Kelley WN. *Kelley's Textbook of Rheumatology.* 9th ed. Philadelphia, PA: Elsevier/Saunders; 2013.
- van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis.* 2013;72:1747-1755.
- Bali G, Karpati S, Sardy M, Brodzsky V, Hidvegi B, Rencz F. Association between quality of life and clinical characteristics in patients with morphea. *Qual Life Res.* 2018;27:2525-2532.
- Kwakkenbos L, Delisle VC, Fox RS, et al. Psychosocial aspects of scleroderma. *Rheum Dis Clin North Am.* 2015;41:519-528.
- Kroft EB, de Jong EM, Evers AW. Psychological distress in patients with morphea and eosinophilic fasciitis. *Arch Dermatol.* 2009;145:1017-1022.
- Klimas NK, Shedd AD, Bernstein IH, Jacobe H. Health-related quality of life in morphea. *Br J Dermatol.* 2015;172:1329-1337.
- Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992;30:473-483.
- Arkachaisri T, Vilayuk S, Torok KS, Medsger TA Jr. Development and initial validation of the localized scleroderma skin damage index and physician global assessment of disease damage: a proof-of-concept study. *Rheumatology (Oxford).* 2010;49:373-381.
- Orechowski NM, Davis DM, Mason TG 3rd, Crowson CS, Reed AM. Health-related quality of life in children and adolescents with juvenile localized scleroderma. *Rheumatology (Oxford).* 2009;48:670-672.
- Kunzler E, Florez-Pollack S, Teske N, O'Brien J, Prasad S, Jacobe H. Linear morphea: clinical characteristics, disease course, and treatment of the Morphea in Adults and Children cohort. *J Am Acad Dermatol.* 2019;80:1664-1670.
- Palmero ML, Uziel Y, Laxer RM, Forrest CR, Pope E. En coup de sabre scleroderma and Parry-Romberg syndrome in adolescents: surgical options and patient-related outcomes. *J Rheumatol.* 2010;37:2174-2179.
- Jewett LR, Razikov I, Hudson M, Baron M, Thombs BD, Canadian Scleroderma Research Group. Prevalence of current, 12-month and lifetime major depressive disorder among patients with systemic sclerosis. *Rheumatology (Oxford).* 2013;52:669-675.
- Thombs BD, Taillefer SS, Hudson M, Baron M. Depression in patients with systemic sclerosis: a systematic review of the evidence. *Arthritis Rheum.* 2007;57:1089-1097.
- Baubet T, Ranque B, Taieb O, et al. Mood and anxiety disorders in systemic sclerosis patients. *Presse Med.* 2011;40:e111-e119.
- Seravina OF, Lisitsyna TA, Starovoitova MN, Desinova OV, Kovalevskaya OB, Veltishchev DY. Chronic stress and mental disorders in patients with systemic scleroderma: results of an interdisciplinary study [in Russian]. *Ter Arkh.* 2017;89:26-32.
- Thombs BD, Jewett LR, Kwakkenbos L, Hudson M, Baron M, Canadian Scleroderma Research Group. Major depression diagnoses among patients with systemic sclerosis: baseline and one-month followup. *Arthritis Care Res (Hoboken).* 2015; 67:411-416.
- Thombs BD, van Lankveld W, Bassel M, et al. Psychological health and well-being in systemic sclerosis: state of the science and consensus research agenda. *Arthritis Care Res (Hoboken).* 2010;62:1181-1189.
- Dinsdale G, Murray A, Moore T, et al. A comparison of intense pulsed light and laser treatment of telangiectases in patients with systemic sclerosis: a within-subject randomized trial. *Rheumatology (Oxford).* 2014;53:1422-1430.
- Halachmi S, Gabari O, Cohen S, Koren R, Amitai DB, Lapidoth M. Telangiectasia in CREST syndrome and systemic sclerosis: correlation of clinical and pathological features with response to pulsed dye laser treatment. *Lasers Med Sci.* 2014; 29:137-140.
- Onesti MG, Monarca C, Rizzo MI, Mazzocchi M, Scuderi N. Minimally invasive combined treatment for Parry-Romberg syndrome. *Aesthetic Plast Surg.* 2009;33:452-456.
- Murray AK, Moore TL, Richards H, Ennis H, Griffiths CE, Herrick AL. Pilot study of intense pulsed light for the treatment of systemic sclerosis-related telangiectases. *Br J Dermatol.* 2012;167:563-569.
- Goldberg DJ. New collagen formation after dermal remodeling with an intense pulsed light source. *J Cutan Laser Ther.* 2000;2:59-61.
- Comstedt LR, Svensson A, Troilius A. Improvement of microstomia in scleroderma after intense pulsed light: a case series of four patients. *J Cosmet Laser Ther.* 2012;14:102-106.

31. Alantar A, Cabane J, Hachulla E, et al. Recommendations for the care of oral involvement in patients with systemic sclerosis. *Arthritis Care Res (Hoboken)*. 2011;63:1126-1133.
32. Bennani I, Lopez R, Bonnet D, et al. Improvement of microstomia in scleroderma after carbon dioxide laser treatment. *Case Rep Dermatol*. 2016;8:142-150.
33. Kineston D, Kwan JM, Uebelhoer NS, Shumaker PR. Use of a fractional ablative 10.6-microm carbon dioxide laser in the treatment of a morphea-related contracture. *Arch Dermatol*. 2011;147:1148-1150.
34. Prignano F, Campolmi P, Bonan P, et al. Fractional CO₂ laser: a novel therapeutic device upon photobiomodulation of tissue remodeling and cytokine pathway of tissue repair. *Dermatol Ther*. 2009;22(suppl 1):S8-S15.
35. Shalaby SM, Bosseila M, Fawzy MM, Abdel Halim DM, Sayed SS, Allam RS. Fractional carbon dioxide laser versus low-dose UVA-1 phototherapy for treatment of localized scleroderma: a clinical and immunohistochemical randomized controlled study. *Lasers Med Sci*. 2016;31:1707-1715.
36. Bottomley WW, Goodfield MJ, Sheehan-Dare RA. Digital calcification in systemic sclerosis: effective treatment with good tissue preservation using the carbon dioxide laser. *Br J Dermatol*. 1996;135:302-304.
37. Chamberlain AJ, Walker NP. Successful palliation and significant remission of cutaneous calcinosis in CREST syndrome with carbon dioxide laser. *Dermatol Surg*. 2003;29:968-970.
38. Apfelberg DB, Varga J, Greenbaum SS. Carbon dioxide laser resurfacing of peri-oral rhytids in scleroderma patients. *Dermatol Surg*. 1998;24:517-519.
39. Coleman SR. Structural fat grafts: the ideal filler? *Clin Plast Surg*. 2001;28:111-119.
40. Mura S, Fin A, Parodi PC, Denton CP, Howell KJ, Rampino Cordaro E. Autologous fat transfer in the successful treatment of upper limb linear morphea. *Clin Exp Rheumatol*. 2018;36(suppl 113):183.
41. Mineda K, Kuno S, Kato H, et al. Chronic inflammation and progressive calcification as a result of fat necrosis: the worst outcome in fat grafting. *Plast Reconstr Surg*. 2014;133:1064-1072.
42. Jiang T, Xie Y, Zhu M, et al. The second fat graft has significantly better outcome than the first fat graft for Romberg syndrome: a study of three-dimensional volumetric analysis. *J Plast Reconstr Aesthet Surg*. 2016;69:1621-1626.
43. Denadai R, Raposo-Amaral CA, da Silva SA, Buzzo CL, Raposo-Amaral CE. Complementary fat graft retention rates are superior to initial rates in craniofacial contour reconstruction. *Plast Reconstr Surg*. 2019;143:823-835.
44. Chen B, Wang X, Long X, et al. Supportive use of adipose-derived stem cells in cell-assisted lipotransfer for localized scleroderma. *Plast Reconstr Surg*. 2018;141:1395-1407.
45. Gheisari M, Ahmadzadeh A, Nobari N, Iranmanesh B, Mozafari N. Autologous fat grafting in the treatment of facial scleroderma. *Dermatol Res Pract*. 2018;2018:6568016.
46. Blezien O, D'Andrea F, Nicoletti GF, Ferraro GA. Effects of fat grafting containing stem cells in microstomia and microcheilia derived from systemic sclerosis. *Aesthetic Plast Surg*. 2017;41:839-844.
47. Cervelli V, Gentile P. Use of cell fat mixed with platelet gel in progressive hemifacial atrophy. *Aesthetic Plast Surg*. 2009;33:22-27.
48. Ortega VG, Sastoque D. New and successful technique for the management of Parry-Romberg syndrome's soft tissue atrophy. *J Craniofac Surg*. 2015;26:e507-e510.
49. Koh KS, Oh TS, Kim H, et al. Clinical application of human adipose tissue-derived mesenchymal stem cells in progressive hemifacial atrophy (Parry-Romberg disease) with microfat grafting techniques using 3-dimensional computed tomography and 3-dimensional camera. *Ann Plast Surg*. 2012;69:331-337.
50. Karaaltin MV, Akpinar AC, Baghaki S, Akpinar F. Treatment of "en coup de sabre" deformity with adipose-derived regenerative cell-enriched fat graft. *J Craniofac Surg*. 2012;23:e103-e105.
51. Chang Q, Li J, Dong Z, Liu L, Lu F. Quantitative volumetric analysis of progressive hemifacial atrophy corrected using stromal vascular fraction-supplemented autologous fat grafts. *Dermatol Surg*. 2013;39:1465-1473.
52. Castro-Govea Y, De La Garza-Pineda O, Lara-Arias J, et al. Cell-assisted lipotransfer for the treatment of Parry-Romberg syndrome. *Arch Plast Surg*. 2012;39:659-662.
53. Yoshimura K, Sato K, Aoi N, et al. Cell-assisted lipotransfer for facial lipoatrophy: efficacy of clinical use of adipose-derived stem cells. *Dermatol Surg*. 2008;34:1178-1185.
54. Almadori A, Griffin M, Ryan CM, et al. Stem cell enriched lipotransfer reverses the effects of fibrosis in systemic sclerosis. *PLoS One*. 2019;14:e0218068.
55. Jianhui Z, Chenggang Y, Binglun L, et al. Autologous fat graft and bone marrow-derived mesenchymal stem cells assisted fat graft for treatment of Parry-Romberg syndrome. *Ann Plast Surg*. 2014;73(suppl 1):S99-S103.
56. Bunnell BA, Flaatt M, Gagliardi C, Patel B, Ripoll C. Adipose-derived stem cells: isolation, expansion and differentiation. *Methods*. 2008;45:115-120.
57. Gimble JM, Katz AJ, Bunnell BA. Adipose-derived stem cells for regenerative medicine. *Circ Res*. 2007;100:1249-1260.
58. Mouthon L, Rannou F, Berezne A, et al. Development and validation of a scale for mouth handicap in systemic sclerosis: the Mouth Handicap in Systemic Sclerosis scale. *Ann Rheum Dis*. 2007;66:1651-1655.
59. Sautereau N, Daumas A, Truillet R, et al. Efficacy of autologous microfat graft on facial handicap in systemic sclerosis patients. *Plast Reconstr Surg Glob Open*. 2016;4:e660.
60. Magalon G, Daumas A, Sautereau N, Magalon J, Sabatier F, Granel B. Regenerative approach to scleroderma with fat grafting. *Clin Plast Surg*. 2015;42:353-364. viii-ix.
61. Yang X, Wu R, Bi H, et al. Autologous fat grafting with combined three-dimensional and mirror-image analyses for progressive hemifacial atrophy. *Ann Plast Surg*. 2016;77:308-313.
62. Slack GC, Tabit CJ, Allam KA, Kawamoto HK, Bradley JP. Parry-Romberg reconstruction: beneficial results despite poorer fat take. *Ann Plast Surg*. 2014;73:307-310.
63. Szczekowska-Dobosz A, Olszewska B, Lemanska M, Purzycka-Bohdan D, Nowicki R. Acquired facial lipoatrophy: pathogenesis and therapeutic options. *Postepy Dermatol Alergol*. 2015;32:127-133.
64. Gogolewski S, Jovanovic M, Perren SM, Dillon JG, Hughes MK. Tissue response and in vivo degradation of selected poly-hydroxyacids: polylactides (PLA), poly(3-hydroxybutyrate) (PHB), and poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHB/VA). *J Biomed Mater Res*. 1993;27:1135-1148.
65. Onesti MG, Troccola A, Scuderi N. Volumetric correction using poly-L-lactic acid in facial asymmetry: Parry Romberg syndrome and scleroderma. *Dermatol Surg*. 2009;35:1368-1375.
66. Clauser LC, Tieghi R, Consorti G. Parry-Romberg syndrome: volumetric regeneration by structural fat grafting technique. *J Craniomaxillofac Surg*. 2010;38:605-609.
67. Markey AC, Glogau RG. Autologous fat grafting: comparison of techniques. *Dermatol Surg*. 2000;26:1135-1139.
68. Grimaldi M, Gentile P, Labardi L, Silvi E, Trimarco A, Cervelli V. Liposculpture technique in Romberg syndrome. *J Craniofac Surg*. 2008;19:1089-1091.

69. Wang F, Garza LA, Kang S, et al. In vivo stimulation of de novo collagen production caused by cross-linked hyaluronic acid dermal filler injections in photodamaged human skin. *Arch Dermatol.* 2007;143:155-163.
70. Narins RS, Dayan SH, Brandt FS, Baldwin EK. Persistence and improvement of nasolabial fold correction with nonanimal-stabilized hyaluronic acid 100,000 gel particles/mL filler on two retreatment schedules: results up to 18 months on two retreatment schedules. *Dermatol Surg.* 2008;34(suppl 1):S2-S8. discussion S8.
71. Choksi AN, Orringer JS. Linear morphea-induced atrophy treated with hyaluronic acid filler injections. *Dermatol Surg.* 2011;37:880-883.
72. Sivek R, Emer J. Use of a blunt-tipped microcannula for soft tissue filler injection in the treatment of linear scleroderma (en coup de sabre). *Dermatol Surg.* 2014;40:1439-1441.
73. Watchmaker J, Saadeh D, Lam C, Vashi NA. A case of bilateral Parry-Romberg syndrome successfully treated with hyaluronic acid filler augmentation [epub ahead of print]. *J Cosmet Dermatol.* 2020. <https://doi.org/10.1111/jocd.12948>. Accessed May 11, 2020.
74. Melvin OG, Hunt KM, Jacobson ES. Hyaluronidase treatment of scleroderma-induced microstomia. *JAMA Dermatol.* 2019; 155:857-859.
75. Carvalho Costa IM, Salaro CP, Costa MC. Polymethylmethacrylate facial implant: a successful personal experience in Brazil for more than 9 years. *Dermatol Surg.* 2009;35:1221-1227.
76. Franco JP, Serra MS, Lima RB, D'Acri AM, Martins CJ. Scleroderma en coup de sabre treated with polymethylmethacrylate - case report. *An Bras Dermatol.* 2016;91:209-211.
77. Cox SE, Soderberg JM. Idiopathic hemifacial atrophy treated with serial injections of calcium hydroxylapatite. *Dermatol Surg.* 2010;36:542-545.
78. Chen JT, Schmid DB, Israel JS, Siebert JW. A 26-year experience with microsurgical reconstruction of hemifacial atrophy and linear scleroderma. *Plast Reconstr Surg.* 2018;142: 1275-1283.
79. Knobler R, Moinzadeh P, Hunzelmann N, et al. European Dermatology Forum S1-guideline on the diagnosis and treatment of sclerosing diseases of the skin, part 1: localized scleroderma, systemic sclerosis and overlap syndromes. *J Eur Acad Dermatol Venereol.* 2017;31:1401-1424.
80. Tollefson MM, Witman PM. En coup de sabre morphea and Parry-Romberg syndrome: a retrospective review of 54 patients. *J Am Acad Dermatol.* 2007;56:257-263.
81. Roh MR, Jung JY, Chung KY. Autologous fat transplantation for depressed linear scleroderma-induced facial atrophic scars. *Dermatol Surg.* 2008;34:1659-1665.
82. Mertens JS, Seyger MMB, Thurlings RM, Radstake T, de Jong E. Morphea and eosinophilic fasciitis: an update. *Am J Clin Dermatol.* 2017;18:491-512.
83. Tolkachjov SN, Patel NG, Tollefson MM. Progressive hemifacial atrophy: a review. *Orphanet J Rare Dis.* 2015;10:39.
84. Slack GC, Tabit CJ, Allam KA, Kawamoto HK, Bradley JP. Parry-Romberg reconstruction: optimal timing for hard and soft tissue procedures. *J Craniofac Surg.* 2012;23(7 suppl 1):1969-1973.
85. Guerrerosantos J, Guerrerosantos F, Orozco J. Classification and treatment of facial tissue atrophy in Parry-Romberg disease. *Aesthetic Plast Surg.* 2007;31:424-434.
86. Lee JH, Lim SY, Lee JH, Ahn HC. Surgical management of localized scleroderma. *Arch Craniofac Surg.* 2017;18:166-171.
87. Barin EZ, Cinal H, Cakmak MA, Tan O. Treatment of linear scleroderma (en coup de sabre) with dermal fat grafting. *J Cutan Med Surg.* 2016;20:269-271.
88. Lapierre JC, Aasi S, Cook B, Montalvo A. Successful correction of depressed scars of the forehead secondary to trauma and morphea en coup de sabre by en bloc autologous dermal fat graft. *Dermatol Surg.* 2000;26:793-797.
89. Kim KT, Sun H, Chung EH. A surgical approach to linear scleroderma using Medpor and dermal fat graft. *Arch Craniofac Surg.* 2019;20:112-115.
90. Agrawal K, Desai V, Choudhary S, Vora S, Gupta S, Bachhav M. A new minimally invasive aesthetic procedure for correction of frontal coup de sabre deformity in Romberg's syndrome. *J Maxillofac Oral Surg.* 2015;14(suppl 1):401-406.
91. Qiao J, Gui L, Fu X, et al. A novel method of mild to moderate Parry-Romberg syndrome reconstruction: computer-assisted surgery with mandibular outer cortex and fat grafting. *J Craniofac Surg.* 2017;28:359-365.
92. Eisen D, Alster TS. Use of a 585 nm pulsed dye laser for the treatment of morphea. *Dermatol Surg.* 2002;28:615-616.
93. Ciatti S, Varga J, Greenbaum SS. The 585 nm flashlamp-pumped pulsed dye laser for the treatment of telangiectases in patients with scleroderma. *J Am Acad Dermatol.* 1996;35(3 pt 1):487-488.
94. St Surin-Lord S, Obagi S. Scleroderma and raynaud's phenomenon improve with high-peak power laser therapy: a case report. *Dermatol Surg.* 2011;37:1531-1535.
95. Chodkiewicz HM, Greenway HT Jr, Housman L. Successful treatment of a scleroderma-associated leg ulcer with endovenous laser ablation. *Dermatol Surg.* 2018;44:1153-1155.
96. Zanelato TP, Marquesini G, Colpas PT, Magalhaes RF, Moraes AM. Implantation of autologous fat globules in localized scleroderma and idiopathic lipoptrophy—report of five patients. *An Bras Dermatol.* 2013;88(6 suppl 1):120-123.
97. Oh CK, Lee J, Jang BS, et al. Treatment of atrophies secondary to trilinear scleroderma en coup de sabre by autologous tissue cocktail injection. *Dermatol Surg.* 2003;29:1073-1075.
98. Del Papa N, Caviggioli F, Sambataro D, et al. Autologous fat grafting in the treatment of fibrotic perioral changes in patients with systemic sclerosis. *Cell Transplant.* 2015;24:63-72.
99. Clauser LC, Tieghi R, Galie M, Carinci F. Structural fat grafting: facial volumetric restoration in complex reconstructive surgery. *J Craniofac Surg.* 2011;22:1695-1701.
100. Hammer-Hansen N, Akram J, Damsgaard TE. The versatility of autologous fat transplantation in correction of facial deformities: a single-center experience. *Plast Surg Int.* 2015; 2015:703535.
101. Hunstad JP, Shifrin DA, Kortesis BG. Successful treatment of Parry-Romberg syndrome with autologous fat grafting: 14-year follow-up and review. *Ann Plast Surg.* 2011;67:423-425.
102. Avelar RL, Goelzer JG, Azambuja FG, de Oliveira RB, de Oliveira MP, Pase PF. Use of autologous fat graft for correction of facial asymmetry stemming from Parry-Romberg syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2010;109:e20-e25.
103. Sterodimas A, Huanquipaco JC, de Souza Filho S, Bornia FA, Pitanguy I. Autologous fat transplantation for the treatment of Parry-Romberg syndrome. *J Plast Reconstr Aesthet Surg.* 2009;62:e424-e426.
104. Alencar JC, Andrade SH, Pessoa SG, Dias IS. Autologous fat transplantation for the treatment of progressive hemifacial atrophy (Parry-Romberg syndrome: case report and review of medical literature). *An Bras Dermatol.* 2011;86(4 suppl 1):S85-S88.
105. Consorti G, Tieghi R, Clauser LC. Frontal linear scleroderma: long-term result in volumetric restoration of the fronto-orbital area by structural fat grafting. *J Craniofac Surg.* 2012;23:e263-e265.

106. Ho-Asjoe M, Khan J, Frame JD. Dermal grafting for a patient with scleroderma. *Case report. Scand J Plast Reconstr Surg Hand Surg.* 1996;30:325-327.
107. Longobardi G, Pellini E, Diana G, Finocchi V. Rhytidectomy associated with autologous fat transplantation in Parry-Romberg syndrome. *J Craniofac Surg.* 2011;22:1031-1034.
108. Rodby KA, Kaptein YE, Roring J, et al. Evaluating autologous lipofilling for Parry-Romberg syndrome-associated defects: a systematic literature review and case report. *Cleft Palate Craniofac J.* 2016;53:339-350.
109. Van der Cruyssen FM, Schoenaers J, Politis J, Parry C. Romberg syndrome: a long-term retrospective cohort study of 10 patients. *Oral Maxillofac Surg Cases.* 2018;4:73-83.
110. Cortese A, Savastano G, Felicetta L. Free fat transplantation for facial tissue augmentation. *J Oral Maxillofac Surg.* 2000;58:164-169. discussion 169-170.
111. Moscona R, Ullman Y, Har-Shai Y, Hirshowitz B. Free-fat injections for the correction of hemifacial atrophy. *Plast Reconstr Surg.* 1989;84:501-507. discussion 508-509.
112. Xie Y, Li Q, Zheng D, Lei H, Pu LL. Correction of hemifacial atrophy with autologous fat transplantation. *Ann Plast Surg.* 2007;59:645-653.
113. Roddi R, Riggio E, Gilbert PM, Hovius SE, Vaandrager JM, van der Meulen JC. Clinical evaluation of techniques used in the surgical treatment of progressive hemifacial atrophy. *J Craniomaxillofac Surg.* 1994;22:23-32.
114. Chajchir A, Benzaquen I. Fat-grafting injection for soft-tissue augmentation. *Plast Reconstr Surg.* 1989;84:921-934. discussion 935.
115. Harp A, Liu YF, Inman JC, Ardestirpour F. Autologous lipoinjection in Parry-Romberg syndrome. *Ear Nose Throat J.* 2018;97:151-152.
116. Scuderi N, Ceccarelli S, Onesti MG, et al. Human adipose-derived stromal cells for cell-based therapies in the treatment of systemic sclerosis. *Cell Transplant.* 2013;22:779-795.
117. Virzi F, Bianca P, Giannona A, et al. Combined platelet-rich plasma and lipofilling treatment provides great improvement in facial skin-induced lesion regeneration for scleroderma patients. *Stem Cell Res Ther.* 2017;8:236.
118. Onesti MG, Fioramonti P, Carella S, Fino P, Marchese C, Scuderi N. Improvement of mouth functional disability in systemic sclerosis patients over one year in a trial of fat transplantation versus adipose-derived stromal cells. *Stem Cells Int.* 2016;2016:2416192.
119. Thareja SK, Sadhwani D, Alan Fenske N. En coup de sabre morphea treated with hyaluronic acid filler. Report of a case and review of the literature. *Int J Dermatol.* 2015;54:823-826.
120. Arsiwala SZ. Persistence of hyaluronic acid filler for subcutaneous atrophy in a case of circumscribed scleroderma. *J Cutan Aesthet Surg.* 2015;8:69-71.
121. Ozturk S, Acarturk TO, Yapici K, Sengezer M. Treatment of 'en coup de sabre' deformity with porous polyethylene implant. *J Craniofac Surg.* 2006;17:696-701.
122. Ye XD, Li CY, Wang C, Yu YS. Superficial temporal fascial flap plus lipofilling for facial contour reconstruction in bilateral progressive facial hemiatrophy. *Aesthetic Plast Surg.* 2010;34:534-537.
123. Denadai R, Buzzo CL, Raposo-Amaral CA, Raposo-Amaral CE. Facial contour symmetry outcomes after site-specific facial fat compartment augmentation with fat grafting in facial deformities. *Plast Reconstr Surg.* 2019;143:544-546.
124. Liapakis IE, Tzouganakis AC, Paschalidis EI, et al. Parry-Romberg syndrome treatment with fat transfer and a new bleaching formula [epub ahead of print]. *J Cosmet Dermatol.* 2020. <https://doi.org/10.1111/jocd.12819>. Accessed May 9.
125. Eguchi T, Harii K, Sugawara Y. Repair of a large "coup de sabre" with soft-tissue expansion and artificial bone graft. *Ann Plast Surg.* 1999;42:207-210.
126. Robitschek J, Wang D, Hall D. Treatment of linear scleroderma "en coup de sabre" with AlloDerm tissue matrix. *Otolaryngol Head Neck Surg.* 2008;138:540-541.
127. Chai G, Tan A, Yao CA, et al. Treating Parry-Romberg syndrome using three-dimensional scanning and printing and the anterolateral thigh dermal adipofascial flap. *J Craniofac Surg.* 2015;26:1826-1829.

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Cosmetic treatment in patients with autoimmune connective tissue diseases

Best practices for patients with lupus erythematosus

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Learning objectives

After completing this learning activity, participants will be able to review cutaneous manifestations of systemic sclerosis and morphea, including en coup de sabre and progressive hemifacial atrophy, and discuss the physiological and psychological burden of these diseases; discuss and compare different laser treatments, injectables, and surgical options for cutaneous deficits attributable to these diseases; and describe objective and subjective outcomes of these procedures including long-term follow up data and associated side effects among this unique population.

Disclosures

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The cutaneous manifestations of lupus, especially chronic cutaneous lupus erythematosus, are a source of significant morbidity and can negatively impact patient quality of life. While the active inflammatory component of the disease may be adequately treated, patients are frequently left with residual skin damage and disfiguring aesthetic deficits. Dermatologists lack guidelines regarding the use and safety of various reconstructive and cosmetic interventions in this patient population. Laser treatments are largely avoided in the lupus population because of the possible photodamaging effects of ultraviolet and visible light. Similarly, given the autoimmune nature of this disease, some physicians avoid injectable treatment and grafts because of the concern for disease reactivation via antigenic stimulation. In the second article in this continuing medical education series we compile available data on this topic with the goal of providing evidence-based guidance on the cosmetic treatment of patients with lupus erythematosus with a focus on chronic cutaneous lupus erythematosus. (J Am Acad Dermatol 2020;83:343-63.)

Key words: calcium hydroxyapatite; fat transfer; hyaluronic acid; injectables; intense pulsed light; laser treatment; lipoinjection; lupus; mental health; poly-L-lactic acid; polymethylmethacrylate; pulsed dye laser; quality of life.

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Abbreviations used:

ACLE:	acute cutaneous lupus erythematosus
CCLE:	chronic cutaneous lupus erythematosus
DLE:	discoid lupus erythematosus
HA:	hyaluronic acid
IPL:	intense pulsed light
Nd:YAG:	neodymium-doped yttrium aluminum garnet
QoL:	quality of life
PDL:	pulsed dye laser
SCLE:	subacute cutaneous lupus erythematosus
SLE:	systemic lupus erythematosus

CUTANEOUS MANIFESTATIONS OF CHRONIC CUTANEOUS LUPUS ERYTHEMATOSUS

Cutaneous manifestations of lupus, especially chronic cutaneous lupus erythematosus (CCLE), are a source of significant morbidity and can negatively impact patient quality of life (QoL).¹ While the active inflammatory component of the disease may be adequately treated, patients are frequently left with residual skin damage and disfiguring aesthetic deficits.² Cutaneous lupus erythematosus (CLE) is comprised of 3 major subcategories, each with unique clinical characteristics: acute CLE (ACLE), subacute CLE (SCLE), and CCLE. Patients with systemic lupus erythematosus (SLE) can present with any form of cutaneous lupus; however, the association with systemic disease in patients presenting with skin disease tends to be highest with ACLE and lowest with CCLE.³⁻⁵

[F1-4/C] Patients with ACLE and SCLE (Fig 1) typically have more transient skin disease and fewer post-inflammatory changes than patients with CCLE. Discoid lupus erythematosus (DLE), lupus profundus/panniculitis, and tumid lupus are a few of the more common variants of CCLE. While there are limited epidemiologic data available about CCLE, the annual incidence is estimated to be about 4 per 100,000 with a prevalence of 70 per 100,000.⁶ African American females represent the largest demographic of CCLE patients,⁷ which is particularly problematic given often more severe and bothersome scarring and pigmentary changes are seen in this subset with darker Fitzpatrick skin phototypes. Patients with CCLE subtypes seek cosmetic intervention more commonly than patients with ACLE and SCLE, and therefore will be primarily discussed in this article.

Discoid lupus erythematosus

Discoid lesions are characterized by erythematous, well-demarcated plaques with overlying



Fig 1. Photodistributed erythematous, scaly plaques of subacute cutaneous lupus erythematosus.

adherent scale and follicular plugging (Fig 2). **[F2-4/C]** Plaques are often indurated and are commonly found on the scalp, face, and ears. Scarring is an important concern and is a common sequela in long-standing lesions. Atrophic, hypertrophic, cribriform, and acneiform scarring have all been described in patients with DLE.² In addition, dyspigmentation with central hypopigmentation and peripheral hyperpigmentation, alopecia, and telangiectasia are common sequelae of DLE.

Lupus profundus/panniculitis

Lupus panniculitis occurs when there is inflammation of the subcutaneous fat, which leads to indurated, painful, inflammatory nodules (Fig 3). Some experts refer to this condition as lupus **[F3-4/C]** profundus when there are overlying discoid features in addition to panniculitis. Common locations for lupus panniculitis/profundus include the proximal extremities, chest, and face. Lipoatrophy with significant contour change is frequently seen in the post-inflammatory phase.⁸⁻¹⁰

Lupus erythematosus tumidus

Lupus erythematosus tumidus is characterized by photodistributed erythematous, edematous smooth plaques without epidermal involvement. Typically, these lesions resolve without sequela unlike the other subtypes of CCLE.¹¹⁻¹³

IMPACT ON QUALITY OF LIFE AND PSYCHOLOGICAL WELL-BEING

Lupus is a cosmetically disfiguring condition, and its occurrence on easily visible skin, specifically the face and upper extremities, may have a profound impact on QoL¹ and psychological well-being leading to anxiety, depression, and low self-esteem.¹⁴ Although there is limited literature measuring the



Fig 2. **A**, Plaques of discoid lupus erythematosus with hyperpigmented and telangiectatic components on the nose, upper vermillion border, and chin. **B**, Discoid lupus with resultant scarring and hypopigmentation. **C**, Discoid lupus lesions on the chest with peripheral hyperpigmentation, erythema, and central hypopigmentation.



Fig 3. **A** and **B**, Lupus panniculitis in patients on systemic immunosuppression.

impact of cosmetic treatment in patients with lupus, studies using cosmetic camouflage reported improvement in health-related quality of life measures by the Dermatology Life Quality Index,¹⁵ and cognitive behavior therapy and appearance enhancement counseling have been found to improve body image and QoL.¹⁶ A prospective study analyzing disease activity and quality of life measured by Skindex-29 among patients with cutaneous lupus reported that disease improvement does not seem to directly correlate with an improvement in quality of life,¹⁷ suggesting that disease damage and subsequent cosmetic sequelae also play a role. In addition, facial lesions, younger age, and female gender have been found to impair QoL.¹⁸

USE OF LASER AND LIGHT-BASED THERAPY

Key points

- The use of low fluences is hypothesized to reduce the risk of laser-induced disease exacerbation
- Early treatment with pulsed dye laser is hypothesized to prevent progression to scarring disease
- Many published reports document the positive response to laser and intense pulsed light treatment in patients with lupus erythematosus

In the past, the use of laser therapy in patients with lupus has been controversial given the photosensitive nature of this disease. In addition, the potential side effects from laser and intense pulsed light (IPL) treatments may be particularly concerning in patients with darker Fitzpatrick skin phototypes who comprise the majority of patients with DLE. A combination of photoprotection and medical management with topical immune-modulators and systemic antimalarial medications remains the first-line treatment for cutaneous lupus.¹⁹ However, in recent years, multiple case reports, case series, and 1 double blind randomized controlled trial have described the distinct use of lasers to treat refractory lupus-associated erythema of active disease and hyperpigmentation and scarring of inactive disease. It must be noted that objective evaluation methods of treatment efficacy for cutaneous lupus are limited; in addition, the few established disease activity scoring systems, such as the Cutaneous Lupus Erythematosus Disease Area and Severity Index, are not validated for lupus panniculitis/profundus.¹⁹⁻²²

Discoid lesions of lupus erythematosus are particularly challenging to treat because they are comprised of telangiectasia, dermal hyperpigmentation, and scarring. A combination of IPL and Q-switched neodymium-doped yttrium aluminum garnet (Nd:YAG) was reportedly well-tolerated in treating 1 patient with active DLE given that IPL can target the more superficial telangiectasia and Nd:YAG can target the dermal melanosomes.^{23,24} Nd:YAG is a nonablative laser used for its horizontal scattering within the dermis that can induce dermal collagen formation while reducing the risk of epidermal wounds.²⁵ Erbium-doped yttrium aluminum garnet laser has also been reported for the treatment of discoid lupus scarring.^{26,27} This ablative laser modality sacrifices efficacy in dermal collagen remodeling for decreased tissue damage and decreased healing times when compared with



Fig 4. Patient with systemic lupus erythematosus with persistent malar erythema before treatment with a pulsed dye laser.



Fig 5. A, A patient with lupus tumidus before pulsed dye laser treatment. **B,** Immediately after pulsed dye laser treatment (wavelength 595 nm, spot size 5 mm, pulse 3 msec, fluence 7.5 J) showing expected response with minimal to no purpura with recommended treatment parameters of low fluence and short pulse duration.

CO₂ ablative lasers.^{28,29} In addition, argon lasers (nonablative) have been used to treat erythematous, hyperkeratotic plaques, and telangiectasia of active DLE with subjective resolution of lesions and no scarring or pigmentary changes at 6 months of follow-up.³⁰ Argon lasers were once commonly used for vascular and pigmentary lesions, but the advantage of selective thermolysis and, thus, reduced scarring and pigmentary changes seen in newer pulsed dye lasers (PDLs) has led to decreased use.³¹

IPL has been used with positive response in treating the chronic facial erythema and burning [F4-4/C] associated with active SLE (Fig 4).³² In addition to IPL, several studies have shown that PDL, when used at low fluences, is well tolerated when treating the vascular component of cutaneous lupus lesions and [F5-4/C] may even prevent disease progression (Fig 5).^{26,33-35}

Therefore, some authors advocate for the early use of PDL given that end stage lesions are more resistant to laser treatment.^{26,33,34} It has been hypothesized that the selective destruction of dermal microvasculature by PDL inhibits the migration of inflammatory cells and thus prevents disease progression.²² This theory is supported by the histopathologic results of biopsy

Table I. Argon laser therapy for lupus

Authors/study type	N	Disease	Age/skin type	Treatment/ location	Settings	Cooling/ postoperative	Sessions/ interval	Perioperative medication	Results	Follow-up	Side effects
Kuhn et al, ³⁰ 2000 case report	1	DLE	59 with 15-year disease history, active disease	Argon laser to cheek	Wavelength: 514 nm; power/ fluence: 2W; pulse size: 100 ms; spot size: 1 mm; no overlapping	NR	5 sessions at NR 1-month intervals	Subjective significant improvement after 2 sessions, complete resolution after 5	6 months	No pigment changes or scarring	Laser-induced DLE
Wolfe et al, ³⁷ 1997 case report	1	Nasal bridge telangiectasia, laser-induced DLE	32 with Fitzpatrick skin type III with no history of lupus	Argon laser to nose	Wavelength: 514 nm; power/ fluence: 4.9 W, 2.2-30 J/cm ² ; pulse size: 36-48 ms; spot size: 13 mm hexagon, 1 mm individual spot	Topical polymyxin B sulfate	1	NR	Sharply demarcated purple plaque, biopsy showed lymphocytic infiltrate with vacuolar alteration and keratinocyte necrosis	2 weeks	

Table II. Intense pulsed light therapy for lupus

Authors/ study type	N	Disease	Age	Treatment/ location	Settings	Cooling/ postoperative	Sessions/ interval	Perioperative medication	Results	Follow-up	Side effects
Byun et al, ²³ 2017 case report	1	DLE	42 with 20-year disease history	IPL on cheek and later combination treatment with Q-switched Nd:YAG (see Table III)	Wavelength: 555-950 nm; power/fluence: 11-12 J/cm ² ; pulse size: 8 mm	NR	3 sessions at 3- to 5-week intervals	NR	Subjective improvement in erythema but not hyperpigmentation	1 year	Mild erythema and oozing during treatment
Ekback and Troilius, ²⁶ 2013 retrospective case series	4	DLE/ SCLE	28-69 (mean 54)	IPL on face, scalp, shoulder, lower leg, nail matrix, arms (1 patient also treated with PDL)	Wavelength: 530-750 nm; power/fluence: 8-13 J/cm ² ; pulse: 8-13 ms	NR	3-5 sessions	1 patient treated with 5 mg prednisolone and clobetasol	Cleared (n = 2), improved (n = 1), cleared face/ improved arms (n = 1)	3-24 months	Blushing and swelling
Levy ³² 2000 case report	1	SLE	33 with 5-year disease history, patient reported disease currently active	IPL on face	Wavelength: 515-1200 nm; pulse/fluence: 22 J/cm ²	NR	2 sessions at 2-month interval	100 mg antimalarial daily	Subjective 75% improvement, flushing and burning relieved for 1 year	1 year, patient requested repeat yearly treatments	None

DLE, Discoid lupus erythematosus; IPL, intense pulsed light; NR, not reported; PDL, pulsed dye laser; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus.

Table III. Erbium-doped yttrium aluminum garnet and neodymium-doped yttrium aluminum garnet laser therapy for lupus

Authors/ study type	N	Disease	Age	Treatment/ location	Settings	Cooling/ postoperative	Sessions/ interval	Perioperative medication	Results	Follow-up	Side effects
Byun et al, ²³ 2017 case report	1	DLE	42 with 20-year disease history	Q-switched Nd:YAG (alone and combined with IPL) on cheek after previous IPL treatment failed to improve hyperpigmentation	Wavelength: 1064 nm; power/fluence: 6-6.5 J/cm ² ; frequency: 10 Hz; spot size: 3 mm	NR	3 sessions at NR 3- to 5-week intervals	Subjective improvement in hyperpigmentation (alone and combination) and erythema (combination only)	1 year	Mild erythema and oozing during treatment	
Ekback and Troilius, ²⁶ 2013 retrospective case series	1	DLE	39	Erbium YAG laser to face	NR	NR	1 session	None	Scarring persistent but improved	10 months	None
Tremblay and Carey, ²⁷ 2001 case report	1	DLE	66 with 25-year disease history, currently inactive	Er:YAG laser to lips, nose, chin	Wavelength: 2940 nm; power/fluence: 10.2-28.3 J/cm ² ; frequency: 5 pulses/second; spot size: 3-5 mm, 6-10 passes	5 days hydrogel sheet dressing changed daily	2 sessions at 3-week interval (different lesions treated at each session)	NR, although states that patient's disease had been controlled with potent topical steroids	Good subjective cosmetic result	2 years	Mild erythema at 3 weeks; no scarring; no reactivation in treated or other areas
Park et al, ⁶⁶ 2011 case report	1	DLE	24 with 2-year disease history	Nd:YAG to cheek	Wavelength: 1064 nm; power/fluence: 45 J/cm ² ; pulse: 20 ms; spot size: 5 mm	NR	3 sessions at NR 3-week intervals	Subjective significant improvement with good cosmetic results	1 year	Slight erythema and swelling 1 day after treatment	

DLE, Discoid lupus erythematosus; Er:YAG, erbium-doped yttrium aluminum garnet; Nd:YAG, neodymium-doped yttrium aluminum garnet; NR, not reported.

Table IV. CO₂ laser therapy for lupus

Authors/ study type	N	Disease	Age	Treatment/ location	Settings	Cooling/ postoperative	Sessions/ interval	Perioperative medication	Results	Follow-up	Side effects
Ekback and Troilius, ²⁶ 2013 retrospective case series	1	DLE with severe scarring	50	CO ₂ laser to face	NR	NR	1 session	Chloroquine	Improved	1 month	None
Henderson and Odom, ⁶⁷ 1986 case report	1	DLE	36 with disease since 23	CO ₂ laser to forehead, nose, lips, chin, cheeks	Wavelength: 10.6 μm; power/fluence: 20 W with 2-mm spot size and 200-mm focal length	NR	5 sessions at 5- to 12-month intervals	NR	Subjective dramatic improvement of skin texture, majority of areas of active disease were inactivated; small areas of recurrence surrounding lasered areas and in the more superficially lasered areas after the first session, but the deeply lasered areas have remained free of disease	Unclear	Hypopigmentation
Walker and Harland, ⁶⁸ 2000 case report	1	DLE	45 with disease activity controlled by topical medication	CO ₂ laser to face	Power/fluence: 16 W; multiple passes until yellowish hue of dermal collagen visible	Topical chloramphenicol	1 session	Mepacrine 125 mg daily, clobetasol propionate cream	Patient satisfied with the result	16 months	None

CO₂, Carbon dioxide; DLE, discoid lupus erythematosus; NR, not reported.

Table V. Pulsed dye laser treatment for lupus

Authors/ study type	N	Disease	Age/skin type	Treatment/ location	Settings	Cooling/ postoperative	Sessions/ interval	Perioperative medication	Results	Follow-up	Side effects
Raulin et al, ³³ 1999 case series	12	DLE, SLE, SCLE, and CLE	26-62 (mean 44.1)	Flashlamp PDL on face, back, scalp, shoulder	Wavelength: 585 nm; power/ fluence for each pulse diameter: 3.4-3.5 J/cm ² for 10 mm; 3-7 J/cm ² for 7 mm; 6-7 J/cm ² for 5 mm; pulse size: 0.3-0.45 ms	NR	Mean: 5.1 sessions (1-10)	Chloroquine (n = 5), oral steroids (n = 2), topical steroids (n = 1); no medications (n = 5)	70% clearance (n = 9), no clearance (n = 1), no clearance but reduction in pain/itch (n = 2)	Median: 7 months (range 3-32), relapse in only 1 case after 6 months	Purple erythematous maculae, edema, and occasional crusts developed in the treated areas, healed after 6-14 days; 2 patients had transient hyperpigmentation that resolved after 4- 5 months
Baniandres et al, ⁴² 2003 retrospective case series	14	DLE and SLE	22-49, Fitzpatrick skin type II (n = 7), III (n = 5), IV (n = 2)	Flashlamp PDL (n = 3), long PDL (n = 11) on face, cheeks, trunk, arms, hands, scalp	FPDL: wavelength: 585 nm; power/ fluence: 5.75 J/cm ² ; pulse: 0.45 ms; spot size: 5 mm; LPDL: wavelength: 595 nm; power/fluence: 6-13 J/cm ² ; pulse: 1.5-10 ms; spot size: 7 mm	Dynamic cooling device of 20-20 to 60-20 ms	Repeated as long as improvement observed with 2- to 3-month intervals	Unable to determine if medications were concurrent with therapy	Average clearance rate of 60%	Median: 10 months; partial relapse in 3 patients after 1 year	Hyperpigmentation (n = 4) that resolved in 4-6 months, all in patients with Fitzpatrick type III/IV skin; mild atrophic scarring (n = 1) likely because of pulse stacking
Erceg et al, ²² 2009 prospective case series	12	DLE, all had ≥ 1 active CDLE lesion	37-69 (mean 52.8)	PDL to nose, scalp, forehead, lip, back, cheek, arm	Wavelength: 585 nm; power/fluence: 5.5 J/cm ² ; pulse: 0.45 ms; spot size: 7 mm with 1 pass and 10-20% overlap	Cooling device during and after	3 sessions at 6-week intervals	Oral medications continued if stable treatment schedule for previous 6 months, otherwise no oral medications	3.1-point decrease in active CLASI (erythema, scaling, hypertrophy), no effect on damage CLASI (scarring, atrophy, panniculitis)	6 weeks	Mild hyperpigmentation (n = 1)
Nunez et al, ⁶⁹ 1996 case series	4	SLE	42-46; age at treatment not provided for 2 patients	Flashlamp PDL to face, cheeks, hands, trunk	Wavelength: 585 nm; power/fluence: 6.75-7.75 J/cm ² ; pulse: 0.45 ms; spot size: 5 mm	NR	3-6 sessions, interval NR	NR	>75% of lesions cleared	16 weeks	Mild transient hyperpigmentation (n = 1)
Ekback and Troilius, ²⁶ 2013 retrospective case series	12	DLE, SCLE	28-69 (mean 54)	PDL to face, scalp, shoulder, arms, breast, leg	Setting 1: 585 nm, 5 mm spot, 0.45 ms, 5.75-6.75 J/cm ² , endpoint was slight erythema; setting 2: 595 nm, 7 mm spot size, 0.45-1.5 ms pulse, 7.5-9 J/cm ² , endpoint was slight erythema	3/20 dynamic cooling device	Mean of 5 sessions (range 1-11)	6 patients on oral meds: chloroquine (n = 6), prednisolone 5 mg (n = 1), beta-methasone (n = 1)	All patients' lesions were 3-130 months (mean either cleared or improved; 2 patients had recurrence of lesions, and 2 patients had appearance of new lesions	44 months	None
Gupta et al, ⁷⁰ 1999 case report	1	SCLE	39 with 14-year disease history	PDL to face	Wavelength: 585 nm; power/fluence: 5.3 J/cm ² ; pulse: 0.45 ms; spot size: 5 mm	NR	4 sessions at 1-month intervals	NR	Subjective marked improvement of erythema	NR	NR

Diez et al, ⁴³ 2011 prospective open label	9	DLE, SLE, LE tumidus, all patients had ≥ 1 active CLE lesion	31-69 (mean 45.3)	PDL to face, hands, back, arm	Wavelength: 595 nm; power/fluence: 11 J/cm ² ; pulse: 2 ms; spot size: 7 mm	Air cooling system	NR	Systemic medication continued if no changes in past 6 months, 4-week washout for topical medication	4 had "total improvement" of erythema and scaling, 4 had "improvement," no changes in 1; no changes in pigmentation, scarring, or atrophy; all patients satisfied, regardless of objective results	NR	None
Nunez et al, ⁷¹ 1995 case report	1	LE telangiectoides	42	Flashlamp PDL to cheek	Wavelength: 585 nm; power/fluence: 7.25-8.75 J/cm ² ; pulse: 0.45 ms; spot size: 5 mm; superimposed double pulse to areas of thicker telangiectasia	NR	5 sessions, interval NR	None	Excellent subjective response	16 weeks	None
Truchuelo et al, ³⁶ 2012 prospective study	10	Lupus tumidus (none met criteria for SLE)	36-62 (mean 46)	PDL to back, thorax, face, arms, buttocks, legs	Wavelength: 595 nm; power/fluence: 8 J/cm ² ; pulse: 0.5 ms; spot size: 10 mm	Air cooling system	1 session	8-week washout for topical and systemic medication	Mean patient satisfaction 8.5/10, all showed clinical improvement, 9/10 had reduced dermal lymphocytic infiltrate on biopsy	At 6 months, 5/10 patients had new lesions nearby or distant to treated areas	Purpura (necessary to achieve results): n = 10, immediate postoperative pain (n = 6), transient hypopigmentation (n = 1), transient hyperpigmentation (n = 2)
Izikson et al, ⁷² 2008 case report	2	SLE port wine stain	Patient 1: 49, skin type II; patient 2: 27, skin type II-III	Patient 1: PDL and later alexandrite laser to forehead; patient 2: PDL arm, hand, shoulder	Patient 1 PDL: wavelength: 595 nm; power/ fluence: 8-12.5 J/cm ² ; pulse: 0.45-1.5 ms; spot size: 7 mm 20-57 pulses; patient 1 Alexandrite: wavelength: 755 nm; power/fluence: 40- 55 J/cm ² ; pulse: 1.5 ms; spot size: 8 mm 8-9 pulses; patient 2 PDL: wavelength: 595 nm; power/fluence: 7-8 J/cm ² ; pulse: 0.45 ms; spot size: 7 mm 325-700 pulses	Patient 1 PDL: dynamic cooling device 20/20-40/20; patient 1 alexandrite: dynamic cooling device 40/40; patient 2 PDL: dynamic cooling device 30/20	Patient 1: 19 PDL sessions at 1-month interval, 2 alexandrite sessions at 1-month interval; patient 2: 3 sessions at 4- to 5-week intervals	Patient 1: hydroxychloroquine, methotrexate, synthroid folic acid; patient 2: hydroxychloroquine	Patient 1: initially responded well but later became treatment resistant and switched to alexandrite laser with mild improvement after each session; patient 2: treated areas 70-80% lighter at 1 month	NR	Prolonged pain/swelling of arm, blisters on forearm and fingers that resolved over 5 weeks with mild desquamation and no residual scarring after treatment with 1% cortisone cream and Tylenol for pain; hypopigmented areas on shoulder; purpura and erythema, but no lupus flare or other pigmentary alteration

Continued

Table V. Cont'd

Authors/ study type	N	Disease	Age/skin type	Treatment/ location	Settings	Cooling/ postoperative	Sessions/ interval	Perioperative medication	Results	Follow-up	Side effects
Rernknimitr et al, ³⁵ 2018 DBRCT	9	DLE	Mean 38.5 with 6.23-year disease duration; Fitzpatrick skin type III (n = 2), IV (n = 7)	PDL to half of face, upper extremity, or trunk; lesions on opposite side served as control	Wavelength: 595 nm; power/fluence: 8 J/cm ² ; pulse: 6 ms; spot size: 7 mm; single pass, 10% overlap	Dynamic cooling device 30/20	4 sessions at 4-week intervals	Hydroxychloroquine (n = 8), prednisolone (n = 8), azathioprine (n = 3), cyclosporine (n = 1); no previous laser treatment and/ or topical therapy for DLE 4 weeks before the study	Lesions treated with the 24 weeks from first session, 3 months after last session	PDL demonstrated significantly more decreases in erythema index, texture index and improvement in Physician Global Assessment scores compared with the control; no significant difference in mCLASI	Tolerable pain, minimal hyperpigmentation in 10.41% of treated lesions
Yelamos et al, ⁷³ 2013 case report	1	DLE	9 with 1-year disease history	PDL to cheek, hands	Wavelength: 585 nm; power/fluence: 5.5 J/cm ² on cheeks; 7 J/cm ² on hands; pulse: 0.5 ms; spot size: 10 mm	NR	1 session	Topical steroids, topical tacrolimus, unclear if continued during procedure; hydroxychloroquine 200 mg/day	Hand lesions resolved completely after 1 month	"Almost 2 years"	Hyperpigmentation of cheeks that resolved after 6 months
Bras et al, ³⁴ 2016 case series	3	DLE	27-61, lesion duration 2-15 months, Fitzpatrick skin type III (n = 3)	PDL to eyelids	Wavelength: 595 nm; power/fluence: 8 J/cm ² ; pulse: 0.5 ms; spot size: 10 mm; treated until purpuric, some double passing but no pulse stacking	Air cooling at level 4, lesions covered in ultrasound gel	1-2 sessions at 4-week interval	Hydroxychloroquine (n = 1)	Significant improvement 6-10 months of erythema, scaling, edema, and telangiectasia; no improvement of madarosis	None	

CDLE, Chronic discoid lupus erythematosus; CLE, cutaneous lupus erythematosus; DLE, discoid lupus erythematosus; IPL, intense pulsed light; (m)CLASI, (modified) Cutaneous Lupus Erythematosus Disease Area and Severity Index; NR, not reported; PDL, pulsed dye laser; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus.

Table VI. Strength of recommendations for laser treatment for lupus

Recommendation	Recommendation no.	Level of evidence	Studies
Options for laser treatment in patients with lupus			
PDL	1.1	1B-III	Ekback and Troilius, ²⁶ Raulin et al, ³³ Bras et al, ³⁴ Rerknimitr et al, ³⁵ Truchuelo et al, ³⁶ Baniandres et al, ⁴² Diez et al, ⁴³ Nunez et al, ⁶⁹ Gupta and Roberts, ⁷⁰ Nunez et al, ⁷¹ Izikson et al, ⁷² and Yelamos et al ⁷³
IPL	1.2	III	Byun et al, ²³ Ekback and Troilius, ²⁶ and Levy ³²
Nd:YAG	1.3	III	Byun et al ²³ and Park et al ⁶⁶
Er:YAG	1.4	III	Ekback and Troilius ²⁶ and Tremblay and Carey ²⁷
CO ₂	1.5	III	Ekback and Troilius, ²⁶ Henderson and Odom, ⁶⁷ and Walker and Harland ⁶⁸
1450-nm diode	1.6	III	Jih et al ⁹⁰
PDL, when used at low fluences, appears to be well tolerated when treating the vascular component of cutaneous lupus lesions and may even prevent disease progression	1.7	1B-III	Ekback and Troilius, ²⁶ Raulin et al, ³³ Bras et al, ³⁴ and Rerknimitr et al ³⁵

Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥ 1 randomized controlled trial; level IIA evidence includes evidence from ≥ 1 controlled study without randomization; level IIB evidence includes evidence from ≥ 1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

Er:YAG, Erbium-doped yttrium aluminum garnet; IPL, intense pulsed light; Nd:YAG, neodymium-doped yttrium aluminum garnet; PDL, pulsed dye laser.

specimens from 10 patients with lupus tumidus treated with PDL, of which 9 of 10 showed reduced dermal lymphocytic infiltrate at 4 weeks postoperatively compared with the preoperative histopathologic results.³⁶ In addition, a randomized split-body trial evaluating PDL as an adjuvant treatment compared with no treatment for discoid lesions found improvement in the erythema index, texture index, and physician global assessment score in the treatment group.³⁵

Although most experts recommend only treating inactive disease until more safety data are available, active lesions of chronic DLE have been treated in 12 patients with PDL therapy.²² Overall, there was a significant 3.1-point decrease in the active Cutaneous Lupus Erythematosus Disease Area and Severity Index (erythema, scaling, and hypertrophy), a validated outcome measure for cutaneous lupus, and only 1 patient experienced slight hyperpigmentation. Nine of the 12 patients were continued on their disease-modifying medications during treatment, all

of which were started >6 months before treatment with no dosage changes within that timeframe. Although limited by sample size and the lack of a control group, PDL may be considered for patients with discoid lesions that remain active despite optimal medical management (level of evidence III).

To our knowledge, there is only a single case of potential laser-induced DLE in a previously unaffected patient after argon laser treatment for nasal telangiectasia.³⁷ It remains unclear whether this represented laser-induced disease or if conversely the facial telangiectasia for which the patient sought laser treatment represented the initial stages of lupus activity that was subsequently exacerbated by the argon laser. IPL, in contrast with lasers, emits visible light and therefore has the potential to aggravate cutaneous and systemic disease.²³ While the ability of visible light to induce pigmentary changes has been studied, it may also have the potential to exacerbate lupus.^{38,39} For these reasons, patients with lupus should be advised to use physical

Table VII. Fat transfer for lupus

Author/ study type	N	Age/disease duration	Disease	Treatment	Location/amount	Sessions/ interval	Perioperative medication	Result	Side effects	Follow-up
Cortese et al, ⁷⁴ 2000 case series	1	NR	SLE	Autologous fat transfer	NR	1 session	NR	Poor, 90% resorption attributed to poor vascularization at recipient site	NR	NR
Yoon et al, ⁷⁵ 2012 case report	1	25 with 7-year disease history	Lupus profundus	Autologous fat transfer	Temporal area, amount NR	5 sessions at 1.5- to 2-month intervals	NR	Subjective impressive cosmetic benefit	None	6 months
Gleeson et al, ⁴⁵ 2010 case report	1	37 with 20-year disease history	Lupus profundus	Repeat autologous fat transfer (previously treated with fat transfer 10 years prior)	35 mL each cheek	1	Thalidomide 25 mg daily and prednisolone 7.5 mg daily	NR	Fat embolism and cardiac arrest leading to death	N/A
Lei et al, ⁷⁶ 2016 case series	18	28-50 (mean 37.3), all with stable disease	Lupus panniculitis	Autologous fat graft	3-9 mL to cheek, 5-10 mL to temple, 4-9 mL to zygoma, goal was 10-20% overcorrection	1-3 sessions at 3- to 6-month intervals	All lupus medication stopped ≥6 months prior	33.3% of patients, 27.8% of laypersons, and 38.9% of doctors were satisfied with the results. 44.4% of patients, 55.6% of laypersons, and 50.0% of doctors were mostly satisfied; no more resorption after 90 days	None	Mean 1.5 years
Valdatta et al, ⁷⁷ 2012 case report	1	55	Lupus profundus/ panniculitis	Coleman technique Lipofilling	Submalar, parotideal, perioral, mandibular; session 1: 12 mL; session 2: 15 mL; session 3: 18 mL	3 sessions at 6-month intervals	NR	Stable at 12 months, and submalar and parotideal atrophy was completely filled, natural appearing, and symmetric; cutaneous lesions of lupus syndrome were improved; first graft had unacceptable result, hypothesized to be related to patient's cigarette smoking in the immediate postoperative period	None other than antibiotic intolerance	12 months
Hammer- Hansen et al, ⁷⁸ 2015 case report	1	62	SLE	Autologous fat transfer	8.2 mL to malar area	1 session	NR	Additional treatment sessions planned at time of publication	None	4 months
Polívka et al, ⁷⁹ 2016 case report	2	13-year-old with 18-month history, and 32-year-old with 6-year history of SLE with development of lupus panniculitis lesions	Lupus panniculitis	Lipofilling	Submental and malar	NR	NR	Positive aesthetic outcome was maintained 3 years after the procedure with no signs of the recurrence of panniculitis; Dermatology Quality of Life Index decreased from 16 to 0.6 months postoperatively in 13-year-old patient	None	3 years

Yesilada et al, ⁸⁰ 2012 case report	1	26 with 2-year disease history	DLE	Autologous fat transfer	Session 1: 71.7 mL to frontal bar area, bilateral temples, bilateral malar prominences, bilateral upper eyelids and eyebrows, bilateral medial canthus, bilateral tear trough, and the lower eyelid subcutaneously and subdermally; session 2: 10 mL to frontal bar region and 20 mL to bitemporal regions	2 sessions at 6-month interval	Coenzyme Q10 30 mg TID for 3 months	At 3 months follow-up, down-slanted look on the lateral canthi remained; sunken orbit appearance and especially severe bitemporal hollowing seemed to diminish significantly; estimated 85% graft survival at 3 months	NR	3 months
Yoshimura et al, ⁴⁶ 2008 prospective cohort study with control group	5	25-48	Lupus profundus	Cell assisted lipotransfer (CAL) and non-CAL	Face, non-CAL group: 50-250 mL. CAL group: 90-100 mL; goal was 20% overcorrection	1 session	2 (n = 1 CAL and n = 1 non-CAL) taking oral prednisolone	Non-CAL group: good (n = 1), fair (n = 2). CAL group: good (n = 2); excellent (>80% improvement), good (60%-80% improvement), fair (40%-60% improvement); all patients obtained improvement in facial contour, but the CAL group had a better clinical improvement score than did the non-CAL patients, although the difference did not reach statistical significance	Adipose necrosis in 1 non-CAL case who took perioperative prednisolone; subcutaneous bleeding that resolved in 1-2 weeks; swelling that resolved in 4 weeks	9-10 months

CAL, Cell-assisted lipotransfer; DLE, discoid lupus erythematosus; NR, not reported; SLE, systemic lupus erythematosus; TID, ter en die.

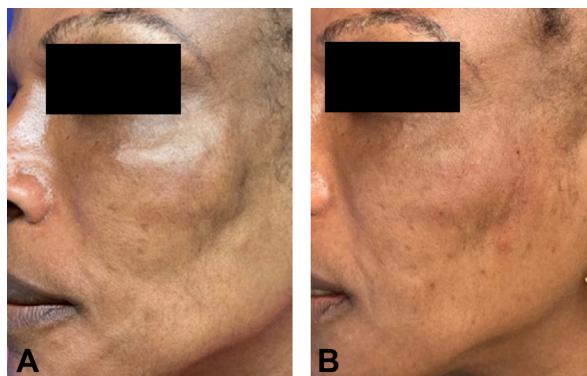


Fig 6. **A**, A patient with overlap connective tissue disease before injection with hyaluronic acid for disease-related atrophy. **B**, A patient with overlap connective tissue disease immediately after 4 cc of hyaluronic filler injection to the cheek and midface. The side effect of nodularity improves with time and can potentially be improved with subcision and expansion before injection.

sunscreen, particularly sunscreens containing iron oxide,⁴⁰ to protect from wavelengths within the visible spectrum.

Because data on safe laser parameters for patients with lupus are limited, many experts have recommended using the lowest fluence possible to achieve efficacious results.^{23,26,35,41-43} Although subjective and device specific, low fluence setting has been proposed as 5.75 to 9 J/cm² for PDL,^{26,44} 11 to 12 J/cm² for IPL,²³ and 6.5 J/cm² for Q-switched Nd:YAG (level of evidence: IV).²³

Further information from studies on the use of laser treatments in patients with lupus is presented in Tables I to V, and treatment recommendations with the associated levels of evidence are summarized in Table VI.

INJECTABLES

Key points

- Despite theoretical risk of disease reactivation after tissue stimulation, there are no reports in the literature of lupus reactivation after reconstructive injectable treatment
- Performing fat transfer during active disease or while on corticosteroid treatment is hypothesized to result in impaired outcomes

Injectable treatment in patients with lupus, similar to other autoimmune or connective tissue disorders, has long been avoided because of the theoretical risk of disease exacerbation or reactivation caused by tissue stimulation.¹⁹ While more controlled studies are needed to understand the pathogenesis of lupus and the tissue effects of injectable material in this patient population, a few studies have demonstrated

success with injectable correction of atrophic cutaneous lupus lesions.

The majority of published cases describing injectable treatment for correction of aesthetic deficits in patients with lupus discuss fat transfer (Table VII).^{45,46} The largest controlled trial for lipotransfer (autologous fat transfer using cannula-assisted liposuction for donor site extraction), involving 5 patients with lupus profundus, compared results of lipotransfer with and without (control group) addition of cultured adipose-derived stem cells. They observed no adverse effects in the patients with lupus other than adipose necrosis of the grafted tissue requiring drainage in 1 patient who was taking oral corticosteroids preoperatively (unspecified duration before treatment).⁴⁶ The authors concluded that steroids taken perioperatively or, possibly, the severity of lupus requiring oral steroids usage, negatively impacts angiogenesis and fat transfer viability. We agree with the authors' conclusion that fat transfer should be performed at a period of quiescent disease (level of evidence II A).

While there are no studies reporting that patients with underlying inflammatory diseases are more prone to postoperative fat transfer complications, 1 publication reports a case of patient mortality after low-volume fat transfer that led to fat embolism and subsequent cardiac arrest.⁴⁵ The authors of this study hypothesize that the patient's underlying inflammatory disease could have contributed to an endothelial reaction that resulted in thrombus formation and heart failure. This case is further complicated by the intake of daily thalidomide, which has been associated with the risk of thromboembolism.⁴⁷ Events like these are not unique to the lupus patient population and, as with any cosmetic intervention, adequate patient counseling and thorough discussion of procedural risks (and possible increased risk in the lupus population) is imperative before any invasive procedure.⁴⁸

Case reports discussing the use of hyaluronic acid (HA), poly-L lactic acid, polyacrylamide hydrogel filler, and polymethyl-methacrylate in the lupus population showed subjective satisfactory results with no adverse reactions or disease aggravation (Fig 6). The first article in this continuing medical [F6-4/C] education series provides further description of these fillers. Not previously described is polyacrylamide, a permanent, biocompatible, nonabsorbable and nonbiodegradable filler composed of 2.5% crosslinked polyacrylamide hydrogel suspended in sterile water that is approved for use outside of the United States. Documented adverse effects have included edema, transient erythema, ecchymosis, hematoma, tenderness, inflammatory/foreign

Table VIII. Injectable treatments in patients with lupus

Authors/ study type	N	Age	Disease	Treatment	Location/amount	Perioperative medication	Sessions/interval	Results	Side effects	Follow-up
Fogo, ⁸¹ 2011 case report	1	30 with 6-year disease history	Lupus profundus	Large particle HA filler (1000 gel particles/mL)	3 mL to right cheek, 1 mL to left temple	NR	1 session	Dermatology Life Quality Index score decreased from 10 to 4; 9% increase in soft tissue thickness on MRI	None	1 month
Eastham et al, ⁸² 2013 case report	1	30 with 9-year history, inactive for many years	Lupus erythematosus panniculitis	PLLA (1:8 dilution) followed by HA filler	Session 1 and 2: 1 vial of PLLA to malar eminence; session 2: 2 mL HA filler to malar eminence and nasolabial fold	Chloroquine and dapsone but unclear if continued during treatment	3 sessions, 4-week interval between PLLA sessions, followed by HA 5 months later	Patient reported high satisfaction with only minimal discomfort	None	11 months
Costa et al, ⁸³ 2009 retrospective case series	3	NR	Lupus profundus	PMMA filler	Face	NR	NR	Subjective good results	None	NR
Gupta et al, ⁸⁴ 2016 case report	1	Age at treatment unclear, with 10-year disease history, currently inactive	Lupus panniculitis	2.5% polyacrylamide hydrogel dermal filler, injected subdermally with 18-G needle using fanning technique	10 mL to face over 1.5 years	None, but before treatment underwent 2 years of hydroxy- chloroquine 200 mg BID and then 3-year observation for disease activity	5 sessions with 3- to 4-month intervals	After 9 years, results are satisfactory and maintained	None	9 years

BID, Bis in die; HA, hyaluronic acid; MRI, magnetic resonance imaging; NR, not reported; PLLA, poly-L-lactic acid; PMMA, polymethyl-methacrylate.

Table IX. Strength of recommendations for injectable treatment for lupus

Recommendation	Recommendation no.	Level of evidence	Studies
Fat transfer should be performed at a period of inactive disease and when the patient is off immunosuppressant medications	2.1	IIA	Yoshimura et al ⁴⁶
Injectable filler options for patients with lupus are:			
Fat transfer	2.2	IIA-III	Gleeson et al, ⁴⁵ Yoshimura et al, ⁴⁶ Cortese et al, ⁷⁴ Yoon et al, ⁷⁵ Lei et al, ⁷⁶ Valdatta et al, ⁷⁷ Hammer-Hansen et al, ⁷⁸ and Yesilada et al ⁸⁰
Hyaluronic acid (excluding Vycross type)	2.3	III	Fogo ⁸¹ and Eastham et al ⁸²
PLLA	2.4	III	Eastham et al ⁸²
PMM	2.5	III	Carvalho Costa et al ⁸³
Polyacrylamide	2.6	III	Gupta et al ⁸⁴

Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥ 1 randomized controlled trial; level IIA evidence includes evidence from ≥ 1 controlled study without randomization; level IIB evidence includes evidence from ≥ 1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

PLLA, Poly-L-lactic acid; PMMA, polymethyl-methacrylate.

body reaction with granuloma formation, and infection.⁴⁹⁻⁵¹ All reported cases of injectable filler were for patients with facial atrophy caused by lupus profundus/panniculitis. None of the patients were taking immunosuppressive medications, but most studies described purposeful timing of the procedure during periods of disease inactivity and stability (Table VIII). As in other immune conditions, given the sometimes profound volume changes, nodularity immediately postinjection is a typical complaint. This improves with time and can be ameliorated with subcision and expansion of underlying tissue with normal saline.

With HA fillers, there has been an increasing number of patients experiencing delayed onset (≤ 1 year) immune-mediated nodules, particularly with fillers of the Vycross family, hypothesized to be related to their inclusion of low molecular weight HA molecules.⁵²⁻⁵⁴ These nodules have been described as treatment resistant, requiring multiple sessions of hyaluronidase and triamcinolone injections to reduce nodule size.⁵³ The use of laser or heat therapy has also been reported to treat delayed-onset noninfectious inflammatory nodules.^{55,56} Until more information is gathered regarding the pathogenesis of these postfiller nodules, we recommend avoiding the use of Vycross technology HA fillers in patients with a history of autoimmune inflammatory disease (level of evidence IV). Treatment recommendations related to injectables and their associated level of evidence are summarized in Table IX.

SURGICAL AND OTHER INTERVENTIONS

Key point

- Invasive surgical procedures in patients with lupus are hypothesized to have an increased risk of complications, including disease reactivation, hypercoagulability, and impaired wound healing related to immunosuppressing medication

The potential risk of disease reactivation from invasive procedures has limited the use of surgical interventions in patients with lupus and other collagen vascular disorders.⁵⁷ Prevention of such disease exacerbation with immunosuppressing medications could potentially impair wound healing and thus negatively impact cosmetic outcomes. Furthermore, a combination of vascular inflammation and production of autoantibodies known to be prothrombotic make hypercoagulability a well-known risk in the operative and postoperative periods for patients with lupus.⁵⁸

In the preoperative period, patients with SLE were more likely than healthy control subjects to be anemic, lymphopenic, hypoalbuminemic, or taking daily aspirin, all of which were independently associated with postoperative complications.⁵⁹ In addition, patients with lupus had an increased risk of major complications (cardiovascular events,⁶⁰ acute renal insufficiency, or deep vein thrombosis), minor complications (surgical site infection),⁶¹ all-cause complications, and mortality in the postoperative period compared with healthy control subjects.⁵⁹ Even when compared with patients with

Table X. Surgical or other interventions in patients with lupus

Authors/ study type	N	Age	Disease	Defect/location	Treatment	Perioperative medication	Results	Side effects	Follow-up
Ratner and Skouge, ⁸⁵ 1990 case report	1	42 with 6-year disease history	DLE	Cribiform scarring to nose and upper lip	2 sessions of dermabrasion, hand engine, diamond fraises, and light freezing with 75% dichloro-tetrafluoroethane plus 25% ethyl chloride	None	Cutaneous disease not exacerbated and did not progress to systemic disease	3 weeks postoperatively, two 5-mm erythematous papules on upper lip that responded to 0.01% fluocinolone acetonide cream BID	2 years
Lewandowicz et al, ⁸⁶ 2014 case report	2	Patient 1: 48 with 30-year disease history; patient 2: 59 with 20-year disease history currently in remission	Patient 1: lupus panniculitis ; patient 2: SLE	Patient 1: lipoatrophy and scarring lesions on face and arms; patient 2: extensive scarring lesion of scalp	Patient 1: lipodermal graft from gluteal fold to both zygomatic areas, nasolabial folds, and skin flaps to arms; patient 2: tissue expander, scar excision and scalp flap	NR	Patient 1: some parietal graft resorption following first procedure but still good subjective outcome; patient 2: good subjective results	None	Patient 1: 2 years; patient 2: 1 year
Wang et al, ⁵⁸ 2012 case series	4	40-48	SLE	Breasts	Muscle-sparing transverse rectus abdominis musculocutaneous flap	Adalimumab NR (n = 1)	Delayed healing of breast and abdomen (n = 1), no vascular complications	NR	
Longaker et al, ⁸⁷ 1996 case series	1	28	SLE	Facial atrophy	Superficial inferior epigastric flap and face lift, left side first, right side 2 months later	NR	Dramatic subjective improvement	Postoperative hematoma requiring operative exploration and evacuation	20 months
Kesiktas et al, ⁸⁸ 2008 case report	1	50 with 30-year disease history	DLE	Squamous cell carcinoma on a DLE lesion on preauricular area	Free radial forearm fasciocutaneous flap	NR	No exacerbation of DLE and no tumor recurrence	1 cm distal flap area necrosed and spontaneously reepithelialized	2 years
Kadam et al, ⁸⁹ 2013 case report	1	36 at procedure, disease started at 22, had been inactive for 1 year	DLE		Radial artery forearm flap and superficial temporal artery flap	NR	No vascular complications and stable results at follow-up	None	6 months

BID, Bis en die; DLE, discoid lupus erythematosus; NR, not reported; SLE, systemic lupus erythematosus.

Table XI. Strength of recommendations for perioperative management of patients with systemic lupus erythematosus undergoing elective total hip or total knee arthroplasty

Recommendation	Recommendation no.	Level of evidence	Studies
Biologic therapies should be withheld for surgery and before surgery for 1 dosing cycle or surgery should be planned for the end of the dosing cycle of that medication	3.1	IV	Goodman et al ⁶⁵
Patients with severe SLE should continue mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus through the surgical period	3.2	IV	Goodman et al, ⁶⁵ Palmisano et al, ⁹¹ and Klement et al ⁹²
Patients with nonsevere SLE should hold mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus 1 week before surgery	3.3	IV	Goodman et al ⁶⁵
Restart biologic therapy when withheld before surgery with evidence of wound healing and no signs of infection or drainage (~14 days)	3.4	IV	Goodman et al ⁶⁵
There is no need/utility to "stress dose steroids" for those taking chronic steroids; the panel recommended the continued use of daily dose glucocorticoids for patients throughout surgery	3.5	IV	Goodman et al ⁶⁵

SLE, Systemic lupus erythematosus.

Table XII. Organizations focused on lupus-related research and patient support

The Us in Lupus	https://www.usinlupus.com
Lupus Canada	https://www.lupuscanada.org/mylupusguide/
The Lupus Initiative	https://thelupusinitiative.org
Lupus Foundation of America	https://www.lupus.org/resources
HealthWell Foundation	https://www.healthwellfoundation.org/fund/systemic-lupus-erythematosus/
American College of Rheumatology (ACR)	https://befiercetakecontrol.org
Lupus Research Alliance	https://www.lupusresearch.org
Lupus and Allied Diseases	https://www.ladainc.org
Looms for Lupus	http://www.thelupusproject.com/exhibitors/looms-for-lupus/
Lupus LA	http://www.thelupusproject.com/exhibitors/lupus-la/
The Howse Foundation	http://www.thelupusproject.com/exhibitors/thehowsefoundation/

rheumatoid arthritis, patients with SLE were more likely to have complications of any cause after orthopedic surgery.⁶² The risk of adverse surgical outcomes was particularly high among patients with a severe lupus flare within the preceding 6 months.⁶³

The American College of Rheumatology developed consensus guidelines for the perioperative management of patients with rheumatic diseases, including patients with SLE.^{64,65} While these guidelines were developed for patients undergoing total joint replacement, we typically follow the same general principles for any invasive procedure in SLE patients (level of recommendation IV): 1) for patients with severe SLE, continue methotrexate, mycophenolate mofetil, azathioprine, cyclosporine,

or tacrolimus through the surgical period, and 2) for patients with nonsevere SLE, mycophenolate mofetil, azathioprine, cyclosporine, and tacrolimus should be withheld 1 week before patients undergo surgery.

For elective cosmetic procedures, however, disease should be well controlled and ideally inactive before any surgical intervention. The use of a test area to assess for complications such as ulceration or koebnerization has been proposed.^{19,21} A collection of studies documenting various surgical and nonsurgical interventions in patients with lupus is detailed in Table X, and a summary of American College of Rheumatology guidelines with associated level of evidence is summarized in Table XI.

SUMMARY AND PATIENT RESOURCES

In the second article in this continuing medical education series, we summarized the available evidence for performing cosmetic treatments in patients with lupus. Although high-quality data are still lacking, we hope that the compiled information will help guide future studies, particularly randomized controlled trials that will allow for more evidence-based treatment recommendations. There is a need for reconstructive treatments within this population given the associated potentially disfiguring cosmetic sequelae, and we hope that this article will help providers determine how to approach cosmetic treatments in patients with lupus patients. To keep patients and clinicians up to date with the latest in lupus information and advocacy, a list of organizations focused on lupus-related research as well as patient support can be found in Table XII.

REFERENCES

1. Vasquez R, Wang D, Tran QP, et al. A multicentre, cross-sectional study on quality of life in patients with cutaneous lupus erythematosus. *Br J Dermatol.* 2013;168:145-153.
2. Al-Refu K, Goodfield M. Scar classification in cutaneous lupus erythematosus: morphological description. *Br J Dermatol.* 2009;161:1052-1058.
3. Chong BF, Song J, Olsen NJ. Determining risk factors for developing systemic lupus erythematosus in patients with discoid lupus erythematosus. *Br J Dermatol.* 2012;166:29-35.
4. Sontheimer RD. Subacute cutaneous lupus erythematosus: 25-year evolution of a prototypic subset (subphenotype) of lupus erythematosus defined by characteristic cutaneous, pathological, immunological, and genetic findings. *Autoimmun Rev.* 2005;4:253-263.
5. Watanabe T, Tsuchida T. Classification of lupus erythematosus based upon cutaneous manifestations. Dermatological, systemic and laboratory findings in 191 patients. *Dermatology.* 1995;190:277-283.
6. Durosaro O, Davis MD, Reed KB, Rohlinger AL. Incidence of cutaneous lupus erythematosus, 1965-2005: a population-based study. *Arch Dermatol.* 2009;145:249-253.
7. Jarukitsopa S, Hoganson DD, Crowson CS, et al. Epidemiology of systemic lupus erythematosus and cutaneous lupus erythematosus in a predominantly white population in the United States. *Arthritis Care Res.* 2015;67:817-828.
8. Martens PB, Moder KG, Ahmed I. Lupus panniculitis: clinical perspectives from a case series. *J Rheumatol.* 1999;26:68-72.
9. Watanabe T, Tsuchida T. Lupus erythematosus profundus: a cutaneous marker for a distinct clinical subset? *Br J Dermatol.* 1996;134:123-125.
10. Peters MS, Su WP. Lupus erythematosus panniculitis. *Med Clin North Am.* 1989;73:1113-1126.
11. Kuhn A, Richter-Hintz D, Oslislo C, Ruzicka T, Megahed M, Lehmann P. Lupus erythematosus tumidus—a neglected subset of cutaneous lupus erythematosus: report of 40 cases. *Arch Dermatol.* 2000;136:1033-1041.
12. Vieira V, Del Pozo J, Yebra-Pimentel MT, Martinez W, Fonseca E. Lupus erythematosus tumidus: a series of 26 cases. *Int J Dermatol.* 2006;45:512-517.
13. Schmitt V, Meuth AM, Amler S, et al. Lupus erythematosus tumidus is a separate subtype of cutaneous lupus erythematosus. *Br J Dermatol.* 2010;162:64-73.
14. Levy LL, Emer JJ. Emotional benefit of cosmetic camouflage in the treatment of facial skin conditions: personal experience and review. *Clin Cosmet Investig Dermatol.* 2012;5:173-182.
15. Boehncke WH, Ochsendorf F, Paeslack I, Kaufmann R, Zollner TM. Decorative cosmetics improve the quality of life in patients with disfiguring skin diseases. *Eur J Dermatol.* 2002;12:577-580.
16. Jolly M, Peters KF, Mikolaitis R, Evans-Raoul K, Block JA. Body image intervention to improve health outcomes in lupus: a pilot study. *J Clin Rheumatol.* 2014;20:403-410.
17. Gaines E, Bonilla-Martinez Z, Albrecht J, et al. Quality of life and disease severity in a cutaneous lupus erythematosus pilot study. *Arch Dermatol.* 2008;144:1061-1062.
18. Chang AY, Ghazi E, Okawa J, Werth VP. Quality of life differences between responders and nonresponders in the treatment of cutaneous lupus erythematosus. *JAMA Dermatol.* 2013;149:104-106.
19. Braunstein I, Werth VP. Update on management of connective tissue panniculitides. *Dermatol Ther.* 2012;25:173-182.
20. Albrecht J, Taylor L, Berlin JA, et al. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. *J Invest Dermatol.* 2005;125:889-894.
21. Hansen CB, Callen JP. Connective tissue panniculitis: lupus panniculitis, dermatomyositis, morphea/scleroderma. *Dermatol Ther.* 2010;23:341-349.
22. Erceg A, Bovenschen HJ, van de Kerkhof PC, de Jong EM, Seyger MM. Efficacy and safety of pulsed dye laser treatment for cutaneous discoid lupus erythematosus. *J Am Acad Dermatol.* 2009;60:626-632.
23. Byun YS, Son JH, Cho YS, et al. Intense pulsed light and Q-switched 1,064-nm neodymium-doped yttrium aluminum garnet laser treatment for the scarring lesion of discoid lupus erythematosus. *Ann Dermatol.* 2017;29:331-333.
24. Vachiramon V, Panmanee W, Techapichetvanich T, Chanpraphak K. Comparison of Q-switched Nd: YAG laser and fractional carbon dioxide laser for the treatment of solar lentigines in Asians. *Lasers Surg Med.* 2016;48:354-359.
25. Goldberg DJ. Full-face nonablative dermal remodeling with a 1320 nm Nd:YAG laser. *Dermatol Surg.* 2000;26:915-918.
26. Ekback MP, Troilius A. Laser therapy for refractory discoid lupus erythematosus when everything else has failed. *J Cosmet Laser Ther.* 2013;15:260-265.
27. Tremblay JF, Carey W. Atrophic facial scars secondary to discoid lupus erythematosus: treatment using the Erbium:YAG laser. *Dermatol Surg.* 2001;27:675-677.
28. Khatri KA, Ross V, Grevelink JM, Magro CM, Anderson RR. Comparison of erbium:YAG and carbon dioxide lasers in resurfacing of facial rhytides. *Arch Dermatol.* 1999;135:391-397.
29. Manstein D, Herron GS, Sink RK, Tanner H, Anderson RR. Fractional photothermolysis: a new concept for cutaneous remodeling using microscopic patterns of thermal injury. *Lasers Surg Med.* 2004;34:426-438.
30. Kuhn A, Becker-Wegerich PM, Ruzicka T, Lehmann P. Successful treatment of discoid lupus erythematosus with argon laser. *Dermatology.* 2000;201:175-177.
31. Geronemus RG. Argon laser for the treatment of cutaneous lesions. *Clin Dermatol.* 1995;13:55-58.
32. Levy JL. Intense pulsed light treatment for chronic facial erythema of systemic lupus erythematosus: a case report. *J Cutan Laser Ther.* 2000;2:195-198.
33. Raulin C, Schmidt C, Hellwig S. Cutaneous lupus erythematosus-treatment with pulsed dye laser. *Br J Dermatol.* 1999;141:1046-1050.
34. Bras S, Gonzalez B, Segurado-Miravalles G, Boixeda P. Treatment of lupus erythematosus of the eyelids with pulsed dye laser. *Lasers Med Sci.* 2018;33:215-219.

35. Kerknimitr P, Tekacharin N, Pancharateep R, et al. Pulsed-dye laser as an adjuvant treatment for discoid lupus erythematosus: a randomized, controlled trial. *J Dermatolog Treat.* 2019; 30:81-86.
36. Truchuelo MT, Boixeda P, Alcantara J, Moreno C, de las Heras E, Olasolo PJ. Pulsed dye laser as an excellent choice of treatment for lupus tumidus: a prospective study. *J Eur Acad Dermatol Venereol.* 2012;26:1272-1279.
37. Wolfe JT, Weinberg JM, Elenitas R, Uberti-Benz M. Cutaneous lupus erythematosus following laser-induced thermal injury. *Arch Dermatol.* 1997;133:392-393.
38. Sanders CJ, Van Weelden H, Kazzaz GA, Sigurdsson V, Toonstra J, Bruijnzeel-Koomen CA. Photosensitivity in patients with lupus erythematosus: a clinical and photobiological study of 100 patients using a prolonged phototest protocol. *Br J Dermatol.* 2003;149:131-137.
39. Ahluwalia J, Marsch A. Photosensitivity and photoprotection in patients with lupus erythematosus. *Lupus.* 2019;28:697-702.
40. Bissonnette R, Nigen S, Bolduc C, Mery S, Nocera T. Protection afforded by sunscreens containing inorganic sunscreeing agents against blue light sensitivity induced by aminolevulinic acid. *Dermatol Surg.* 2008;34:1469-1476.
41. Brauer JA, Gordon Spratt EA, Geronemus RG. Laser therapy in the treatment of connective tissue diseases: a review. *Dermatol Surg.* 2014;40:1-13.
42. Baniandres O, Boixeda P, Belmar P, Perez A. Treatment of lupus erythematosus with pulsed dye laser. *Lasers Surg Med.* 2003;32:327-330.
43. Diez MT, Boixeda P, Moreno C, Gonzalez JA, Zamorano ML, Olasolo PJ. Histopathology and immunohistochemistry of cutaneous lupus erythematosus after pulsed dye laser treatment. *Dermatol Surg.* 2011;37:971-981.
44. Rostan E, Bowes LE, Iyer S, Fitzpatrick RE. A double-blind, side-by-side comparison study of low fluence long pulse dye laser to coolant treatment for wrinkling of the cheeks. *J Cosmet Laser Ther.* 2001;3:129-136.
45. Gleeson CM, Lucas S, Langrish CJ, Barlow RJ. Acute fatal fat tissue embolism after autologous fat transfer in a patient with lupus profundus. *Dermatol Surg.* 2011;37:111-115.
46. Yoshimura K, Sato K, Aoi N, et al. Cell-assisted lipotransfer for facial lipoatrophy: efficacy of clinical use of adipose-derived stem cells. *Dermatol Surg.* 2008;34:1178-1185.
47. Franks ME, Macpherson GR, Figg WD. Thalidomide. *Lancet.* 2004;363:1802-1811.
48. Astarita DC, Scheinin LA, Sathyavagiswaran L. Fat transfer and fatal macroembolization. *J Forensic Sci.* 2015;60:509-510.
49. Alijotas-Reig J, Garcia-Gimenez V, Miro-Mur F, Vilardell-Tarres M. Delayed immune-mediated adverse effects related to polyacrylamide dermal fillers: clinical findings, management, and follow-up. *Dermatol Surg.* 2009;35(suppl 1):360-366.
50. Narins RS, Coleman WP 3rd, Rohrich R, et al. 12-month controlled study in the United States of the safety and efficacy of a permanent 2.5% polyacrylamide hydrogel soft-tissue filler. *Dermatol Surg.* 2010;36(suppl 3):1819-1829.
51. Amin SP, Marmur ES, Goldberg DJ. Complications from injectable polyacrylamide gel, a new nonbiodegradable soft tissue filler. *Dermatol Surg.* 2004;30(12 pt 2):1507-1509.
52. Beleznay K, Carruthers JD, Carruthers A, Mumment ME, Humphrey S. Delayed-onset nodules secondary to a smooth cohesive 20 mg/mL hyaluronic acid filler: cause and management. *Dermatol Surg.* 2015;41:929-939.
53. Sadeghpour M, Quatrano NA, Bonati LM, Arndt KA, Dover JS, Kaminer MS. Delayed-onset nodules to differentially cross-linked hyaluronic acids: comparative incidence and risk assessment. *Dermatol Surg.* 2019;45:1085-1094.
54. Artzi O, Loizides C, Verner I, Landau M. Resistant and recurrent late reaction to hyaluronic acid-based gel. *Dermatol Surg.* 2016;42:31-33.
55. Lee SJ, Seok J, Park KY, Kim BJ, Kim YK. Reduction of early nodules after injection of hyaluronic acid filler. *J Am Acad Dermatol.* 2017;77:e5-e6.
56. Graivier MH, Bass LM, Lorenc ZP, Fitzgerald R, Goldberg DJ, Lemperle G. Differentiating nonpermanent injectable fillers: prevention and treatment of filler complications. *Aesthet Surg J.* 2018;38(suppl 1):S29-S40.
57. King-Smith D. External irritation as a factor in the causation of lupus erythematosus discoides. *Arch Derm Syphilol.* 1926;14:547-549.
58. Wang TY, Serletti JM, Kolaskinski S, Low DW, Kovach SJ, Wu LC. A review of 32 free flaps in patients with collagen vascular disorders. *Plast Reconstr Surg.* 2012;129:421e-427e.
59. Quintanilla-Gonzalez L, Torres-Villalobos G, Hinojosa-Azaola A. Risk factors for development of early infectious and noninfectious complications in systemic lupus erythematosus patients undergoing major surgery. *Lupus.* 2018;27:1960-1972.
60. Yazdanyar A, Wasko MC, Scalzi LV, Kraemer KL, Ward MM. Short-term perioperative all-cause mortality and cardiovascular events in women with systemic lupus erythematosus. *Arthritis Care Res.* 2013;65:986-991.
61. Roberts JE, Mandl LA, Su EP, et al. Patients with systemic lupus erythematosus have increased risk of short-term adverse events after total hip arthroplasty. *J Rheumatol.* 2016;43:1498-1502.
62. Merayo-Chalico J, Gonzalez-Contreras M, Ortiz-Hernandez R, Alcocer-Varela J, Marcial D, Gomez-Martin D. Total hip arthroplasty outcomes: an 18-year experience in a single center: is systemic lupus erythematosus a potential risk factor for adverse outcomes? *J Arthroplasty.* 2017;32:3462-3467.
63. Lin JA, Liao CC, Lee YJ, Wu CH, Huang WQ, Chen TL. Adverse outcomes after major surgery in patients with systemic lupus erythematosus: a nationwide population-based study. *Ann Rheum Dis.* 2014;73:1646-1651.
64. Gualtierotti R, Parisi M, Ingegnoli F. Perioperative management of patients with inflammatory rheumatic diseases undergoing major orthopaedic surgery: a practical overview. *Adv Ther.* 2018;35:439-456.
65. Goodman SM, Springer B, Guyatt G, et al. 2017 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients With Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty. *Arthritis Rheumatol.* 2017;69:1538-1551.
66. Park KY, Lee JW, Li K, Seo SJ, Hong CK. Treatment of refractory discoid lupus erythematosus using 1,064-nm long-pulse neodymium-doped yttrium aluminum garnet laser. *Dermatol Surg.* 2011;37:1055-1056.
67. Henderson DL, Odom JC. Laser treatment of discoid lupus (case report). *Lasers Surg Med.* 1986;6:12-15.
68. Walker SL, Harland CC. Carbon dioxide laser resurfacing of facial scarring secondary to chronic discoid lupus erythematosus. *Br J Dermatol.* 2000;143:1101-1102.
69. Nunez M, Boixeda P, Miralles ES, de Misa RF, Ledo A. Pulsed dye laser treatment of telangiectatic chronic erythema of cutaneous lupus erythematosus. *Arch Dermatol.* 1996;132:354-355.
70. Gupta G, Roberts DT. Pulsed dye laser treatment of subacute cutaneous lupus erythematosus. *Clin Exp Dermatol.* 1999;24: 498-499.
71. Nunez M, Boixeda P, Miralles ES, de Misa RF, Ledo A. Pulsed dye laser treatment in lupus erythematosus telangiectoides. *Br J Dermatol.* 1995;133:1010-1011.
72. Izikson L, Avram M, Tannous Z. Treatment of port wine stains with pulsed dye laser in patients with systemic lupus

- erythematosus: practical considerations and complications. *J Cosmet Laser Ther.* 2008;10:223-225.
73. Yelamos O, Roe E, Baselga E, Puig L. Pediatric cutaneous lupus erythematosus treated with pulsed dye laser. *Pediatr Dermatol.* 2014;31:113-115.
74. Cortese A, Savastano G, Felicetta L. Free fat transplantation for facial tissue augmentation. *J Oral Maxillofac Surg.* 2000;58:164-169; discussion 169-170.
75. Yoon J, Kim HM, Kim TH, Kim CW, Sun YW, Yoon TJ. Autologous fat transfer in a patient with lupus erythematosus profundus. *Case Rep Dermatol.* 2012;4:207-210.
76. Lei H, Ma GE, Liu Z. Evaluation of repairing facial depression deformities secondary to lupus erythematosus panniculitis with autologous fat grafting. *J Craniofac Surg.* 2016;27:1765-1769.
77. Valdatta L, Cherubino M, Tamborini F, Pellegatta I, Maggiulli F. A case of facial lipoatrophy secondary to lupus profundus managed with lipofilling technique. *Case Rep Dermatol Med.* 2012;2012:720518.
78. Hammer-Hansen N, Akram J, Damsgaard TE. The versatility of autologous fat transplantation in correction of facial deformities: a single-center experience. *Plast Surg Int.* 2015;2015: 703535.
79. Polivka L, Revol M, Battistella M, Bachelez H. Lipofilling: a new therapeutic option for the treatment of lupus panniculitis-induced atrophy. *Case Rep Dermatol.* 2016;8:323-326.
80. Yesilada AK, Sevim KZ, Sirvan SS, Irmak F, Tatlidede HS. Severe symmetrical facial lipoatrophy in a patient with discoid lupus erythematosus. *J Craniofac Surg.* 2012;23:e461-e463.
81. Fogo A. Facial lipoatrophy secondary to lupus profundus: treatment with large particle hyaluronic acid [abstract]. *J Am Acad Dermatol.* 2011;64:AB165.
82. Eastham AB, Liang CA, Femia AN, Lee TC, Vleugels RA, Merola JF. Lupus erythematosus panniculitis-induced facial atrophy: effective treatment with poly-L-lactic acid and hyaluronic acid dermal fillers. *J Am Acad Dermatol.* 2013;69:e260-e262.
83. Carvalho Costa IM, Salaro CP, Costa MC. Polymethylmethacrylate facial implant: a successful personal experience in Brazil for more than 9 years. *Dermatol Surg.* 2009;35:1221-1227.
84. Gupta K, Bhari N, Verma KK, Gupta S. Permanent injectable polyacrylamide hydrogel dermal filler for a large subcutaneous defect secondary to lupus panniculitis. *Dermatol Surg.* 2017;43: 152-154.
85. Ratner D, Skouge JW. Discoid lupus erythematosus scarring and dermabrasion: a case report and discussion. *J Am Acad Dermatol.* 1990;22(2 pt 1):314-316.
86. Lewandowicz E, Zielinski T, Iljin A, Fijalkowska M, Kasielska-Trojan A, Antoszewski B. Surgical treatment of skin lesions in lupus erythematosus. *Postepy Dermatol Alergol.* 2014;31:405-409.
87. Longaker MT, Flynn A, Siebert JW. Microsurgical correction of bilateral facial contour deformities. *Plast Reconstr Surg.* 1996; 98:951-957.
88. Kesiktas E, Yavuz M, Gencel E, Kesiktas NN. Squamous cell carcinoma in discoid lupus erythematosus: reconstruction with a free forearm fasciocutaneous flap. *Scand J Plast Reconstr Surg Hand Surg.* 2008;42:271-273.
89. Kadam D, Pillai V, Bhandary S, Hukkeri RY, Kadam M. Facial contour deformity correction with microvascular flaps based on the 3-dimensional template and facial moulage. *Indian J Plast Surg.* 2013;46:521-528.
90. Jih MH, Friedman PM, Kimyai-Asadi A, Friedman ES, Hymes SR, Goldberg LH. Lupus miliaris disseminatus faciei: treatment with the 1450-nm diode laser. *Arch Dermatol.* 2005;141:143-145.
91. Palmisano AC, Kuhn AW, Urquhart AG, Pour AE. Post-operative medical and surgical complications after primary total joint arthroplasty in solid organ transplant recipients: a case series. *Int Orthop.* 2017;41:13-19.
92. Klement MR, Penrose CT, Bala A, Wellman SS, Bolognesi MP, Seyler TM. How do previous solid organ transplant recipients fare after primary total knee arthroplasty? *J Arthroplasty.* 2016; 31:609-615.e1.

Answers to CME examination

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1. d
2. b



Field cancerization: Definition, epidemiology, risk factors, and outcomes

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Learning objectives

After completing this learning activity, participants should be able to define field cancerization and discuss how this condition differs from actinic keratoses; explain the pathogenesis of field cancerization; and describe the morbidity, mortality, and cost considerations associated with untreated or undertreated field cancerization.

Disclosures

Editors

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Field cancerization was first described in 1953 when pathologic atypia was identified in clinically normal tissue surrounding oropharyngeal carcinomas. The discovery of mutated fields surrounding primary tumors raised the question of whether the development of subsequent tumors within the field represented recurrences or additional primary tumors. Since this initial study, field cancerization has been applied to numerous other epithelial tissues, including the skin. Cutaneous field cancerization occurs in areas exposed to chronic ultraviolet radiation, which leads to clonal proliferations of p53-mutated fields and is characterized by multifocal actinic keratoses, squamous cell carcinomas in situ, and cutaneous squamous cell carcinomas. In the first article in this continuing medical education series, we define field cancerization, review the available grading systems, and discuss the epidemiology, risk factors, and outcomes associated with this disease. (J Am Acad Dermatol 2020;83:709-17.)

Key words: actinic damage; actinic keratoses; cutaneous oncology; cutaneous squamous cell carcinoma; field cancerization; field change; field damage; field therapy; immunosuppression; keratinocyte carcinoma; actinic keratosis; NOTCH; NOTCH1; p53; p-53 clonal fields; squamous cell carcinoma; TP53.

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Abbreviations used:

AK:	actinic keratosis
AKASI:	Actinic Keratosis Area and Severity Index
AK-FAS:	Actinic Keratosis Field Assessment Scale
BCC:	basal cell carcinoma
CSCC:	cutaneous squamous cell carcinoma
FC:	field cancerization
KC:	keratinocyte carcinoma
QoL:	quality of life
SOTR:	solid organ transplant recipient
UVR:	ultraviolet radiation

The concept of field cancerization (FC) was first described in 1953 by Slaughter et al¹ in epithelial tissue surrounding oropharyngeal carcinomas. In that landmark study, 782 cases of oropharyngeal squamous cell carcinoma were examined and observed to have pathologic atypia in normal appearing adjacent tissue. Multiple new secondary tumors were found to subsequently arise within this field that were clinically suggestive of tumor recurrence, but were in fact second primary tumors. At the cellular level, FC is the growth of a mutant clone that creates a field of cells predisposed to subsequent tumor growth.² Since its inception, the concept of FC has become widely accepted in other tumors, including cancers of the vulva, head and neck, cervix, breast, and colon.²

Cutaneous tissue is uniquely susceptible to FC given the chronic ultraviolet radiation (UVR) exposure in sun-exposed areas. Areas affected by FC have an incredibly high burden of both clinical and subclinical actinic damage and, therefore, are at high risk for developing multiple cutaneous squamous cell carcinomas (CSCCs). Multiple CSCC formation leads to high morbidity for the patient from multiple surgical procedures and carries a high cost to society.^{3,4}

The accurate identification of patients with cutaneous FC is of paramount importance because it identifies patients who are at highest risk for multiple CSCC formation and, thus, those at the greatest risk for developing poor disease-related outcomes.⁵ Unfortunately, there is no standard or widely accepted definition for cutaneous FC. In addition, FC is not considered a distinct diagnosis from actinic keratosis (AK), as evidenced by the lack of separate *International Classification of Diseases, 10th revision, Clinical Modification* code for AK and FC. However, patients with FC have a disease process that behaves differently than those with multiple

discrete AKs. A lack of understanding of FC may falsely lead clinicians to undertreat patients with FC when these patients require a more aggressive approach. In the first article in this continuing medical education series, we provide a clear definition of FC including visual examples of this disease, compare and contrast AKs with FC, and discuss the pathogenesis, risk factors, and outcomes of this condition.

EPIDEMIOLOGY AND RISK FACTORS

Key points

- The prevalence of AKs and FC is rising across the world
- Risk factors for the development of FC include male sex, light skin, increasing age, immunosuppression, and exposure to UVR

Prevalence and incidence

As there are limited data regarding the epidemiology of FC, both AK and CSCC are proxies that may be used to estimate the prevalence and incidence of FC. AK epidemiologic figures are calculated based on patients with ≥ 1 AK.⁶ Unfortunately, these data rarely stratify patients with 1 versus extensive AKs, which is a more clinically relevant measure for patients with FC.

AKs represent the most common dermatologic diagnosis in patients ≥ 45 years of age in the United States,⁷ with an estimated 5.2 million visits annually.⁸ The number of treated AKs per 1000 Medicare patients rose 14.6% (917.2 to 1051.1) from 2007 to 2015, demonstrating the increasing prevalence of this disease.⁹

Incidence data on AKs is sparse given the difficulty in tracking individual AKs over time.⁶ In a study from South Wales of patients > 60 years of age, there was an incidence of 149 AKs per 1000 person-years.¹⁰ Incidence rates of AKs were as high as 60% in Australian patients who had a history of previous AKs.¹¹

There was a 35% increased incidence of keratinocyte carcinoma (KC) in the United States between 2006 and 2012.¹² While the risk of transformation of individual AKs to invasive CSCC is low (0-0.53% per lesion-year; 2.88% at 5 years),^{13,14} patients with FC carry significantly higher risks of invasive CSCC because of the high burden of actinic damage.¹⁵

At-risk populations

The risk factors for FC are similar to the risk factors for AK and CSCC, namely exposure to UVR, fair skin, increasing age, male sex, and immunosuppression.

Age. AKs have been shown in many studies to increase significantly with age.¹⁶⁻²⁰ A study of 1,375 patients in Baltimore showed a >5-fold increase in AKs in patients 70 to 79 years of age versus those 50 to 59 years of age.²⁰ A German study of >90,000 patients demonstrated a 4-fold increased risk of AKs in persons 61 to 70 years of age compared with the total study population.¹⁹

Sex. Males have consistently higher rates of AKs compared with females.^{16,17,20-25} In a population-based German study, there was a nearly 4-fold increased risk of AKs in men.¹⁷ Males also have a 3 times higher prevalence of extensive actinic damage (defined as ≥ 10 AKs) compared with females,²⁵ which is more likely related to differences in sun exposure and protection behaviors between the 2 groups rather than inherent susceptibility.

Body site. AKs are seen almost exclusively in sites of extensive sun exposure, including the scalp, face, dorsal aspects of the hands, and the forearms.²⁶⁻²⁹ The density of AKs is 18 times higher on the face than the trunk and extremities.²⁶ In a population-based study from the Netherlands, the single strongest risk factor for the development of ≥ 10 AKs was severe baldness in males.²⁵

Skin type. Fair-skinned patients have a significantly higher risk of developing AKs because of their susceptibility to UVR.^{17-19,21,25,30} In a case-control, multicenter study across 8 European countries, there was a 9- and 4-fold increased risk of AKs in Fitzpatrick type I and II skin, respectively.¹⁸

UVR. AKs and CSCCs are related to the amount of cumulative UVR an individual experiences over his or her lifetime.³¹⁻³³ The amount of ambient UVR exposure has repeatedly been shown to affect the incidence of CSCCs,³³⁻³⁶ with those living closer to the equator being exposed to more UVR. Occupations with high rates of daily sun exposure have also been shown to have increased rates of actinic damage.^{18,32,37,38}

Immunosuppression. The risk for AKs and CSCCs is significantly increased in immunosuppressed patients, such as solid organ transplant recipients (SOTRs) or patients with chronic lymphocytic leukemia.^{15,39-41} In the authors' experience, this group of patients is at the highest risk of developing FC. Decreased immune surveillance allows for high rates of skin tumorigenesis and predisposes patients to the development of FC.⁶

A 2015 study of 452 SOTRs showed a 17% prevalence rate of FC, which increased with the length of immunosuppression.⁴² Furthermore, SOTRs with FC were shown to be 4 times more likely to develop CSCCs compared with those with AKs, but without FC.⁴² Although there are no

studies evaluating FC in patients with chronic lymphocytic leukemia, these patients have a 5- to 8.6-fold increased risk of CSCC⁴³⁻⁴⁵ with significantly elevated rates of recurrence, metastasis, and death from CSCC.⁴⁶⁻⁴⁹

DEFINING AND ASSESSING FIELD CANCERIZATION

Key points

- The clinical manifestations of FC lie on a continuum between AK and CSCC
- A clear and concise definition of FC is lacking
- Multiple grading systems for FC have recently been developed

Definition of FC

FC has been used to describe actinic dysplasia and KCs of the skin, but a clear and concise definition is lacking. There are several proposed definitions of cutaneous FC with most studies requiring a subclinical mutated field as a defining feature of the disease.⁵⁰⁻⁵⁴ While it is clear that UVR-induced sub-clinical atypia surrounds visible AKs and likely precedes their development, this has limited clinical utility because obtaining a biopsy specimen from the skin would be required to diagnose FC. Furthermore, it would not be possible to identify the field margins without evidence of visible AKs. Other proposed definitions of FC require a history of CSCC within the actinally damaged field.^{54,55} Although visible field change is paramount, the necessity of invasive CSCC may exclude patients with FC who have yet to develop their first CSCC and preclude these high-risk patients from receiving early field-directed intervention.

We have developed an updated definition of FC to help guide and standardize both the discussion and treatment of this disease. We define FC as multifocal clinical atypia characterized by AKs or squamous cell carcinomas in situ with or without invasive disease, occurring in a field exposed to chronic UVR. Compared with patients with diffuse AKs, patients with FC are more likely to have broad and hyperkeratotic scaly lesions, suggesting progression to squamous cell carcinoma in situ or early invasive CSCC, although this is not a required feature for diagnosis. These patients may have a history of multiple invasive CSCCs within the involved field if the FC was not diagnosed early. Clinical examples of FC are provided in Fig 1.

Current grading systems for FC

Despite the ubiquitous nature of AKs in dermatology, effective systems to grade FC are limited.



Fig 1. Field cancerization. Examples of field cancerization of the (A) scalp, (B) face, and (C) upper extremity in 3 patients. Note the extensive, confluent hyperkeratotic actinic keratoses and squamous cell carcinomas in situ.

Most studies measure AK counts⁵⁶; however, because of the varied morphology of AKs, counts are challenging and multiple studies have shown that they are imprecise.^{57,58} In patients affected by FC, AK counts are also impractical because these lesions often coalesce, and individual lesions are hard to identify and can spontaneously regress.

The Actinic Keratosis Area and Severity Index (AKASI) was developed with the intent of classifying actinic damage across a field.⁵⁹ This tool stratifies FC on the face and scalp in a similar manner to the Psoriasis Area Severity Index score in psoriasis.⁵⁹ A score is calculated by taking into account 3 parameters: area (scalp, forehead, right face, and left face), percentage of actinically damaged skin in each area, and the extent of clinical AK severity, including erythema, thickness, and distribution, with higher scores indicating worse actinic damage. Studies show that higher AKASI scores are associated with a greater risk of CSCC and basal cell carcinoma (BCC) (AKASI score 6.9 for CSCC vs 3.3 for BCC).⁵¹ A second scale, the Actinic Keratosis Field Assessment Scale (AK-FAS), was created with the similar goal of evaluating FC of the skin.⁶⁰ This tool applies to the face and scalp and uses a combination of sun damage and hyperkeratosis to determine the extent of actinic damage. To date, this gradation system has only been tested in photographs and has not been applied in clinical settings.

The main disadvantage of both AKASI and AK-FAS is that the scoring systems are time-

consuming and cumbersome for routine clinical practice. Neither tool fully measures FC because they do not account for the burden of squamous cell carcinomas in situ or invasive CSCCs within the sun-damaged field. Furthermore, neither tool has been validated in a large, prospective fashion. A simple, validated tool to evaluate FC in the clinical setting could help to better stratify those patients at greatest risk of CSCC progression.

PATHOGENESIS

Key points

- Chronic UVR is the primary carcinogen responsible for the formation of FC and KC
- p53-clonal fields are key to the formation of FC
- TP53 and NOTCH are recognized as early driver mutations in the progression from AK and FC to KC

Gene mutations caused by chronic UVR exposure are the main driver of FC. The mutagenic signature of UVB, C-T and CC-TT substitutions at dipyrimidine dimer sites, has been identified in several key driver genes in sun-exposed skin, AKs, and CSCCs.⁶¹⁻⁶⁴

TP53 is the most common driver mutation found in CSCCs, identified in >90% of specimens,⁶² and is suspected to be the key player in the formation of FC. P53 plays critical roles in both apoptosis and cell cycle arrest following DNA damage, and UVR-related loss of function leads to the resistance of apoptosis.^{65,66} Multiple studies

have shown that the clonal expansion of p53-mutated fields occurs in an exponential fashion in response to chronic UVR.^{67,68} This expansion occurs secondary to low doses of UVR at or below the energy needed to cause erythema.⁶⁹ In murine models, the number of p53-mutant clonal fields decreases 60% to 70% 2 to 4 weeks after removal of a chronic UVB stimulus.⁶⁸ These findings support epidemiologic data that actinic damage and CSCCs occur in response to chronic UVR, not short, high intensity events.⁶⁸

TP53 mutations have been identified in clinically normal sun-exposed skin, as well as photodamaged skin and AKs, but are nearly absent in sun-protected areas.⁷⁰⁻⁷⁵ The clonal expansion of p53-mutated fields in clinically normal tissue indicates that *TP53* mutations occur early in the progression towards FC and CSCC. Furthermore, subclones of other key CSCC driver mutations have been identified within these p53-mutant clonal patches, but not in adjacent skin outside of the clonal fields.⁷⁶ *NOTCH* (present in 75% to 82% of CSCCs)^{61,77-81} and *MAPK*⁸²⁻⁸⁶ have been identified as key driver mutations. Other notable driver mutations that are suspected to play a role in the progression to CSCC include *CDKN2A*,^{61,87} *FAT1*,^{61,88} *RAS*,^{87,89} *RIPK4*,⁸⁷ and *MMP1*.^{90,91} CSCCs possess the second highest (BCCs have the highest) mutational burden of any human malignancy with 33.3 to 50 mutations per megabase of coding DNA,^{61,92,93} and therefore it is difficult to determine which of the above mutations are key to the development of FC and CSCC.

OUTCOMES

Key points

- FC is associated with a significantly higher risk of CSCC formation compared with discrete AKs
- Recognition and treatment of FC before transformation to CSCC could provide significant cost reduction
- FC impacts quality of life similar to other chronic dermatologic diseases

Morbidity, mortality, and multiple skin cancer formation

The risk of CSCC increases with greater numbers of AKs. In SOTRs, those with 1 to 49 and ≥ 50 AKs had a 4.1- and 12.1-fold increased risk of CSCC formation, respectively.¹⁵ Similarly, in a study of immunocompetent patients, those with ≥ 15 AKs carried a 5.7 times increased risk of invasive CSCC on the face and ears compared with those without AKs.⁹⁴ Given the confluent nature of the actinic damage, patients with FC are at even higher risk of

CSCC formation compared with patients with multiple AKs.

In FC, the extensive subclinical premalignant change lends itself to the development of multiple primary skin cancers in the cancerized field.¹ Eighty-two percent of patients with ≥ 2 KCs will develop a new KC compared with only 43% of patients with 1 KC.⁹⁵ As patients develop multiple skin cancers, the morbidity associated with numerous surgical procedures increases substantially and the risk of metastatic CSCC also increases. Patients with ≥ 10 CSCCs have a 3.8 and 4.2 times increased risk for local recurrence and nodal metastasis, respectively, compared with those with 1 previous CSCC.⁵ Once metastatic disease develops, the mortality is high, with a median survival of 2.19 years for patients with stage IV CSCC.⁹⁶

Based on the above data, patients with FC are at higher risk of developing multiple CSCCs and often suffer significant morbidity and mortality from their disease. In our experience, early diagnosis of these patients is of paramount importance. Aggressive, early intervention to decrease premalignant change in the cancerized field and early CSCC detection can prevent the negative sequelae of untreated disease.

Cost

Given the high prevalence of AKs and an aging population, it is not unexpected that management of AKs and FC comes with a large economic cost. The combined management of AKs and KC accounts for $>15\%$ of all medical costs related to skin disease, with an estimated cost in the United States of \$1.68 and \$4.59 billion for AK and KC treatment, respectively.⁹⁷ However, overall, the treatment of AKs is less costly than the treatment of CSCCs. In Medicare patients, the per patient cost of KC (\$791) was almost \$650 more per year than the cost of treating AKs (\$143).⁹⁸ Field therapy for AKs in the form of topical chemotherapies and immunomodulators, a treatment often reserved for patients with FC, increased by 32% between 2011 to 2015.⁹⁹ In a study of high-risk Veterans Health Administration patients, there was a 3-year, \$741 savings in patients treated with 5-fluorouracil vs placebo.¹⁰⁰ Given the high prevalence of AK and CSCC in our society, the identification of patients with FC and aggressive treatment of AKs and early CSCCs may lead to significant cost reductions to the health care system.

Patient perception

While dermatologists often consider AK to be a premalignant diagnosis, the ongoing sequelae from chronic UVR suggests that actinic damage may also be viewed as a chronic disease.¹⁰¹ Actinic damage

can affect patient quality of life (QoL) in a number of ways, including fear about progression to cancer, cosmesis, and clinical symptoms.¹⁰² QoL scores for patients with AKs are comparable to other chronic diseases, including psoriasis and atopic dermatitis.¹⁰²

Patients with AKs have been shown to have a significantly lower QoL than those without AKs.^{101,103} While there are no studies examining the QoL in patients with FC, multiple studies have shown that QoL decreases as the number of AKs increases,^{101,102,104,105} suggesting that patients with FC may have a worse QoL than those patients without FC. Previous treatment with 5-fluorouracil, suggesting FC, is also strongly associated with lower QoL scores.¹⁰¹ Other factors associated with lower QoL in patients with actinic damage include female sex and age <60 years.^{102,106,107}

FUTURE DIRECTIONS

Given the high morbidity associated with FC, it is imperative that dermatologists understand this condition and the aggressive management required for these patients. A clear, widely accepted definition of FC will allow for these patients to be identified early. Future studies are needed that focus on identification of FC, risk factors, outcomes, and efficacy of clinical interventions.

REFERENCES

1. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. *Cancer*. 1953;6:963-968.
2. Braakhuis BJ, Tabor MP, Kummer JA, Leemans CR, Brakenhoff RH. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. *Cancer Res*. 2003;63:1727-1730.
3. Guy GP, Machlin SR, Ekwueme DU, Yabroff KR. Prevalence and costs of skin cancer treatment in the U.S., 2002-2006 and 2007-2011. *Am J Prev Med*. 2015;48:183-187.
4. Kim JYS, Kozlow JH, Mittal B, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. *J Am Acad Dermatol*. 2018;78:560-578.
5. Levine DE, Karia PS, Schmults CD. Outcomes of patients with multiple cutaneous squamous cell carcinomas: a 10-year single-institution cohort study. *JAMA Dermatol*. 2015;151:1220-1225.
6. Green AC. Epidemiology of actinic keratoses. *Curr Probl Dermatol*. 2015;46:1-7.
7. Landis ET, Davis SA, Taheri A, Feldman SR. Top dermatologic diagnoses by age. *Dermatol Online J*. 2014;20:22368.
8. Warino L, Tusa M, Camacho F, Teuschler H, Fleischer AB, Feldman SR. Frequency and cost of actinic keratosis treatment. *Dermatol Surg*. 2006;32:1045-1049.
9. Yeung H, Baranowski ML, Swerlick RA, et al. Use and cost of actinic keratosis destruction in the Medicare Part B fee-for-service population, 2007 to 2015. *JAMA Dermatol*. 2018;154:1281-1285.
10. Harvey I, Frankel S, Marks R, Shalom D, Nolan-Farrell M. Non-melanoma skin cancer and solar keratoses. I. Methods and descriptive results of the South Wales Skin Cancer Study. *Br J Cancer*. 1996;74:1302-1307.
11. Marks R, Foley P, Goodman G, Hage BH, Selwood TS. Spontaneous remission of solar keratoses: the case for conservative management. *Br J Dermatol*. 1986;115:649-655.
12. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the U.S. population, 2012. *JAMA Dermatol*. 2015;151:1081-1086.
13. Werner RN, Sammain A, Erdmann R, Hartmann V, Stockfleth E, Nast A. The natural history of actinic keratoses: a systematic review. *Br J Dermatol*. 2013;169:502-518.
14. Criscione VD, Weinstock MA, Naylor MF, et al. Actinic keratoses: natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. *Cancer*. 2009;115:2523-2530.
15. Bouwes Bavinck JN, Euvrard S, Naldi L, et al. Keratotic skin lesions and other risk factors are associated with skin cancer in organ-transplant recipients: a case-control study in The Netherlands, United Kingdom, Germany, France, and Italy. *J Invest Dermatol*. 2007;127:1647-1656.
16. Memon AA, Tomenson JA, Bothwell J, Friedmann PS. Prevalence of solar damage and actinic keratosis in a Merseyside population. *Br J Dermatol*. 2000;142:1154-1159.
17. Hensen P, Müller ML, Haschemi R, et al. Predisposing factors of actinic keratosis in a North-West German population. *Eur J Dermatol*. 2009;19:345-354.
18. Traianou A, Ulrich M, Apalla Z, et al. Risk factors for actinic keratosis in eight European centres: a case-control study. *Br J Dermatol*. 2012;167(suppl 2):36-42.
19. Schaefer I, Augustin M, Spehr C, Reusch M, Kornek T. Prevalence and risk factors of actinic keratoses in Germany—analysis of multisource data. *J Eur Acad Dermatol Venereol*. 2014;28:309-313.
20. Yaldiz M. Prevalence of actinic keratosis in patients attending the dermatology outpatient clinic. *Medicine (Baltimore)*. 2019;98:e16465.
21. Frost CA, Green AC, Williams GM. The prevalence and determinants of solar keratoses at a subtropical latitude (Queensland, Australia). *Br J Dermatol*. 1998;139:1033-1039.
22. Araki K, Nagano T, Ueda M, et al. Incidence of skin cancers and precancerous lesions in Japanese—risk factors and prevention. *J Epidemiol*. 1999;9(6 suppl):S14-S21.
23. Kennedy C, Bajdik CD, Willemze R, De Gruyil FR, Bouwes Bavinck JN, Leiden Skin Cancer Study. The influence of painful sunburns and lifetime sun exposure on the risk of actinic keratoses, seborrheic warts, melanocytic nevi, atypical nevi, and skin cancer. *J Invest Dermatol*. 2003;120:1087-1093.
24. Naruse K, Ueda M, Nagano T, et al. Prevalence of actinic keratoses in Japan. *J Dermatol Sci*. 1997;15:183-187.
25. Flohil SC, van der Leest RJ, Dowlatshahi EA, Hofman A, de Vries E, Nijsten T. Prevalence of actinic keratosis and its risk factors in the general population: the Rotterdam Study. *J Invest Dermatol*. 2013;133:1971-1978.
26. Youl PH, Janda M, Aitken JF, Del Mar CB, Whiteman DC, Baade PD. Body-site distribution of skin cancer, premalignant and common benign pigmented lesions excised in general practice. *Br J Dermatol*. 2011;165:35-43.
27. Rigel DS. Cutaneous ultraviolet exposure and its relationship to the development of skin cancer. *J Am Acad Dermatol*. 2008;58(5 suppl 2):S129-S132.
28. Franceschi S, Levi F, Randimbison L, La Vecchia C. Site distribution of different types of skin cancer: new aetiological clues. *Int J Cancer*. 1996;67:24-28.

29. Pearl DK, Scott EL. The anatomical distribution of skin cancers. *Int J Epidemiol*. 1986;15:502-506.
30. Naldi L, Chatenoud L, Piccitto R, et al. Prevalence of actinic keratoses and associated factors in a representative sample of the Italian adult population: results from the Prevalence of Actinic Keratoses Italian Study, 2003-2004. *Arch Dermatol*. 2006;142:722-726.
31. Woodhead AD, Setlow RB, Tanaka M. Environmental factors in nonmelanoma and melanoma skin cancer. *J Epidemiol*. 1999;9(6 suppl):S102-S114.
32. Strickland PT, Vitasa BC, West SK, Rosenthal FS, Emmett EA, Taylor HR. Quantitative carcinogenesis in man: solar ultraviolet B dose dependence of skin cancer in Maryland watermen. *J Natl Cancer Inst*. 1989;81:1910-1913.
33. Xiang F, Lucas R, Hales S, Neale R. Incidence of nonmelanoma skin cancer in relation to ambient UV radiation in white populations, 1978-2012: empirical relationships. *JAMA Dermatol*. 2014;150:1063-1071.
34. Staples M, Marks R, Giles G. Trends in the incidence of non-melanocytic skin cancer (NMSC) treated in Australia 1985-1995: are primary prevention programs starting to have an effect? *Int J Cancer*. 1998;78:144-148.
35. Holme SA, Malinovszky K, Roberts DL. Changing trends in non-melanoma skin cancer in South Wales, 1988-98. *Br J Dermatol*. 2000;143:1224-1229.
36. Stern RS. The mysteries of geographic variability in non-melanoma skin cancer incidence. *Arch Dermatol*. 1999;135:843-844.
37. Fartasch M, Diepgen TL, Schmitt J, Drexler H. The relationship between occupational sun exposure and non-melanoma skin cancer: clinical basics, epidemiology, occupational disease evaluation, and prevention. *Dtsch Arztebl Int*. 2012;109:715-720.
38. Oldenburg M, Kuechmeister B, Ohnemus U, Baur X, Moll I. Actinic keratosis among seafarers. *Arch Dermatol Res*. 2013;305:787-796.
39. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med*. 2003;348:1681-1691.
40. Lindelöf B, Sigurgeirsson B, Gäbel H, Stern RS. Incidence of skin cancer in 5356 patients following organ transplantation. *Br J Dermatol*. 2000;143:513-519.
41. O'Reilly Zwald F, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part I. Epidemiology of skin cancer in solid organ transplant recipients. *J Am Acad Dermatol*. 2011;65:253-261.
42. Wallingford SC, Russell SA, Vail A, Proby CM, Lear JT, Green AC. Actinic keratoses, actinic field change and associations with squamous cell carcinoma in renal transplant recipients in Manchester, UK. *Acta Derm Venereol*. 2015;95:830-834.
43. Greene MH, Hoover RN, Fraumeni JF. Subsequent cancer in patients with chronic lymphocytic leukemia—a possible immunologic mechanism. *J Natl Cancer Inst*. 1978;61:337-340.
44. Adami J, Frisch M, Yuen J, Glimelius B, Melbye M. Evidence of an association between non-Hodgkin's lymphoma and skin cancer. *BMJ*. 1995;310:1491-1495.
45. Levi F, Randimbison L, Te VC, La Vecchia C. Non-Hodgkin's lymphomas, chronic lymphocytic leukaemias and skin cancers. *Br J Cancer*. 1996;74:1847-1850.
46. Royle JA, Baade PD, Joske D, Girschik J, Fritsch L. Second cancer incidence and cancer mortality among chronic lymphocytic leukaemia patients: a population-based study. *Br J Cancer*. 2011;105:1076-1081.
47. Velez NF, Karia PS, Vartanov AR, Davids MS, Brown JR, Schmults CD. Association of advanced leukemic stage and skin cancer tumor stage with poor skin cancer outcomes in patients with chronic lymphocytic leukemia. *JAMA Dermatol*. 2014;150:280-287.
48. Brewer JD, Shanafelt TD, Khezri F, et al. Increased incidence and recurrence rates of nonmelanoma skin cancer in patients with non-Hodgkin lymphoma: a Rochester Epidemiology Project population-based study in Minnesota. *J Am Acad Dermatol*. 2015;72:302-309.
49. Mehrany K, Weening RH, Lee KK, Pittelkow MR, Otley CC. Increased metastasis and mortality from cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia. *J Am Acad Dermatol*. 2005;53:1067-1071.
50. Figueras Nart I, Cerio R, Dirschka T, et al. Defining the actinic keratosis field: a literature review and discussion. *J Eur Acad Dermatol Venereol*. 2018;32:544-563.
51. Schmitz L, Gambichler T, Gupta G, Stücker M, Dirschka T. Actinic keratosis area and severity index (AKASI) is associated with the incidence of squamous cell carcinoma. *J Eur Acad Dermatol Venereol*. 2018;32:752-756.
52. Fernandez Figueras MT. From actinic keratosis to squamous cell carcinoma: pathophysiology revisited. *J Eur Acad Dermatol Venereol*. 2017;31(suppl 2):5-7.
53. Markowitz O, Schwartz M, Feldman E, et al. Defining field cancerization of the skin using noninvasive optical coherence tomography imaging to detect and monitor actinic keratosis in ingenol mebutate 0.015%-treated patients. *J Clin Aesthet Dermatol*. 2016;9:18-25.
54. Vatve M, Ortonne JP, Birch-Machin MA, Gupta G. Management of field change in actinic keratosis. *Br J Dermatol*. 2007;157(suppl 2):21-24.
55. Christensen SR. Recent advances in field cancerization and management of multiple cutaneous squamous cell carcinomas. *F1000Res*. 2018;7:F1000 Faculty Rev-690.
56. Epstein E. Quantifying actinic keratosis: assessing the evidence. *Am J Clin Dermatol*. 2004;5:141-144.
57. Whited JD, Horner RD, Hall RP, Simel DL. The influence of history on interobserver agreement for diagnosing actinic keratoses and malignant skin lesions. *J Am Acad Dermatol*. 1995;33:603-607.
58. Weinstock MA, Bingham SF, Cole GW, et al. Reliability of counting actinic keratoses before and after brief consensus discussion: the VA topical tretinoin chemoprevention (VATTC) trial. *Arch Dermatol*. 2001;137:1055-1058.
59. Dirschka T, Pellacani G, Micali G, et al. A proposed scoring system for assessing the severity of actinic keratosis on the head: actinic keratosis area and severity index. *J Eur Acad Dermatol Venereol*. 2017;31:1295-1302.
60. Dréno B, Cerio R, Dirschka T, et al. A novel actinic keratosis field assessment scale for grading actinic keratosis disease severity. *Acta Derm Venereol*. 2017;97:1108-1113.
61. South AP, Purdie KJ, Watt SA, et al. NOTCH1 mutations occur early during cutaneous squamous cell carcinogenesis. *J Invest Dermatol*. 2014;134:2630-2638.
62. Brash DE, Rudolph JA, Simon JA, et al. A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. *Proc Natl Acad Sci U S A*. 1991;88:10124-10128.
63. Pfeifer GP, Besaratinia A. UV wavelength-dependent DNA damage and human non-melanoma and melanoma skin cancer. *Photochem Photobiol Sci*. 2012;11:90-97.
64. Ratushny V, Gober MD, Hick R, Ridky TW, Seykora JT. From keratinocyte to cancer: the pathogenesis and modeling of

- cutaneous squamous cell carcinoma. *J Clin Invest.* 2012;122:464-472.
65. Jiang W, Ananthaswamy HN, Muller HK, Kripke ML. p53 protects against skin cancer induction by UV-B radiation. *Oncogene.* 1999;18:4247-4253.
 66. Lu YP, Lou YR, Yen P, Mitchell D, Huang MT, Conney AH. Time course for early adaptive responses to ultraviolet B light in the epidermis of SKH-1 mice. *Cancer Res.* 1999;59:4591-4602.
 67. Zhang W, Remenyik E, Zelterman D, Brash DE, Wikonkal NM. Escaping the stem cell compartment: sustained UVB exposure allows p53-mutant keratinocytes to colonize adjacent epidermal proliferating units without incurring additional mutations. *Proc Natl Acad Sci U S A.* 2001;98:13948-13953.
 68. Klein AM, Brash DE, Jones PH, Simons BD. Stochastic fate of p53-mutant epidermal progenitor cells is tilted toward proliferation by UV B during preneoplasia. *Proc Natl Acad Sci U S A.* 2010;107:270-275.
 69. Roshan A, Jones PH. Chronic low dose UV exposure and p53 mutation: tilting the odds in early epidermal preneoplasia? *Int J Radiat Biol.* 2012;88:682-687.
 70. Jonason AS, Kunala S, Price GJ, et al. Frequent clones of p53-mutated keratinocytes in normal human skin. *Proc Natl Acad Sci U S A.* 1996;93:14025-14029.
 71. Ziegler A, Jonason AS, Leffell DJ, et al. Sunburn and p53 in the onset of skin cancer. *Nature.* 1994;372:773-776.
 72. Ling G, Persson A, Berne B, Uhlén M, Lundeberg J, Ponten F. Persistent p53 mutations in single cells from normal human skin. *Am J Pathol.* 2001;159:1247-1253.
 73. Ortonne JP. From actinic keratosis to squamous cell carcinoma. *Br J Dermatol.* 2002;146(suppl 61):20-23.
 74. Nakazawa H, English D, Randell PL, et al. UV and skin cancer: specific p53 gene mutation in normal skin as a biologically relevant exposure measurement. *Proc Natl Acad Sci U S A.* 1994;91:360-364.
 75. Rebel H, Kram N, Westerman A, Banus S, van Kranen HJ, de Grujil FR. Relationship between UV-induced mutant p53 patches and skin tumours, analysed by mutation spectra and by induction kinetics in various DNA-repair-deficient mice. *Carcinogenesis.* 2005;26:2123-2130.
 76. Albibas AA, Rose-Zerilli MJJ, Lai C, et al. Subclonal evolution of cancer-related gene mutations in p53 immunopositive patches in human skin. *J Invest Dermatol.* 2018;138:189-198.
 77. Swiatek PJ, Lindsell CE, del Amo FF, Weinmaster G, Gridley T. Notch1 is essential for postimplantation development in mice. *Genes Dev.* 1994;8:707-719.
 78. Aster J, Pear W, Hasserjian R, et al. Functional analysis of the TAN-1 gene, a human homolog of Drosophila notch. *Cold Spring Harb Symp Quant Biol.* 1994;59:125-136.
 79. Jen WC, Wettstein D, Turner D, Chitnis A, Kintner C. The Notch ligand, X-Delta-2, mediates segmentation of the paraxial mesoderm in Xenopus embryos. *Development.* 1997;124:1169-1178.
 80. Washburn T, Schweighoffer E, Gridley T, et al. Notch activity influences the alphabeta versus gammadelta T cell lineage decision. *Cell.* 1997;88:833-843.
 81. Wang NJ, Sanborn Z, Arnett KL, et al. Loss-of-function mutations in Notch receptors in cutaneous and lung squamous cell carcinoma. *Proc Natl Acad Sci U S A.* 2011;108:17761-17766.
 82. Einspahr JG, Calvert V, Alberts DS, et al. Functional protein pathway activation mapping of the progression of normal skin to squamous cell carcinoma. *Cancer Prev Res (Phila).* 2012;5:403-413.
 83. Hameetman L, Commandeur S, Bavinck JN, et al. Molecular profiling of cutaneous squamous cell carcinomas and actinic keratoses from organ transplant recipients. *BMC Cancer.* 2013;13:58.
 84. Hatzivassiliou G, Song K, Yen I, et al. RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. *Nature.* 2010;464:431-435.
 85. Poulikakos PI, Zhang C, Bollag G, Shokat KM, Rosen N. RAF inhibitors transactivate RAF dimers and ERK signalling in cells with wild-type BRAF. *Nature.* 2010;464:427-430.
 86. Ribas A, Flaherty KT. BRAF targeted therapy changes the treatment paradigm in melanoma. *Nat Rev Clin Oncol.* 2011;8:426-433.
 87. Pickering CR, Zhou JH, Lee JJ, et al. Mutational landscape of aggressive cutaneous squamous cell carcinoma. *Clin Cancer Res.* 2014;20:6582-6592.
 88. Quintana RM, Dupuy AJ, Bravo A, et al. A transposon-based analysis of gene mutations related to skin cancer development. *J Invest Dermatol.* 2013;133:239-248.
 89. Su F, Viros A, Milagre C, et al. RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. *N Engl J Med.* 2012;366:207-215.
 90. Van Haren R, Feldman D, Sinha AA. Systematic comparison of nonmelanoma skin cancer microarray datasets reveals lack of consensus genes. *Br J Dermatol.* 2009;161:1278-1287.
 91. Lambert SR, Mladkova N, Gulati A, et al. Key differences identified between actinic keratosis and cutaneous squamous cell carcinoma by transcriptome profiling. *Br J Cancer.* 2014;110:520-529.
 92. Durinck S, Ho C, Wang NJ, et al. Temporal dissection of tumorigenesis in primary cancers. *Cancer Discov.* 2011;1:137-143.
 93. Jayaraman SS, Rayhan DJ, Hazany S, Kolodney MS. Mutational landscape of basal cell carcinomas by whole-exome sequencing. *J Invest Dermatol.* 2014;134:213-220.
 94. Xiong MY, Rizzo AE, Cohen TS, et al. Predictors of squamous cell carcinoma in high-risk patients in the VATTC trial. *J Invest Dermatol.* 2013;133:1521-1532.
 95. Wehner MR, Linos E, Parvataneni R, Stuart SE, Boscardin WJ, Chren MM. Timing of subsequent new tumors in patients who present with basal cell carcinoma or cutaneous squamous cell carcinoma. *JAMA Dermatol.* 2015;151:382-388.
 96. Zhu GA, Lynn Su Chang A. Overall and progression-free survival of stage 4 cutaneous squamous cell carcinoma at a single large referral center. *J Am Acad Dermatol.* 2015;73:165-166.
 97. Lim HW, Collins SAB, Resneck JS, et al. The burden of skin disease in the United States. *J Am Acad Dermatol.* 2017;76:958-972.e2.
 98. Housman TS, Feldman SR, Williford PM, et al. Skin cancer is among the most costly of all cancers to treat for the Medicare population. *J Am Acad Dermatol.* 2003;48:425-429.
 99. Song H, Adamson AS, Mostaghimi A. Trends in Medicare spending on topical immunomodulators and chemotherapies. *J Am Acad Dermatol.* 2018;78:173-175.
 100. Yoon J, Phibbs CS, Chow A, Weinstock MA, Veterans Affairs Keratinocyte Carcinoma Chemoprevention Trial Group. Impact of topical fluorouracil cream on costs of treating keratinocyte carcinoma (nonmelanoma skin cancer) and actinic keratosis. *J Am Acad Dermatol.* 2018;79:501-507.e2.
 101. Weinstock MA, Lee KC, Chren MM, Marcolivio K, Group VT. Quality of life in the actinic neoplasia syndrome: the VA Topical Tretinoin Chemoprevention (VATC) Trial. *J Am Acad Dermatol.* 2009;61:207-215.
 102. Tennvall GR, Norlin JM, Malmberg I, Erlendsson AM, Hædersdal M. Health related quality of life in patients with actinic keratosis—an observational study of patients treated in dermatology specialist care in Denmark. *Health Qual Life Outcomes.* 2015;13:111.

103. Miller IM, Vinding G, Zarchi K, Esman S, Murrell DF, Jemec GB. Differences in disease-specific quality of life in patients with actinic keratosis in Australia and Denmark. *Acta Dermatovenerol Croat.* 2016;24:25-28.
104. Lee K, Weinstock M. Prospective quality of life impact of actinic keratoses: observations from the veterans affairs topical tretinoin chemoprevention trial. *Acta Derm Venereol.* 2011;91:101-102.
105. Vis K, Waalboer-Spuij R, Snels DGCT, Hollestein LM. Validity and reliability of the Dutch adaptation of the Actinic Keratosis Quality of Life Questionnaire (AKQoL). *Dermatology.* 2018;234:60-65.
106. Philipp-Dormston WG, Müller K, Novak B, et al. Patient-reported health outcomes in patients with non-melanoma skin cancer and actinic keratosis: results from a large-scale observational study analysing effects of diagnoses and disease progression. *J Eur Acad Dermatol Venereol.* 2018;32:1138-1146.
107. Longo I, Serra-Guillén C. Quality of life, behaviour and attitudes towards actinic keratosis in Spain: the PIQA Study. *Actas Dermosifiliogr.* 2018;109:331-339.

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Field cancerization: Treatment

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Learning objectives

After completing this learning activity, participants should be able to discuss therapeutic options for the management of field cancerization; explain the utility of a multimodal treatment approach; and define the role of lesion-directed, field, and oral treatment in field cancerization management.

Disclosures

Editors

The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

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The goal of field cancerization treatment is to reduce the risk of developing keratinocyte carcinoma. Selecting the appropriate therapy depends on the degree of field cancerization and the number of invasive cutaneous squamous cell carcinomas. Other considerations include treatment efficacy, cost, side effects, and patient preference. Field therapies are preferred because they address clinically visible disease and subclinical atypia. However, lesion-directed therapies are useful for lesions that are more difficult to treat or those where a histologic diagnosis is required. Patients with extensive field cancerization benefit from a combination of field-directed and lesion-directed treatments. The second article in this continuing medical education series provides a framework to guide evidence-based decision making for field cancerization treatment. (*J Am Acad Dermatol* 2020;83:719-30.)

Key words: actinic keratoses; cutaneous squamous cell carcinoma; field cancerization; keratinocyte carcinoma; solid organ transplant recipient.

The goal of field cancerization (FC) treatment is to reduce the risk of developing keratinocyte carcinoma (KC). Selecting the appropriate therapy depends on the degree of FC and the

number of invasive cutaneous squamous cell carcinomas (CSCCs).^{1,2} Other considerations include treatment efficacy, cost, side effects, and patient preference.

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Abbreviations used:

5-FU:	5-fluorouracil
AK:	actinic keratosis
BCC:	basal cell carcinoma
c-PDT:	conventional photodynamic therapy
CRR:	complete response rate
CSCC:	cutaneous squamous cell carcinoma
FC:	field cancerization
FDA:	US Food and Drug Administration
IL:	intraleisional
KC:	keratinocyte carcinoma
RCT:	randomized controlled trial
SCCis:	squamous cell carcinoma in situ
SOTR:	solid organ transplant recipient

FIELD TREATMENTS

Key points

- **Field-directed treatments reduce cutaneous squamous cell carcinoma formation**
- **5-fluorouracil is the most effective field therapy**
- **Combination 5-fluorouracil and calcipotriol reduces treatment duration and has synergistic effects on field disease**
- **Daylight photodynamic therapy has comparable efficacy to conventional photodynamic therapy, but less treatment-associated discomfort**

Field-directed therapy reduces actinic keratosis (AK) burden as well as the number of new cutaneous squamous cell carcinomas (CSCCs).³⁻⁶ Although there is substantial literature to support various field therapies, comparing different modalities is difficult because of heterogeneous study endpoints and the lack of standardized, objective methods for assessing field disease. While many studies report short-term response rates, long-term responses are critical given the chronic nature of FC. Nevertheless, patients with FC often require multiple courses of field-directed treatment. The choice of treatment is largely dictated by patient and physician preferences; however, increasing evidence from randomized trials with long-term follow-up and direct comparison between treatments will allow physicians to make evidence-based recommendations (Table I).²⁵

5-Fluorouracil

5-Fluorouracil (5-FU) is a pyrimidine analogue approved by the US Food and Drug Administration (FDA) for the treatment of AKs and superficial basal cell carcinomas (BCCs). Local inflammatory reactions are expected (Fig 1), although patients may experience fewer adverse effects with repeat courses due to improvement in keratinocyte dysplasia in the previously treated field.⁵

The Veterans Affairs Keratinocyte Carcinoma Chemoprevention trial demonstrated that 2 to 4 weeks of 5-FU therapy reduced AK counts and lesion-directed treatments for >2 years.⁴ Additional data published from the trial showed a 75% reduction in the risk of SCC at 1 year.⁵ No differences were seen between the placebo group and the 5-FU group at 4 years, underscoring the chronic and relapsing nature of FC and the importance of repeated treatment for continued chemopreventive effect.⁵ Although the literature on 5-FU for the treatment of squamous cell carcinoma in situ (SCCis) is less robust, response rates of 48% to 85% have been reported.^{8,26,27}

A recent multicenter, single-blind, randomized controlled trial (RCT) of 624 patients found that 5-FU 5% is superior to imiquimod cream 5%, methyl aminolevulinate photodynamic therapy, and ingenol mebutate gel 0.015% for the treatment of AKs at 12 months.²⁵ Similar findings were reported in 2 metaanalyses.^{28,29}

Imiquimod

Imiquimod is a topical immune response modifier that is approved by the FDA for the treatment of nonhypertrophic AKs on the face and scalp and low-risk, superficial BCCs in immunocompetent adults. The most common adverse events are local erythema, scabbing or crusting, flaking, erosion, edema, and weeping.⁹ Imiquimod in solid organ transplant recipients (SOTRs) has been shown to be safe with no observed effects on systemic immunity.³⁰

A metaanalysis of 5 RCTs ($n = 1293$) reported complete AK clearance in 50% of patients treated with imiquimod cream 5%.⁹ Lower concentrations may have reduced clinical efficacy.³¹ Imiquimod is beneficial for the off-label treatment of SCCis, with complete response rates (CRRs) of 75% to 93%.^{10,32,33}

5-Fluorouracil/calcipotriol

Combination therapy with calcipotriol (also known as calcipotriene) plus 5-FU has been shown to have a synergistic effect in the treatment of AKs by inducing a CD4⁺ T cell-mediated immune response.^{6,11} A RCT with 130 subjects receiving either a twice-daily 4-day regimen of 5-FU 5% plus calcipotriol ointment 0.005% or 5-FU 5% plus petroleum jelly showed a mean AK reduction of 88% vs 26% and CRR of 27% vs 0%, respectively.¹¹ The combination regimen was also associated with a reduced long-term risk of CSCC, which may be related to the induction of a long-lasting T cell immunity in the skin.⁶

Table I. Field-directed therapies

Therapy	Indications and recommended application	Mechanism of action	Level of evidence*
5-FU ^{7,8}	AKs 5% cream: twice daily ×2-4 weeks 0.5% cream: daily for up to 4 weeks SCCis (off-label) 5% cream: twice daily ×3-6 weeks; treatment can be continued for ≤12 weeks	Inhibition of TS and DNA and RNA misincorporation, leading to cell death of atypical and rapidly proliferating keratinocytes	AK: IA; SCCis: IB
Imiquimod ^{9,10}	AKs 5% cream: twice weekly ×16 weeks (limit treatment area to ≤25 cm ²) 2.75% cream and 3.5% cream: daily ×2 weeks for 2 treatment cycles separated by a 2-week rest period SCCis (off-label) 5% cream: daily ×16 weeks	Stimulation of innate and adaptive immune response pathways resulting in antitumor and antiviral activity	AK: IA; SCCis: IB
5-FU plus calcipotriol ¹¹	AKs (off label): twice daily ×4 days	Induction of thymic stromal lymphopoietin and robust CD4 ⁺ T cell immunity against AKs	IB
Chemowraps with 5-FU ¹²⁻¹⁵	AKs and SCCis of the extremities (off-label): apply weekly ×4 weeks or until desired clinical response		III
Ingenol mebutate ¹⁶	AKs Face or scalp: apply 0.015% gel once daily to affected area for 3 consecutive days (limit treatment area to ≤25 cm ²) Trunk or extremities: apply 0.05% gel once daily to affected area for 2 consecutive days (limit treatment area to ≤25 cm ²)	Mitochondrial disruption leading to necrosis and localized inflammatory response via activation of protein kinase C pathway and apoptosis ¹⁷	IB
PDT ^{18,19}	c-PDT ALA 20% solution/blue light (BLU-U 400 nm) ALA 10% nanoemulsion/red light (BF-RhodoLED 635 nm) MAL 16.8% cream [†] /red light dl-PDT: MAL or ALA 10% nanoemulsion/ambient light ²⁰ Protocols used by the authors: 1. Instruct patients sit in a shady area on a nonrainy day ≥60°F within 60 min of ALA application for a total duration of 2.5 hours ²¹ 2. 10-min ALA incubation activated by exposure to blue light (16 min, 40 sec) followed by daylight (45 min) (manuscript under review) 3. Sequential treatment with removal of hyperkeratotic material, application of 5% 5-FU twice daily (5 days on the face and scalp or 7 days on the arms), and c-PDT with 1-hour incubation time ^{‡22}	Photochemical reaction following exposure of topically administered precursors of photoactive porphyrins (ALA or MAL) to light of appropriate wavelength and energy; preferential accumulation of photoactive porphyrins in both malignant and pre-malignant cells leads to selective destruction of atypical keratinocytes ²³	IB

5-FU, 5-Fluorouracil; AK, actinic keratosis; ALA, aminolevulinic acid; c-PDT, conventional photodynamic therapy; dl-PDT, daylight photodynamic therapy; MAL, methyl aminolevulinate; PDT, photodynamic therapy; SCCis, squamous cell carcinoma in situ; TS, thymidylate synthase.

*Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥1 randomized controlled trial; level IIA evidence includes evidence from ≥1 controlled study without randomization; level IIB evidence includes evidence from ≥1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

[†]Not available in the United States.

[‡]Sequential 5-FU and PDT have been shown to improve AK clearance through enhanced photosensitizer accumulation and expression of p53.²⁴

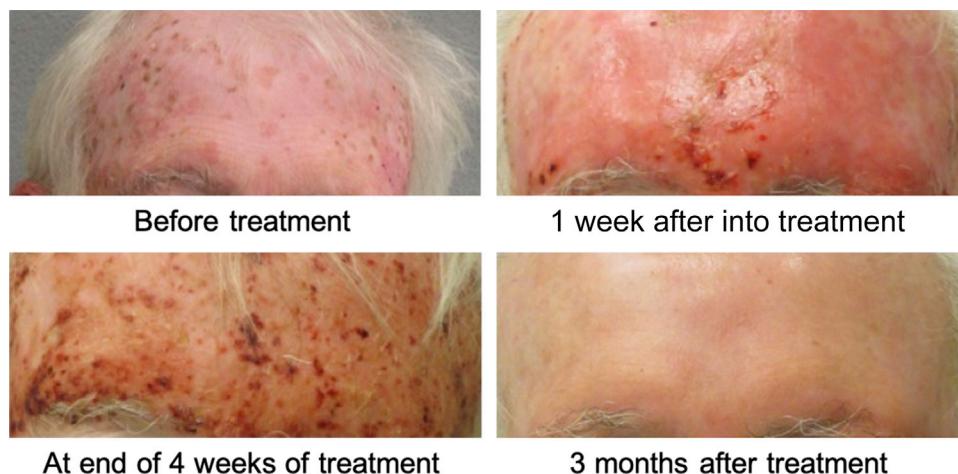


Fig 1. Field cancerization treatment. Local inflammatory reaction and response to 5-fluorouracil at different time points.

Treatment with calcipotriol plus 5-FU is associated with more inflammation than 5-FU alone and peaks approximately 10 days after the initiation of therapy and usually resolves by 2 weeks.¹¹ The addition of calcipotriol may result in better patient compliance because of the shorter treatment duration. However, the regimen may be more expensive because it requires 2 separate prescriptions or ordering through a compounding pharmacy. In our experience, some patients require a treatment course that is longer than 4 days to induce an adequate response and other patients develop an exuberant reaction with only 4 days of treatment.

Chemowraps

Weekly wraps with 5-FU occluded with zinc-impregnated gauze (Unna wrap) covered by a compression wrap and gauze bandages is effective for FC involving the extremities.¹²⁻¹⁵ Treatment is typically continued for 4 weeks, with the wraps changed weekly.²¹ Given the mode of application, patient compliance is high; however, some patients are reluctant to undergo a treatment that prohibits bathing for a week. Patients can cut the wrap off and shower before the weekly visit. An alternative to traditional wraps is 5-FU twice daily for 4 weeks with occlusion overnight via a plastic or compression wrap.²¹ This approach allows daily bathing and obviates the need for weekly visits.

A retrospective study of 25 patients with multiple AKs treated with chemowraps noted an AK response rate of 60%, with 20% CRR after an average of 9.6 sessions (range 1-64 sessions).¹⁴ As an adjuvant to surgery, chemowraps may help define tumor borders and minimize the extent of surgery required in

patients with significant FC.¹³⁻¹⁵ Chemowraps are also an option for palliative management of lower leg CSCCs on patients who are poor surgical candidates or refuse surgery.^{13,15}

Ingenol mebutate

Ingenol mebutate is approved by the FDA for the treatment of nonhyperkeratotic AKs. Several RCTs have demonstrated 8-week CCRs of 34% to 41% for the trunk and extremities and 42% to 62% for the face and scalp.^{16,34,35} In patients who achieved complete clearance at 8 weeks, around half had sustained clearance at 12 months.¹⁶ Local skin reactions are generally mild to moderate and peak at days 4 to 8.¹⁶ Although treatment is indicated for areas $\leq 25 \text{ cm}^2$ of contiguous, AK-affected skin, acceptable tolerability without quantifiable systemic exposure was seen in patients treated with 0.05% gel to areas $\leq 100 \text{ cm}^2$.³⁶

Photodynamic therapy

Conventional photodynamic therapy (c-PDT) is approved by the FDA in 3 drug/light combinations for the treatment of nonhyperkeratotic AKs (Table I). PDT can be performed in 1 treatment, with 1 to 2 optional repeat treatments 4 to 8 weeks apart. FC patients who have failed or cannot perform other field-directed therapies benefit from cyclic PDT.³⁷ There are many PDT regimens, including variations on pretreatment (curettage, microneedling, laser-assisted, etc), photosensitizer incubation time, and light source. Thermally modulated PDT has been used to improve AK clearance rates on the extremities.^{38,39} Daylight PDT uses ambient visible light to activate the photosensitizer. This approach minimizes pain and allows for exposure of large fields,

2 limiting factors of c-PDT. Daylight PDT has similar AK reduction rates compared with c-PDT.⁴⁰⁻⁴⁵ After treatment the photosensitizer is removed with soap and water and patients are instructed to wear sun-protective clothing and to apply zinc- or titanium-based sunscreen to all exposed areas for 48 hours.

Other therapies

There is a paucity of data to support laser or chemical peel resurfacing techniques as monotherapy for field disease. Evidence appears to favor ablative lasers as an adjunct to current therapies, particularly for more difficult-to-treat AKs (such as hyperkeratotic or acral lesions) because they may facilitate the delivery of topical agents.⁴⁶ Other novel therapies are being investigated in clinical trials (Table II).⁵²

LESION-DIRECTED THERAPIES

Key points

- **Lesion-directed therapies are recommended for KCs that are dermally invasive on clinical examination, focal hyperkeratotic AK, or AK failing field treatments**
- **Cryotherapy of isolated AKs can be highly effective if performed correctly**
- **Surgery or shave removal is indicated for lesions requiring histologic confirmation of margin clearance**

Cryotherapy

Cryotherapy is the mainstay of treatment for isolated AKs because of its ease of use and good tolerability. In a RCT of cryotherapy, 5-FU, and imiquimod 5%, cryotherapy was associated with a 68% initial AK clearance rate, but only a 28% sustained clearance rate at 12 months.⁵³ Freeze time is an important determinant of treatment efficacy with CRRs of 83%, 69%, and 39% at 3 months with freeze times >20 seconds, 5-20 seconds, and <5 seconds, respectively.⁵⁴ Despite higher efficacy, longer freeze durations may result in greater discomfort and localized cutaneous reactions, including hypopigmentation and scarring. Combining cryotherapy of hypertrophic AKs with field-directed therapy can improve response rates.^{55,56} Cryotherapy may also be used after field therapy to treat persistent AKs.

Surgical management

Shave removal of persistent hyperkeratotic lesions is diagnostic and therapeutic. Surgical excision of invasive KCs arising within areas of field damage remains the standard of care. Surgical removal with an appropriate margin of clinically normal skin can be a challenge in FC patients and it is often not

feasible to surgically remove extensive areas of in situ disease. Patients benefit from pre- or postoperative field treatment. Complete circumferential peripheral and deep margin control with Mohs micrographic surgery is recommended for high-risk CSCCs unless the wound can be closed primarily or reconstruction delayed until clear margins are confirmed.^{57,58}

Intralesional 5-FU

Intralesional 5-FU (IL 5-FU) is an effective treatment for eruptive squamous atypia (also termed eruptive keratoacanthoma) and is a noninvasive option for low-risk CSCC, particularly in patients who are poor candidates for surgery. Data supporting IL 5-FU for CSCC treatment are largely derived from case reports and 1 prospective trial, which reported a 96% cure rate of well-differentiated CSCC in 25 patients treated with a proprietary injectable 5-FU gel.⁵⁹⁻⁶²

IL 5-FU is quick and easy to administer.⁶³⁻⁶⁶ Side effects are generally mild and include erythema, dyspigmentation, crusting, and shallow erosions or ulcerations, which typically heal within 2 to 4 weeks.^{65,66} There are no reported cases of systemic adverse events. Drawbacks include the lack of histologic confirmation of clear margins, a risk of significant recurrence if undiagnosed aggressive CSCC fails treatment, and the need for multiple injection visits. Thus, we prefer shave excision for small low-risk CSCCs arising in FC and reserve IL 5-FU for eruptive squamous atypia or lower extremity low-risk CSCC who decline excision because of the risk of poor wound healing.

There is no standard guideline for the administration of IL 5-FU and the dose varies by tumor size (Table III). Smaller (<1.5 cm) and thinner lesions are more likely to respond. Any lesions that grow or that do not respond should be removed surgically. Adjuvant therapies such as topical 5-FU under occlusion, cryotherapy, and oral acitretin can help achieve clearance.⁶⁶

ORAL TREATMENTS

Key points

- **Nicotinamide is a low-cost chemopreventive agent that reduces AKs and CSCCs and requires no monitoring**
- **Oral retinoids may be added for patients who continue to form multiple CSCCs despite comprehensive treatment of FC**
- **Long-term acitretin is required for chemoprevention given the risk of renewed CSCC formation after treatment cessation**

Table II. Investigational agents with recent or ongoing clinical trials in the United States for treatment of actinic keratoses

Investigational agents	Proposed mechanism of action	Study identifier
SR-T100: antiproliferative agent (contains solamargine, solasodine, and solasonine)	Induces apoptosis via death receptors and the mitochondrial pathway ⁴⁷	NCT01516515
KX2-391: Src tyrosine kinase inhibitor	Inhibits Src tyrosine kinase and tubulin polymerization, reducing downstream signaling and proliferation of tumor cells overexpressing Src ⁴⁸	NCT02838628 NCT03285477 NCT03285490
SOR007: uncoated nanoparticulate paclitaxel ointment	Binds to tubulin and inhibits the disassembly of microtubules, leading to inhibition of cell division and halting the proliferation of rapidly dividing tumor cells ⁴⁹	NCT03083470
VDA-1102: antineoplastic agent	Prevents glycolysis and triggers apoptosis in voltage-dependent anion channel/hexokinase 2-expressing tumor cells ⁵⁰	NCT03538951
Cold atmospheric plasma device	Increases oxidative stress via reactive oxygen species, leading to DNA damage and cell cycle arrest of malignant proliferative cells ⁵¹	NCT02759900

Table III. Examples of protocols used by the authors for injections of intralesional 5-fluorouracil 50 mg/mL for treatment of eruptive squamous atypia and cutaneous squamous cell carcinoma

Dose	Frequency	Notes
1 mL total to a lesion >1 cm OR distributed amongst a few smaller lesions (up to approximately 1-2 cm ²)	Twice weekly ×2 weeks, then weekly ×3 weeks OR weekly ×7 weeks (up to 7 injections total)	Treat until ulceration, which is typically achieved within 4-5 injections for larger lesions
0.1-2 mL per lesion for a maximum total dose per session of 250 mg	Reinject persistent lesions at 2- to 4-week intervals	Surgical removal is recommended for lesions that do not respond to 2 injections

- **Oral capecitabine may be considered for patients with significant FC and high rates of CSCC formation, or who failed other treatments of extensive FC**

Nicotinamide

Nicotinamide (also known as niacinamide), a water-soluble vitamin B₃ derivative, has modest effects on AK and KC reduction.⁶⁷⁻⁶⁹ Nicotinamide reduces ultraviolet-associated immunosuppression and ultraviolet-induced depletion of nicotinamide adenine dinucleotide and adenosine triphosphate, which provide the cellular energy required for repair of ultraviolet-induced DNA damage.⁷⁰⁻⁷² Nicotinamide is well-tolerated at pharmacologic doses, but can cause liver failure at high doses (>3 g/day).^{73,74} Increased insulin resistance and flushing, which can occur with nicotinic acid, are not seen in nicotinamide.⁷⁵ No safety concerns have been identified in SOTRs receiving up to 1 g daily.^{68,76}

A phase 3, double-blind RCT showed that nicotinamide 500 mg twice daily reduced the rate of new SCCs by 30% ($P = .05$) and number of AKs compared with baseline by 13% ($P = .001$) at 12 months.⁶⁷ No significant difference in KC rates were seen upon discontinuation, suggesting that nicotinamide must be continued to maintain its chemoprotective effect.

The evidence of nicotinamide's chemoprotective effect in immunocompromised patients is limited. A phase 2 RCT of nicotinamide 500 mg twice daily for 6 months in 22 renal transplant recipients found no significant reduction in AKs or new CSCCs, but this may be related to the small sample size.⁷⁶ In a case-control trial involving 38 SOTRs, reduced AK size and complete AK regression was seen in 88% and 42% of patients receiving nicotinamide 500 mg daily, respectively.⁶⁸ No new AKs or skin cancers were seen in the nicotinamide group at 6 months. In contrast, 91% of the control group showed an increase in AKs and 7 preexisting AKs progressed to CSCCs.

While the benefits of nicotinamide are promising, there is a lack of long-term prospective studies documenting its effects on skin cancer prevention. Given nicotinamide's low cost and favorable safety profile at doses <3 g daily, it is reasonable to offer nicotinamide to patients with FC or who have had >1 CSCC.²¹

Acitretin

Acitretin is an oral retinoid that is used for chemoprevention.⁷⁷⁻⁸¹ Continuous treatment appears to be required to maintain a chemotherapeutic effect.^{77,81,82} Though it is not expected to alter the course of existing KC, acitretin decreases the likelihood of new primary tumors. A systematic review showed a 60% reduction in CSCC formation.⁸³ Acitretin has also been shown to reduce AKs by ≤50%.⁸⁰

Acitretin may be considered in patients with ≥5 KCs over the course of 2 to 3 years, significant field disease with diffuse AKs/SCCis despite treatment, high-risk KC, or metastatic KC.^{21,84} It can also be considered in high-risk SOTRs with FC before first KC. Though acitretin typically does not cross-react with transplant immunosuppression, initiation should be done in conjunction with the transplant team. The minimal effective dose varies.⁸⁵ The typical practice is to start at a low dose, such as 10 mg daily or every other day, and gradually escalate to goal dose of 20 to 30 mg daily.⁸⁶ This slow increase minimizes adverse effects and identifies the best dose tolerated. One of the more common adverse effects is hyp triglyceridemia. Other adverse effects are dose-related and include headache, musculoskeletal complaints, mucocutaneous dryness, and alopecia, as well as abnormalities in liver function tests.^{82,86,87} Effective management of side effects and dosage modification often allows for continuation of treatment. A limitation to acitretin utilization in the United States is its high cost.⁸³

Capecitabine

Oral capecitabine, a prodrug of 5-FU, can be useful for patients with FC with high rates of CSCC despite optimization of risk factors and other chemopreventive and field-directed agents. We initiate treatment at 500 mg twice daily every other week for 1 to 3 months and then increase to 1000 mg twice daily for 2 weeks with 1 week off drug between the 2 weeks of treatment. Case reports and small case series have shown capecitabine to reduce both CSCCs and AKs in SOTRs.⁸⁸⁻⁹¹ Although these results are promising, larger studies in other patient populations with long-term follow-up are needed.

The side effects of capecitabine are largely dose-related and include fatigue, diarrhea, hand-foot syndrome, neutropenic fever, and stomatitis. In the literature, treatment-limiting side effects may be observed in ≤30% of patients.⁸⁴ However, in our experience, there are minimal side effects even at higher doses. Before initiating treatment, patients should be screened for dihydropyrimidine dehydrogenase deficiency and renal function impairment. During treatment, renal function and hemoglobin should be monitored monthly.

Treatment algorithms

Our approach to FC treatment is based on the degree of field disease and the risk of subsequent KC formation (Fig 2). Other factors, including tolerability, cost, and the patient's motivation for treatment, may also influence treatment choice. Patients with a higher degree of FC benefit from a combination of lesion- and field-directed therapies, as well as oral chemoprophylaxis.²² These patients require repeated cycles of field-directed therapy, ranging from every few months to every few years.⁹² All patients should be counseled on rigorous ultraviolet light protection. For patients receiving oral chemoprophylaxis, nicotinamide and acitretin are safe in combination. The concurrent use of acitretin and capecitabine has not been studied; however, in our experience the 2 medications can also be administered concurrently.

Clinical visits

The frequency of clinical visits is dictated by individual patient risk factors, such as history of skin cancers, degree of FC, and history of SOTR (Table IV). More frequent screenings may lessen morbidity associated with skin cancer and improve overall quality of life.^{94,95} Patients undergoing field treatment should have close follow-up to confirm that the desired clinical endpoint has been reached.

FIELD CANCERIZATION IN HIGHER-RISK POPULATIONS

Key points

- SOTR and patients with chronic lymphocytic leukemia have an increased risk of AK and KC
- Higher-risk populations benefit from earlier and more aggressive field-directed therapy

Solid organ transplant recipients

Compared with immunocompetent patients, SOTRs are more likely to present with field disease and have higher rates of AK recurrence and progression and a lower rate of spontaneous AK regression.⁹⁶⁻⁹⁸ Lesion-directed therapies may not be

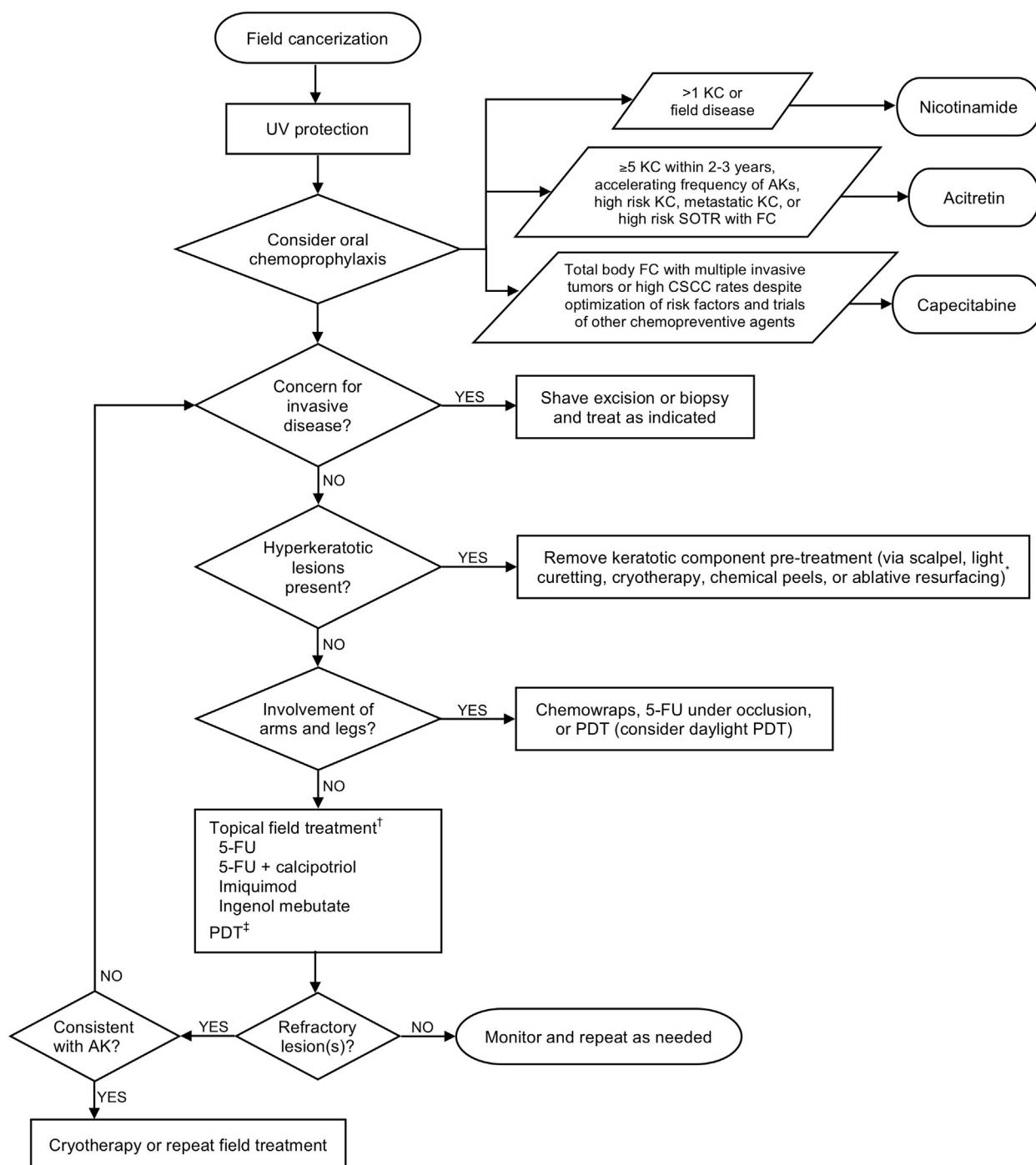


Fig 2. Field cancerization treatment algorithm.^{*}There is a paucity of data supporting the use of ablative resurfacing or chemical peels for field-directed treatment.[†]Contraindications to topical therapies in general include patient noncompliance and inadequate response to topicals.[‡]Contraindications to PDT include known hypersensitivity to any components of the topical photosensitizer, known hypersensitivity to porphyrins, porphyria, or photodermatoses. 5-FU, 5-Fluorouracil; AK, actinic keratosis; CSCC, cutaneous squamous cell carcinoma; FC, field cancerization; KC, keratinocyte carcinoma; PDT, photodynamic therapy; SOTR, solid organ transplant recipient; UV, ultraviolet.

Table IV. Recommended frequency of clinic visits based on severity of field cancerization and keratinocyte carcinoma history*

Risk factors	Interval (months)	
	Immunocompetent	SOTR/ CLL
Degree of field cancerization		
Mild (photodamage with no AKs)	—	12
Moderate (discrete AKs)	12	6
Severe (confluent AKs or SCCIs)	4-6	3-6
Keratinocyte carcinoma history [†]		
Low-risk CSCC	6 ²¹	3-6 ⁹³
Multiple KC	3-6	3 ⁹³
High-risk CSCC	4 ²¹	3 ⁹³
Metastatic CSCC	1-3	1-2 ⁹³

AK, Actinic keratosis; CLL, chronic lymphocytic leukemia; CSCC, cutaneous squamous cell carcinoma; KC, keratinocyte carcinoma; SCCIs, squamous cell carcinoma in situ; SOTR, solid organ transplant recipient.

*The suggested frequencies are largely based on the authors' expert opinions and not official guidelines (except those stated as National Comprehensive Cancer Network guidelines) and the clinician should always consider the individual patient when the frequency of clinic visits.

[†]For patients with local CSCC, National Comprehensive Cancer Network guidelines suggest follow-up every 3 to 6 months for 2 years, then every 6 to 12 months for 3 years, then annually for life. For regional disease, suggested follow-up is every 1 to 3 months for 1 year, every 2 to 4 months for the second year, every 4 to 6 months for the third year, and then every 6 to 12 months for life.⁵⁷

sufficient to achieve disease control, which often requires cyclical use of field-directed therapies. The evidence on efficacy of specific treatments to prevent skin cancers among SOTRs is limited.^{99,100}

A recent systematic review of nonsystemic interventions for AKs in 242 SOTRs found PDT to have the highest lesional clearance rates (46-100%), followed by 5-FU (79%), imiquimod (61-73.7%), and diclofenac (53%).⁹⁸ Overall, the efficacy of treatments in SOTRs appears to be lower than in immunocompetent patients. While PDT is a highly effective approach in SOTRs, cross-trial comparisons should be interpreted cautiously given their small sample sizes and the heterogeneity of the participants and outcomes. For instance, 6 of the 8 included studies investigated some type of PDT, while 5-FU was investigated in only 1 study involving 8 SOTRs.

Depending on FC severity, initiation of oral chemopreventive agents and revision of the immunosuppression regimen should be considered. Adjustment of immunosuppression is considered in SOTRs with high-risk CSCC, metastatic CSCC, or

those that develop >5 to 10 CSCCs per year.⁸⁴ Typical approaches include reduction of dosage or number of immunosuppressive medications and early conversion to mammalian target of rapamycin inhibitors.^{84,101-105} Recent data also suggest that conversion of calcineurin inhibitor-based immunosuppression to belatacept, a cytotoxic T-lymphocyte-associated antigen 4 fusion antibody, may reduce the risk of CSCC.^{106,107} However, because belatacept works to suppress T cell responses in a way opposite to ipilimumab, further work remains to determine belatacept's overall impact on skin cancer risk and outcomes. Alteration of immunosuppression should be done in collaboration with the patient's transplant team.

Chronic lymphocytic leukemia

Patients with chronic lymphocytic leukemia have a 5- to 8.6-fold increased incidence of CSCC compared with the general population.^{108,109} Patients with chronic lymphocytic leukemia with skin cancer have worse outcomes, as evidenced by higher rates of local recurrence, regional metastasis, and death.^{110,111} Aggressive management of FC is critical in this population.

REFERENCES

- Nehal KS, Bichakjian CK. Update on keratinocyte carcinomas. *N Engl J Med.* 2018;379:363-374.
- Rogers EM, Connolly KL, Nehal KS, Dusza SW, Rossi AM, Lee E. Comorbidity scores associated with limited life expectancy in the very elderly with nonmelanoma skin cancer. *J Am Acad Dermatol.* 2018;78:1119-1124.
- Neugebauer R, Levandoski KA, Zhu Z, et al. A real-world, community-based cohort study comparing the effectiveness of topical fluorouracil versus topical imiquimod for the treatment of actinic keratosis. *J Am Acad Dermatol.* 2018;78:710-716.
- Pomerantz H, Hogan D, Eilers D, et al. Long-term efficacy of topical fluorouracil cream, 5%, for treating actinic keratosis: a randomized clinical trial. *JAMA Dermatol.* 2015;151:952-960.
- Weinstock MA, Thwin SS, Siegel JA, et al. Chemoprevention of basal and squamous cell carcinoma with a single course of fluorouracil, 5%, cream: a randomized clinical trial. *JAMA Dermatol.* 2018;154:167-174.
- Rosenberg AR, Tabacchi M, Ngo KH, et al. Skin cancer precursor immunotherapy for squamous cell carcinoma prevention. *JCI Insight.* 2019;4:e125476.
- Askev DA, Mickan SM, Soyer HP, Wilkinson D. Effectiveness of 5-fluorouracil treatment for actinic keratosis—a systematic review of randomized controlled trials. *Int J Dermatol.* 2009;48:453-463.
- Salim A, Leman JA, McColl JH, Chapman R, Morton CA. Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease. *Br J Dermatol.* 2003;148:539-543.
- Hadley G, Derry S, Moore RA. Imiquimod for actinic keratosis: systematic review and meta-analysis. *J Invest Dermatol.* 2006;126:1251-1255.

10. Patel GK, Goodwin R, Chawla M, et al. Imiquimod 5% cream monotherapy for cutaneous squamous cell carcinoma in situ (Bowen's disease): a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol.* 2006;54:1025-1032.
11. Cunningham TJ, Tabacchi M, Eliane JP, et al. Randomized trial of calcipotriol combined with 5-fluorouracil for skin cancer precursor immunotherapy. *J Clin Invest.* 2017;127:106-116.
12. Goon PK, Clegg R, Yong AS, et al. 5-Fluorouracil "chemo-wraps" in the treatment of multiple actinic keratoses: a Norwich experience. *Dermatol Ther (Heidelb).* 2015;5:201-205.
13. Mann M, Berk DR, Petersen J. Chemowraps as an adjuvant to surgery for patients with diffuse squamous cell carcinoma of the extremities. *J Drugs Dermatol.* 2008;7:685-688.
14. Peuvrel L, Saint-Jean M, Quereux G, et al. 5-fluorouracil chemowraps for the treatment of multiple actinic keratoses. *Eur J Dermatol.* 2017;27:635-640.
15. Tallon B, Turnbull N. 5% fluorouracil chemowraps in the management of widespread lower leg solar keratoses and squamous cell carcinoma. *Australas J Dermatol.* 2013;54:313-316.
16. Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. *N Engl J Med.* 2012;366:1010-1019.
17. Stockfleth E, Bastian M. Pharmacokinetic and pharmacodynamic evaluation of ingenol mebutate for the treatment of actinic keratosis. *Expert Opin Drug Metab Toxicol.* 2018;14:911-918.
18. Piacquadio DJ, Chen DM, Farber HF, et al. 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. *Arch Dermatol.* 2004;140:41-46.
19. Reinhold U, Dirschka T, Ostendorf R, et al. A randomized, double-blind, phase III, multicentre study to evaluate the safety and efficacy of BF-200 ALA (Ameluz®) vs. placebo in the field-directed treatment of mild-to-moderate actinic keratosis with photodynamic therapy (PDT) when using the BF-RhodoLED® lamp. *Br J Dermatol.* 2016;175:696-705.
20. Rasanen JE, Neittaanmaki N, Ylitalo L, et al. 5-aminolevulinic acid nanoemulsion is more effective than methyl-5-aminolevulinate in daylight photodynamic therapy for actinic keratosis: a nonsponsored randomized double-blind multicentre trial. *Br J Dermatol.* 2019;181:265-274.
21. Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: management of advanced and high-stage tumors. *J Am Acad Dermatol.* 2018;78:249-261.
22. Jambusaria-Pahlajani A, Ortman S, Schmults CD, Liang C. Sequential curettage, 5-fluorouracil, and photodynamic therapy for field cancerization of the scalp and face in solid organ transplant recipients. *Dermatol Surg.* 2016;42(suppl 1):S66-S72.
23. Jetter N, Chandan N, Wang S, Tsoukas M. Field cancerization therapies for management of actinic keratosis: a narrative review. *Am J Clin Dermatol.* 2018;19:543-557.
24. Maytin EV, Anand S, Riha M, et al. 5-Fluorouracil enhances protoporphyrin IX accumulation and lesion clearance during photodynamic therapy of actinic keratoses: a mechanism-based clinical trial. *Clin Cancer Res.* 2018;24:3026-3035.
25. Jansen MHE, Kessels J, Nelemans PJ, et al. Randomized trial of four treatment approaches for actinic keratosis. *N Engl J Med.* 2019;380:935-946.
26. Morton C, Horn M, Leman J, et al. Comparison of topical methyl aminolevulinate photodynamic therapy with cryotherapy or fluorouracil for treatment of squamous cell carcinoma in situ: results of a multicenter randomized trial. *Arch Dermatol.* 2006;142:729-735.
27. Love WE, Bernhard JD, Bordeaux JS. Topical imiquimod or fluorouracil therapy for basal and squamous cell carcinoma: a systematic review. *Arch Dermatol.* 2009;145:1431-1438.
28. Gupta AK, Paquet M. Network meta-analysis of the outcome 'participant complete clearance' in nonimmunosuppressed participants of eight interventions for actinic keratosis: a follow-up on a Cochrane review. *Br J Dermatol.* 2013;169:250-259.
29. Wu Y, Tang N, Cai L, Li Q. Relative efficacy of 5-fluorouracil compared with other treatments among patients with actinic keratosis: a network meta-analysis. *Dermatol Ther.* 2019;32:e12822.
30. Kovach BT, Stasko T. Use of topical immunomodulators in organ transplant recipients. *Dermatol Ther.* 2005;18:19-27.
31. Swanson N, Abramovits W, Berman B, Kulp J, Rigel DS, Levy S. 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. *J Am Acad Dermatol.* 2010;62:582-590.
32. Rosen T, Harting M, Gibson M. Treatment of Bowen's disease with topical 5% imiquimod cream: retrospective study. *Dermatol Surg.* 2007;33:427-431.
33. Mackenzie-Wood A, Kossard S, de Launey J, Wilkinson B, Owens ML. Imiquimod 5% cream in the treatment of Bowen's disease. *J Am Acad Dermatol.* 2001;44:462-470.
34. Garbe C, Basset-Seguin N, Poulin Y, et al. Efficacy and safety of follow-up field treatment of actinic keratosis with ingenol mebutate 0.015% gel: a randomized, controlled 12-month study. *Br J Dermatol.* 2016;174:505-513.
35. Ulrich M, Reinhold U, Skov T, Elvang Sondergaard R, Gutera P. Histological examination confirms clinical clearance of actinic keratoses following treatment with ingenol mebutate 0.05% gel. *Br J Dermatol.* 2017;176:71-80.
36. Anderson L, Jarratt M, Schmieder G, Shumack S, Katamas J, Welburn P. Tolerability and pharmacokinetics of ingenol mebutate 0.05% gel applied to treatment areas up to 100cm on the forearm(s) of patients with actinic keratosis. *J Clin Aesthet Dermatol.* 2014;7:19-29.
37. Willey A, Mehta S, Lee PK. Reduction in the incidence of squamous cell carcinoma in solid organ transplant recipients treated with cyclic photodynamic therapy. *Dermatol Surg.* 2010;36:652-658.
38. Willey A, Anderson RR, Sakamoto FH. Temperature-modulated photodynamic therapy for the treatment of actinic keratosis on the extremities: a one-year follow-up study. *Dermatol Surg.* 2015;41:1290-1295.
39. Mamalis A, Koo E, Sckisel GD, Siegel DM, Jagdeo J. Temperature-dependent impact of thermal aminolevulinic acid photodynamic therapy on apoptosis and reactive oxygen species generation in human dermal fibroblasts. *Br J Dermatol.* 2016;175:512-519.
40. Lacour JP, Ulrich C, Gilaberte Y, et al. Daylight photodynamic therapy with methyl aminolevulinate cream is effective and nearly painless in treating actinic keratoses: a randomised, investigator-blinded, controlled, phase III study throughout Europe. *J Eur Acad Dermatol Venereol.* 2015;29:2342-2348.
41. Rubel DM, Spelman L, Murrell DF, et al. Daylight photodynamic therapy with methyl aminolevulinate cream as a convenient, similarly effective, nearly painless alternative to conventional photodynamic therapy in actinic keratosis treatment: a randomized controlled trial. *Br J Dermatol.* 2014;171:1164-1171.
42. Wiegell SR, Haedersdal M, Philipsen PA, Eriksen P, Enk CD, Wulf HC. Continuous activation of PpIX by daylight is as

- effective as and less painful than conventional photodynamic therapy for actinic keratoses; a randomized, controlled, single-blinded study. *Br J Dermatol.* 2008;158:740-746.
43. Sotiriou E, Apalla Z, Vrani F, et al. Daylight photodynamic therapy vs. Conventional photodynamic therapy as skin cancer preventive treatment in patients with face and scalp cancerization: an intra-individual comparison study. *J Eur Acad Dermatol Venereol.* 2017;31:1303-1307.
 44. Sotiriou E, Evangelou G, Papadavid E, et al. Conventional vs. daylight photodynamic therapy for patients with actinic keratosis on face and scalp: 12-month follow-up results of a randomized, intra-individual comparative analysis. *J Eur Acad Dermatol Venereol.* 2018;32:595-600.
 45. Fargnoli MC, Piccioni A, Neri L, Tambone S, Pellegrini C, Peris K. Conventional vs. daylight methyl aminolevulinate photodynamic therapy for actinic keratosis of the face and scalp: an intra-patient, prospective, comparison study in Italy. *J Eur Acad Dermatol Venereol.* 2015;29:1926-1932.
 46. Steeb T, Schlager JG, Kohl C, Ruzicka T, Hepp MV, Berking C. Laser-assisted photodynamic therapy for actinic keratosis: a systematic review and meta-analysis. *J Am Acad Dermatol.* 2019;80:947-956.
 47. National Cancer Institute website. SR-T100 gel. Available at: <https://www.cancer.gov/publications/dictionaries/cancer-drug/def/sr-t100-gel>. Accessed March 11, 2020.
 48. National Cancer Institute website. Src kinase inhibitor KX-391. Available at: <https://www.cancer.gov/publications/dictionaries/cancer-drug/def/src-kinase-inhibitor-kx-391>. Accessed March 11, 2020.
 49. National Cancer Institute website. Nanoparticle paclitaxel ointment SOR007. Available at: <https://www.cancer.gov/publications/dictionaries/cancer-drug/def/792258>. Accessed March 11, 2020.
 50. National Cancer Institute. VDAC/HK2 modulator ointment VDA-1102. Available at: <https://www.cancer.gov/publications/dictionaries/cancer-drug/def/vdac-hk2-modulator-ointment-vda-1102>. Accessed March 11, 2020.
 51. Gan L, Zhang S, Poorun D, et al. Medical applications of nonthermal atmospheric pressure plasma in dermatology. *J Dtsch Dermatol Ges.* 2018;16:7-13.
 52. Huang A, Nguyen JK, Austin E, Mamalis A, Jagdeo J. Updates on treatment approaches for cutaneous field cancerization. *Curr Dermatol Rep.* 2019;8:122-132.
 53. Krawtchenko N, Roewert-Huber J, Ulrich M, Mann I, Sterry W, Stockfleth E. 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. *Br J Dermatol.* 2007;157(suppl 2):34-40.
 54. Thai KE, Fergin P, Freeman M, et al. A prospective study of the use of cryosurgery for the treatment of actinic keratoses. *Int J Dermatol.* 2004;43:687-692.
 55. Goldenberg G, Linkner RV, Singer G, Frankel A. An investigator-initiated study to assess the safety and efficacy of imiquimod 3.75% cream when used after cryotherapy in the treatment of hypertrophic actinic keratoses on dorsal hands and forearms. *J Clin Aesthet Dermatol.* 2013;6:36-43.
 56. Hepp MV, Steeb T, Ruzicka T, Berking C. Cryosurgery combined with topical interventions for actinic keratosis: a systematic review and meta-analysis. *Br J Dermatol.* 2019;180:740-748.
 57. National Comprehensive Cancer Network, Inc website. NCCN Clinical Practice Guidelines in Oncology: squamous cell skin cancer. Available at: https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf; 2018. Accessed September 17, 2019.
 58. Work Group, Invited Reviewers, Kim JYS, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. *J Am Acad Dermatol.* 2018;78:560-578.
 59. Kraus S, Miller BH, Swinehart JM, et al. Intratumoral chemotherapy with fluorouracil/epinephrine injectable gel: a nonsurgical treatment of cutaneous squamous cell carcinoma. *J Am Acad Dermatol.* 1998;38:438-442.
 60. Mackey M, Shahsavari A, Mackey VT. Intralesional 5-fluorouracil in the treatment of lower leg squamous cell carcinoma. *J Drugs Dermatol.* 2018;17:1241-1243.
 61. Morse LG, Kendrick C, Hooper D, Ward H, Parry E. Treatment of squamous cell carcinoma with intralesional 5-fluorouracil. *Dermatol Surg.* 2003;29:1150-1153.
 62. Reisinger DM, Cognetta AB Jr, Pynes LT, Paredes AA Jr, Sweeney TJ, Dolson DJ. Treatment of a giant squamous cell carcinoma on the dominant thumb with intralesional 5-fluorouracil. *J Am Acad Dermatol.* 2011;65:219-221.
 63. Chitwood K, Etzkorn J, Cohen G. Topical and intralesional treatment of nonmelanoma skin cancer: efficacy and cost comparisons. *Dermatol Surg.* 2013;39:1306-1316.
 64. Kirby JS, Miller CJ. Intralesional chemotherapy for non-melanoma skin cancer: a practical review. *J Am Acad Dermatol.* 2010;63:689-702.
 65. Metterle L, Nelson C, Patel N. Intralesional 5-fluorouracil (FU) as a treatment for nonmelanoma skin cancer (NMSC): a review. *J Am Acad Dermatol.* 2016;74:552-557.
 66. Que SKT, Compton LA, Schmults CD. Eruptive squamous atypia (also known as eruptive keratoacanthoma): definition of the disease entity and successful management via intralesional 5-fluorouracil. *J Am Acad Dermatol.* 2019;81:111-122.
 67. Chen AC, Martin AJ, Choy B, et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. *N Engl J Med.* 2015;373:1618-1626.
 68. Drago F, Ciccarese G, Cogorno L, Calvi C, Marsano LA, Parodi A. Prevention of non-melanoma skin cancers with nicotinamide in transplant recipients: a case-control study. *Eur J Dermatol.* 2017;27:382-385.
 69. Surjana D, Halliday GM, Martin AJ, Moloney FJ, Damian DL. Oral nicotinamide reduces actinic keratoses in phase II double-blinded randomized controlled trials. *J Invest Dermatol.* 2012;132:1497-1500.
 70. Chen AC, Damian DL. Nicotinamide and the skin. *Australas J Dermatol.* 2014;55:169-175.
 71. Park J, Halliday GM, Surjana D, Damian DL. Nicotinamide prevents ultraviolet radiation-induced cellular energy loss. *Photochem Photobiol.* 2010;86:942-948.
 72. Thompson BC, Surjana D, Halliday GM, Damian DL. Nicotinamide enhances repair of ultraviolet radiation-induced DNA damage in primary melanocytes. *Exp Dermatol.* 2014;23:509-511.
 73. Knip M, Douek IF, Moore WP, et al. Safety of high-dose nicotinamide: a review. *Diabetologia.* 2000;43:1337-1345.
 74. Gale EA, Bingley PJ, Emmett CL, Collier T, European Nicotinamide Diabetes Intervention Trial Group. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes. *Lancet.* 2004;363:925-931.
 75. Guyton JR, Bays HE. Safety considerations with niacin therapy. *Am J Cardiol.* 2007;99(6A):22C-31C.
 76. Chen AC, Martin AJ, Dalzell RA, et al. A phase II randomized controlled trial of nicotinamide for skin cancer chemoprevention in renal transplant recipients. *Br J Dermatol.* 2016;175:1073-1075.

77. Bavinck JN, Tieben LM, Van der Woude FJ, et al. Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. *J Clin Oncol.* 1995; 13:1933-1938.
78. McKenna DB, Murphy GM. Skin cancer chemoprophylaxis in renal transplant recipients: 5 years of experience using low-dose acitretin. *Br J Dermatol.* 1999;140:656-660.
79. George R, Weightman W, Russ GR, Bannister KM, Mathew TH. Acitretin for chemoprevention of non-melanoma skin cancers in renal transplant recipients. *Australas J Dermatol.* 2002; 43:269-273.
80. de Sevaux RG, Smit JV, de Jong EM, van de Kerkhof PC, Hoitsma AJ. Acitretin treatment of premalignant and malignant skin disorders in renal transplant recipients: clinical effects of a randomized trial comparing two doses of acitretin. *J Am Acad Dermatol.* 2003;49:407-412.
81. Harwood CA, Leedham-Green M, Leigh IM, Proby CM. Low-dose retinoids in the prevention of cutaneous squamous cell carcinomas in organ transplant recipients: a 16-year retrospective study. *Arch Dermatol.* 2005;141:456-464.
82. Kovach BT, Sams HH, Stasko T. Systemic strategies for chemoprevention of skin cancers in transplant recipients. *Clin Transplant.* 2005;19:726-734.
83. Badri O, Schnults CD, Karia PS, Ruiz ES. Efficacy and cost analysis for acitretin for basal and squamous cell carcinoma prophylaxis in renal transplant recipients [e-pub ahead of print]. *Dermatol Surg.* doi:10.1097/DSS.0000000000002423, Accessed June 1, 2020.
84. O'Reilly Zwald F, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part II. Management of skin cancer in solid organ transplant recipients. *J Am Acad Dermatol.* 2011;65:263-279.
85. De Graaf YG, Euvrard S, Bouwes Bavinck JN. Systemic and topical retinoids in the management of skin cancer in organ transplant recipients. *Dermatol Surg.* 2004;30(4 pt 2):656-661.
86. Otley CC, Stasko T, Tope WD, Lebwohl M. Chemoprevention of nonmelanoma skin cancer with systemic retinoids: practical dosing and management of adverse effects. *Dermatol Surg.* 2006;32:562-568.
87. Chen K, Craig JC, Shumack S. Oral retinoids for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials. *Br J Dermatol.* 2005;152:518-523.
88. Breithaupt AD, Beynet D, Soriano T. Capecitabine for squamous cell carcinoma reduction in solid organ transplant recipients. *JAAD Case Rep.* 2015;1:S16-S18.
89. Jirakulaporn T, Endrizzi B, Lindgren B, Mathew J, Lee PK, Dudek AZ. Capecitabine for skin cancer prevention in solid organ transplant recipients. *Clin Transplant.* 2011;25:541-548.
90. Endrizzi B, Ahmed RL, Ray T, Dudek A, Lee P. Capecitabine to reduce nonmelanoma skin carcinoma burden in solid organ transplant recipients. *Dermatol Surg.* 2013;39:634-645.
91. Wollina U, Hansel G, Koch A, Kostler E. Oral capecitabine plus subcutaneous interferon alpha in advanced squamous cell carcinoma of the skin. *J Cancer Res Clin Oncol.* 2005;131:300-304.
92. Christensen SR. Recent advances in field cancerization and management of multiple cutaneous squamous cell carcinomas. *F1000Res.* 2018;7:F1000.
93. Stevenson ML, Carucci J, Colegio OR. Skin cancer in transplant recipients: scientific retreat of the international immunosuppression and transplant skin cancer collaborative and skin care in organ transplant patients-Europe. *Clin Transplant.* 2019;33:e13736.
94. Moloney FJ, Keane S, O'Kelly P, Conlon PJ, Murphy GM. The impact of skin disease following renal transplantation on quality of life. *Br J Dermatol.* 2005;153:574-578.
95. O'Reilly F, Traywick C, Pennie ML, Foster JK, Chen SC. Baseline quality of life and anxiety in solid organ transplant recipients: a pilot study. *Dermatol Surg.* 2006;32:1480-1485.
96. Tessari G, Girolomoni G. Nonmelanoma skin cancer in solid organ transplant recipients: update on epidemiology, risk factors, and management. *Dermatol Surg.* 2012;38:1622-1630.
97. Wallingford SC, Russell SA, Vail A, Proby CM, Lear JT, Green AC. Actinic keratoses, actinic field change and associations with squamous cell carcinoma in renal transplant recipients in Manchester, UK. *Acta Derm Venereol.* 2015; 95:830-834.
98. Hepp MV, Steeb T, Niesert AC, et al. Local interventions for actinic keratosis in organ transplant recipients: a systematic review. *Br J Dermatol.* 2019;180:43-50.
99. Chung EYM, Palmer SC, Striploli GFM. Interventions to prevent nonmelanoma skin cancers in recipients of a solid organ transplant: systematic review of randomized controlled trials. *Transplantation.* 2019;103:1206-1215.
100. Werner RN, Nast A. 'Surprisingly little evidence' on how best to treat actinic keratosis in organ transplant recipients. *Br J Dermatol.* 2019;180:11-12.
101. Otley CC, Berg D, Ulrich C, et al. Reduction of immunosuppression for transplant-associated skin cancer: expert consensus survey. *Br J Dermatol.* 2006;154:395-400.
102. Yanik EL, Siddiqui K, Engels EA. Sirolimus effects on cancer incidence after kidney transplantation: a meta-analysis. *Cancer Med.* 2015;4:1448-1459.
103. Funk-Deblets P, Ducroux E, Guillaud O, et al. Subsequent nonmelanoma skin cancers and impact of immunosuppression in liver transplant recipients. *J Am Acad Dermatol.* 2018; 79:84-91.
104. Euvrard S, Morelon E, Rostaing L, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. *N Engl J Med.* 2012;367:329-339.
105. Hoogendoijk-van den Akker JM, Harden PN, Hoitsma AJ, et al. Two-year randomized controlled prospective trial converting treatment of stable renal transplant recipients with cutaneous invasive squamous cell carcinomas to sirolimus. *J Clin Oncol.* 2013;31:1317-1323.
106. Grinyo JM, Del Carmen Rial M, Alberu J, et al. Safety and efficacy outcomes 3 years after switching to belatacept from a calcineurin inhibitor in kidney transplant recipients: results from a phase 2 randomized trial. *Am J Kidney Dis.* 2017;69: 587-594.
107. Wang M, Mittal A, Colegio OR. Belatacept reduces skin cancer risk in kidney transplant recipients. *J Am Acad Dermatol.* 2020;82:996-998.
108. Adamo J, Frisch M, Yuen J, Glimelius B, Melbye M. Evidence of an association between non-Hodgkin's lymphoma and skin cancer. *BMJ.* 1995;310:1491-1495.
109. Levi F, Randimbison L, Te VC, La Vecchia C. Non-Hodgkin's lymphomas, chronic lymphocytic leukaemias and skin cancers. *Br J Cancer.* 1996;74:1847-1850.
110. Brewer JD, Shanafelt TD, Khezri F, et al. Increased incidence and recurrence rates of nonmelanoma skin cancer in patients with non-Hodgkin lymphoma: a Rochester Epidemiology Project population-based study in Minnesota. *J Am Acad Dermatol.* 2015;72:302-309.
111. Onajin O, Brewer JD. Skin cancer in patients with chronic lymphocytic leukemia and non-Hodgkin lymphoma. *Clin Adv Hematol Oncol.* 2012;10:571-576.



Technological advances for the detection of melanoma

Advances in diagnostic techniques

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Learning objectives

After completing this learning activity, participants should be able to describe how total body photography can be used to identify early melanoma; explain how confocal imaging can reduce unnecessary biopsies; and discuss the status of artificial intelligence in melanoma diagnosis.

Disclosures

Editors

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Managing the balance between accurately identifying early stage melanomas while avoiding obtaining biopsy specimens of benign lesions (ie, overbiopsy) is the major challenge of melanoma detection. Decision making can be especially difficult in patients with extensive atypical nevi. Recognizing that the primary screening modality for melanoma is subjective examination, studies have shown a tendency toward overbiopsy. Even low-risk routine surgical procedures are associated with morbidity, mounting health care costs, and patient anxiety. Recent advancements in noninvasive diagnostic modalities have helped improve diagnostic accuracy, especially when managing melanocytic lesions of uncertain diagnosis. Breakthroughs in artificial intelligence have also shown exciting potential in changing the landscape of melanoma detection. In the first article in this continuing medical education series, we review novel diagnostic technologies, such as automated 2- and 3-dimensional total body imaging with sequential digital dermoscopic imaging, reflectance confocal microscopy, and electrical impedance spectroscopy, and we explore the logistics and implications of potentially integrating artificial intelligence into existing melanoma management paradigms. (*J Am Acad Dermatol* 2020;83:983-92.)

Key words: artificial intelligence; confocal microscopy; dermoscopy; electrical impedance spectroscopy; machine learning; melanoma; sequential digital dermoscopic imaging; total body photography.

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Distinguishing early stage melanomas from atypical nevi remains a diagnostic challenge for dermatologists. Examination with the naked eye has limited diagnostic accuracy compared with examination using additional technologies.¹ For example, dermoscopy use enables higher sensitivity, decreased benign-to-malignant ratios, and the detection of thinner melanomas compared to examination with the naked eye.²⁻⁵ For dermoscopically challenging pigmented lesions (ie, “borderline” lesions), novel noninvasive technologies can maximize accurate diagnosis while minimizing preventable morbidity and the cost of additional procedures. Herein, we discuss these technological imaging advancements in depth and provide an update on melanoma detection.

TOTAL BODY PHOTOGRAPHY

Key points

- Total body photography facilitates the identification of new or changing lesions in patients with atypical nevi and has been shown to reduce the number of biopsy specimens obtained from benign lesions
- Automated total body photography enables rapid standardized image collection
- Three-dimensional total body photography is commercially available and allows 360° visualization of all body surfaces

Background

For patients with extensive or atypical nevi, identifying malignant lesions is challenging; total body photography (TBP) has long been used to facilitate this process.⁶ TBP involves capturing high-resolution baseline clinical full-body photographs for use as adjuncts to total body skin examinations (TBSEs) at subsequent visits. This can aid in the identification of new/changing lesions and reassure both the patient and the physician that a lesion has exhibited stability over time. TBP is most useful for patients with extensive or atypical nevi, patients who have undergone many biopsy procedures, or patients with extensive photodamage.⁷

Benefits

Referencing TBPs during the TBSE can help physicians identify new or changing lesions, which may contribute to earlier detection of cutaneous malignancy.^{6,8} In a 5-year cohort study of 977 melanoma patients, 48% of 46 second primary melanomas were diagnosed by TBP.⁹ Furthermore, comparison with baseline photographs can provide evidence of lesion stability and reduce unnecessary biopsy procedure. A study of high-risk patients in 2

pigmented lesion clinics saw a 3.8-fold reduction in nevus biopsy procedures after TBP incorporation.¹⁰ A reduction in biopsy procedures is associated with decreases in both patient morbidity and costs to the health care system.¹⁰ Implementation of TBP has also been shown to decrease cancer worry, which can improve patient quality of life and adherence to screening.¹¹ TBPs can also be referenced during self-skin examinations (SSE), wherein TBP utilization has been shown to improve sensitivity and specificity for detection of new/changing lesions.¹²

Automated TBP

While periodic TBP is a useful tool, obtaining photographs is time-consuming given the multiple body positions, angles, and lighting conditions that must be reliably reproduced. Automated TBP machines (Table 1) use whole-body scanners with multiple cameras that simultaneously capture images from different angles. This facilitates rapid standardized image collection, reduces operator error, and does not require a manual photographer. Costs can range from \$50,000 to \$150,000, so dermatologists need to consider whether their patient population could benefit from these technologies (telephone communication, Canfield Scientific Inc, 2019).

Three-dimensional TBP

Canfield Scientific, Inc offers 2 automated 3-dimensional (3D) TBP devices, the VECTRA WB360 and the VECTRA WB180.¹³ In the WB360 (\$245,000), the patient holds 1 pose and 92 cameras simultaneously capture photographs from all angles. A digital 3D avatar of the patient is generated, allowing for 360° visualization of all body surfaces and manual annotation with dermoscopic images, easing incorporation of TBPs into the TBSE. The VECTRA WB180 (\$135,000) comprises 46 cameras and generates 2 independent avatars of the patient's front and back. However, 3D-TBP is not currently widely used because of the costly equipment and the large device size, which may be difficult to incorporate into existing offices, though the WB180 occupies significantly less space.

Simplified TBP

Because formal TBP can be cost prohibitive, informal, more affordable solutions can be substituted. Smartphones and tablets can be used to import photographs of individual lesions or parts of the body directly into the electronic medical record. MoleMapper (Sage Bionetworks, Seattle, WA) is an example of a free iOS application that patients can download to store photographs on their smartphone for use during SSEs and TBSEs. Simplified TBP can be

Table I. Comparisons of total body photography, sequential digital dermoscopic imaging, and reflectance confocal microscopy

Technology	Key features	Advantages	Limitations and financial information
TBP	Clinical imaging of entire skin surface Automated TBP machines are offered by companies including Canfield Scientific (Parsippany, NJ), DermSpectra (Tucson, AZ), Fotofinder (Columbia, MD), and Melanoscan (Stamford, CT)	Facilitates identification of new or clinically changing lesions Standardized photographs can be taken by office staff or through outside TBP companies	Lengthy photograph acquisition times for manual photocapture Referencing TBPs may lengthen length of office visit CPT code for TBP for patients with dysplastic nevus syndrome or personal or family history of melanoma allows for physician reimbursement in some scenarios Automated units are large and can be expensive (\$50,000-\$150,000): 3D TBP VECTRA minimum space requirements: WB360: 112 in × 135 in × 105 in; WB180: 130 in × 84 in × 102 in
SDDI	Longitudinal dermoscopic imaging of individual suspicious lesions Images are captured using standalone cameras, camera lens attachments, dermatoscopes with camera or smartphone compatibility, or specialized smartphone attachments	Allows short- or long-term monitoring of specific lesions for suspicious changes	Limited by patient compliance Cannot identify new lesions Photograph acquisition and comparison may lengthen office visits Many options for capturing and storing dermoscopic images at a variety of price points (<\$40 for basic smartphone attachments to ~\$2,000 for a dedicated dermoscopic lens for an SLR camera) SDDI is not covered by insurance and physicians are not eligible for reimbursement for utilization
TBP and SDDI	Each lesion mapped on total body photography has longitudinal dermoscopic imaging	Integration of both techniques Allows for identification of new lesions and dermoscopic surveillance of existing lesions Streamlines incorporation of TBP and SDDI into the TBSE	Lengthy photograph acquisition times for manual photocapture Large physical device size and high costs if using an automated unit Limited by patient compliance
RCM (Caliber Imaging and Diagnostics, Inc, Rochester, NY)	Real-time, in vivo imaging with visualization down to the papillary dermis and near-histologic resolution Image capture by a staff member takes ~5 min including setup and preparation Image size up to 8 mm × 8 mm	Can be used on borderline atypical cases or difficult amelanotic or facial lesions Can be used for presurgical mapping of tumor margins and postsurgical monitoring for LM/LMM (technique does not require additional training or technology) Leasing available	High equipment costs (\$98,000 plus \$5000 annual maintenance for the wide-probe RCM VivaScope 1500) Optional add-on handheld probe (VivaScope 3000) for difficult-to-image areas, such as the eyelid, for \$52,500

Continued

Technology	Key features	Advantages	Limitations and financial information
EIS (Nevisense, SciBase AB, Stockholm, Sweden)	Measures electrical impedance, with output scores differing between benign and malignant tissues	Separate CPT codes for confocal image acquisition and interpretation offer reimbursement comparable to that of a skin biopsy procedure with dermatopathologist review One disposable electrode per patient examination; each can be used for up to 10 lesions Measurement takes ~30 seconds	Extensive image-based training needed to gain mastery Nevisense tablet and electrode pen are \$7500 Single-use electrodes cost \$49 each EIS is not covered by insurance, and physicians are not reimbursed for utilization of the device EIS incorrectly classifies a high proportion of seborrheic keratoses as positive because of associated structural changes

3D, 3-Dimensional; CPT, Current Procedural Terminology; EIS, electrical impedance spectroscopy; LM/LMM, lentigo maligna/lentigo maligna melanoma; SDDI, sequential digital dermoscopic imaging; SLR, single-lens reflex; TBP, total body photography; TBSE, total body skin examination.

particularly useful in patients with many nevi concentrated in 1 area of the body (ie, the back).

Limitations

TBP can be time-consuming, and incorporation of photographs into the TBSE lengthens the examination. This emphasizes the importance of selecting patients who are most likely to benefit from TBP. Younger patients who are still developing new nevi may require reimaging over time to maintain a useful standard for comparison. More advanced devices can be costly and space-consuming, although the wide range of available imaging modalities allows providers to find a system that works best for their practice.

It is also important to prioritize patient privacy when choosing how to archive images in an era of increasing shared electronic medical record systems—some patients may feel uncomfortable with the possibility of numerous clinicians having access to TBPs.¹⁴ In this case, physicians might consider alternative methods of image storage, such as local servers, secondary cloud-based storage locations, or patient-owned external storage devices.

SEQUENTIAL DIGITAL DERMOSCOPIC IMAGING

Key points

- Sequential digital dermoscopic imaging allows for direct dermoscopic comparison of borderline lesions over time to monitor for suspicious change
- The use of sequential digital dermoscopic imaging has been demonstrated to reduce unnecessary biopsy procedures and can facilitate earlier detection of melanoma
- Many TBP units have incorporated sequential digital dermoscopic imaging

Background

Dermoscopy use by trained clinicians improves diagnostic accuracy for melanoma compared with visual inspection alone.¹⁵ Sequential digital dermoscopic imaging (SDDI) permits longitudinal dermoscopic monitoring of suspicious lesions and is especially useful for lesions lacking clearly benign or malignant dermoscopic features (Table I). Whereas the clinician may have otherwise obtained biopsy specimens from these equivocal lesions, 3-month SDDI offers a safe alternative through close monitoring for changes indicative of early-stage melanoma¹⁶ (Argenziano et al¹⁷ demonstrated 3 months to be the appropriate interval for short-term monitoring). SDDI can also be used

Table I. Cont'd

together with TBP, and many TBP imaging systems have incorporated SDDI.

Benefits of SDDI

SDDI can facilitate the earlier detection of melanoma, particularly in early disease when tumors may lack classic dermoscopic features, and where the only clue to malignancy may be change over time.¹⁸⁻²⁰ In a 3-year prospective study of 212 high-risk patients, 15 of 17 melanomas were diagnosed solely by changes detected on SDDI, without exhibiting any melanoma-specific features.²¹ Studies have shown a 3.3-fold reduction in unnecessary biopsy procedures and improved specificity for melanoma diagnosis with SDDI.^{22,23}

SDDI with TBP

Although TBP and SDDI can be used independently, diagnostic advantages are greater when combined.^{24,25} TBP allows for localization and identification of new lesions, while SDDI enhances surveillance of preexisting lesions. In 1 prospective study using both techniques, the median depth of the 75 melanomas detected was *in situ*.²⁶ Other studies have also reported detection of more *in situ* and overall thinner melanomas using these modalities.^{25,27}

Limitations

Capturing and comparing dermoscopic images requires additional time and may lengthen visits. SDDI also requires additional follow-up visits, which may increase costs, particularly to patients with no insurance or high deductibles. However, lessening of health care expenditures may still be seen with reduction of unnecessary biopsy procedures. There is also a risk of patients being lost to follow-up—this approach is best used in reliable, compliant patients who can be trusted to return for follow-up imaging.^{28,29}

REFLECTANCE CONFOCAL MICROSCOPY

Key points

- Reflectance confocal microscopy offers *in vivo* near-histologic resolution with visualization of the papillary dermis
- Reflectance confocal microscopy is particularly useful for borderline atypical cases, difficult amelanotic or facial lesions, and presurgical margin mapping
- Reimbursement codes for confocal imaging and interpretation are available

Background

Reflectance confocal microscopy (RCM) uses an 830-nm laser that is reflected back from within the skin to produce an image with cellular detail and *in vivo* near-histologic resolution at 30× (Fig 1; Table I).³⁰⁻³⁴ Imaging depth is 200 μm to 300 μm, allowing for visualization of the papillary dermis.³³⁻³⁵ Particularly useful in borderline atypical cases, RCM is a noninvasive technique that can be used in combination with dermoscopy to improve diagnostic accuracy and reduce unnecessary biopsy procedures.³⁶ It can also assist in presurgical mapping of tumor margins for lentigo maligna (LM)/lentigo maligna melanoma (LMM). Dermatologists can learn to interpret RCM images themselves or can upload images to a skilled RCM reader for interpretation.

Benefits in melanoma detection

RCM may aid in the management of difficult-to-diagnose melanomas. Used alone, a metaanalysis showed pooled sensitivity of 92.7% and specificity of 78.3% for melanoma detection.³⁷ However, RCM has greatest applicability when used for second-level evaluation in combination with dermoscopy for equivocal lesions. In this setting, RCM has been shown to improve diagnostic accuracy compared with visual inspection with dermoscopy, and to prevent removal of ≤70% of benign lesions.^{36,38-41} Prospective studies demonstrated that the use of RCM with dermoscopy reduced the number needed to excise when evaluating equivocal lesions concerning for melanoma, translating to significant cost–benefit advantages.^{39,42}

RCM can be particularly useful for difficult amelanotic lesions and for facial lesions such as LM/LMM.^{43,44} Cinotti et al⁴⁵ found that RCM was more sensitive than dermoscopy for LM/LMM (80% vs 61%), particularly in cases of hypomelanotic or recurrent LM/LMM, and had higher interinvestigator agreement and confidence levels, though RCM was less specific (81% vs 92%).⁴⁵ The differential strengths of RCM and dermoscopy alone suggest that combination of the 2 modalities could improve diagnostic accuracy of clinically and dermoscopically challenging lesions.

Presurgical tumor margin mapping

RCM can assist in presurgical mapping of tumor margins for LM/LMM, which is challenging because of subclinical extension on cosmetically sensitive areas. Pellacani et al⁴⁶ found that RCM accurately determined LM tumor borders in 91% of cases compared to 26% when using dermoscopy, and Guitera et al⁴⁷ used RCM to identify

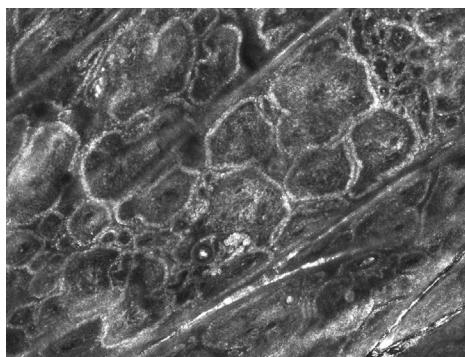


Fig 1. Reflectance confocal microscopy image of a common melanocytic nevus. This is an optical horizontal section through the dermoepidermal junction showing a regular arrangement of small basal cells and melanocytes. Image courtesy of Caliber Imaging and Diagnostics, Inc (Rochester, NY).

subclinical disease >5 mm beyond dermatoscopically detected LM margins in 59% (29/37) of patients. Yélamos et al⁴⁸ found that handheld RCM combined with radial video mosaicing predicted slightly smaller defects than staged excision and reduced the need for scouting biopsy specimens preoperatively while sparing healthy tissue perioperatively.

Financial information

Caliber Imaging and Diagnostics (Rochester, NY) offers the wide-probe RCM VivaScope 1500, which retails for \$98,000 (\$5000/year maintenance). Whereas high costs and lack of reimbursement previously limited access mostly to academic centers, separate Current Procedural Terminology codes for confocal image acquisition and interpretation now offer reimbursement for RCM comparable to that of obtaining a skin biopsy specimen with dermatopathologist review.⁴⁹ Clinicians can be reimbursed for 1 or both procedures. A financial analysis using 2019 Medicare rates estimated a break-even point (after device cost plus maintenance fees) for image acquisition and interpretation at 2 to 3 cases per day.^{50,51} These developments may encourage dermatologists to incorporate RCM into practice.

ELECTRICAL IMPEDANCE SPECTROSCOPY

Key points

- Electrical impedance spectroscopy is an objective adjunct measurement for evaluating suspicious pigmented lesions
- High sensitivity and negative predictive value may help guide whether to obtain

biopsy specimens from lesions that are clinically or dermoscopically suspicious for melanoma

- Electrical impedance spectroscopy often falsely detects seborrheic keratoses as positive, so clinicians must triage only melanocytic lesions for evaluation

Background

Electrical impedance spectroscopy (EIS), marketed as Nevisense (SciBase AB, Stockholm, Sweden), is a minimally invasive device for melanoma diagnosis that uses a handheld probe with an electrode to apply alternating electric current to tissue and measure electrical impedance (Table I).⁵² Disposable electrodes are equipped with gold-covered pins that painlessly penetrate to the stratum corneum, without impacting future histopathologic interpretation.⁵³ Differences in cell size, shape, orientation, and membrane composition result in intrinsic electrical differences between benign and malignant tissues, and the device generates a numeric score (0-10) and dichotomous output (negative/positive).^{52,54}

Benefits in melanoma detection

EIS efficacy was assessed and the scoring system determined in a prospective clinical validation study of 1943 lesions (including 265 melanomas, 85% of which were *in situ* or early invasive) using an EIS score <4 for benign lesions and 4+ for melanomas.⁵⁵ The study reported 96.6% sensitivity, 34.4% specificity, and a negative predictive value of 98.2%. Similar to RCM, EIS is not intended for use in isolation, but rather in combination with dermoscopy and visual inspection. Rocha et al⁵⁶ evaluated the addition of baseline EIS measurements to short-term SDDI in a study of 160 clinically suspicious pigmented lesions, wherein lesions scoring 7 to 10 on EIS were considered high risk for melanoma and excised, while those scoring 4 to 6 were monitored for 3 months using SDDI.⁵⁶ Following this protocol, sensitivity was 100% (5/6 melanomas scored 7+ with EIS; the remaining melanoma [*in situ*] scored 6 but exhibited change on SDDI) and specificity was 69.5%, significantly higher than for EIS alone. The study found that need for SDDI would be reduced by 47% with EIS incorporation.

Svoboda et al⁵⁷ surveyed the impact of EIS results on clinicians' diagnostic accuracy and biopsy decisions, finding that EIS results led to a change in biopsy decision in roughly 25% of cases and improved both sensitivity and specificity.

Table II. Comparisons of convolutional neural network versus dermatologist performance in pigmented lesion classification using dermoscopic images

Study	CNN architecture	Total images (train and test), n	Dermatologists, n	AUROC	
				CNN	Dermatologists
Esteva et al ⁵⁹	GoogleNet Inception v3	129,450	21	0.91	—
Haenssle et al ⁶⁰	GoogleNet Inception v4	>100,000	58	0.86	0.79
Marchetti et al ⁶¹	Fusion algorithm	2310	8	0.86	0.71
Yu et al ⁶²	VGG-16 model	724	2	0.84, 0.8	0.81, 0.82

AUROC, Area under the receiver operating characteristic curve; CNN, convolutional neural network.

Limitations

EIS incorrectly classifies many seborrheic keratoses as positive because of associated structural changes, so clinicians must triage only melanocytic lesions for evaluation.⁵⁵ In addition, although EIS has high sensitivity and negative predictive value, its sensitivity decreases with decreasing Breslow depth. This suggests potential to miss thin melanomas, which was demonstrated in the study by Malvehy et al,⁵⁵ wherein all 9 false negative results were for *in situ* (7/9) or T1a (0.4 mm and 0.6 mm, 2/9) melanomas.⁵⁵ Financial information appears in Table I.

ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING

Key points

- Convolutional neural networks are computer algorithms that can be trained to recognize melanoma and have the potential to serve as adjunct tools for clinicians to improve diagnostic accuracy
- Studies have reported comparable performances between convolutional neural networks and board-certified dermatologists in melanoma diagnosis
- Artificial intelligence could potentially transform the delivery of care and increase access to specialty services via telemedicine in the future

Machine learning principles

The field of dermatology has witnessed unprecedented breakthroughs in artificial intelligence (AI) in recent years, especially regarding melanoma diagnosis. Machine learning can potentially create powerful, easily accessible tools that improve diagnostic accuracy, revolutionizing melanoma detection and patient care.

Convolutional neural networks (CNNs) constitute a branch of machine learning involving computer algorithms that are trained and refined for a specific task, such as image classification. In melanoma

research, CNNs are trained to differentiate melanomas from benign lesions or keratinocytic carcinomas using large sets of labeled dermoscopic or clinical images. Computational filters detect features including size, edges, color, and contrast.⁵⁸ The algorithm improves itself whenever errors are encountered, allowing for progressive refinement and improving predictions for subsequent inputs. While the studies discussed in this section directly compare CNN performance to that of dermatologists, AI would be best used as an adjunct to clinical analysis by an experienced physician.

AI in melanoma diagnosis

In their landmark 2017 study, Esteva et al⁵⁹ showed that CNN performance was comparable or superior to most dermatologists in differentiating benign from malignant lesions (Table II). This CNN was trained on a dataset of 129,450 clinical images (including 3374 dermoscopic images); performance was compared to that of 21 board-certified dermatologists regarding melanoma and keratinocytic neoplasm classification using clinical images and melanoma classification using dermoscopic images.

Haenssle et al⁶⁰ subsequently compared diagnostic performance of Google's Inception v4 CNN architecture to an international group of 58 dermatologists using dermoscopic images; most dermatologists were outperformed by the CNN. Marchetti et al⁶¹ reported the results of the 2016 International Symposium on Biomedical Imaging Challenge hosted by the International Skin Imaging Collaboration, a public archive of approximately 24,000 biopsy-proven skin lesions. The top-performing fusion algorithm out of 25 teams had a greater area under the receiver operating characteristic curve than that of 8 experienced dermatologists from 4 countries, with performance better than some but not all dermatologists. Similar results were also seen in the study by Yu et al,⁶² which showed that the CNN performed similarly to

dermatologists for dermoscopic diagnosis of acral melanoma.

Limitations

Although machine learning holds tremendous promise in melanoma detection, there are noteworthy limitations. As the logic at which CNNs arrive at their final diagnosis remains a black box, in cases where dermatologists and AI disagree there is no way to identify the point of discrepancy to facilitate improvement on either end.

Furthermore, the efficacy and output of these CNNs is only as good as the datasets on which they are trained. The strength of the network depends on dataset size and breadth, and each model may have different sensitivities, specificities, and biases depending on training images. This principle is important when considering implications of AI-predicted melanoma detection for patients with skin-of-color (SOC). As Adamson et al⁶³ noted, there may already be inherent bias in machine learning algorithms given the lack of SOC lesions, which can look different in darker skin types, in training datasets. Although melanoma incidence is higher among whites, the lack of SOC lesions suggests that no matter how well-developed the CNN algorithm it may underperform on lesions in patients with SOC. This blind spot in machine learning could potentially have grave consequences and exacerbate existing health care disparities if not addressed. To this end, the International Dermoscopy Society has studies aimed at collecting standardized dermoscopic images in patients with SOC. Future studies involving CNNs should include more photographs of patients with SOC in training datasets to help circumvent this bias.

Practical applications

AI could greatly expand access to dermatologic care. Given the near-ubiquity of mobile devices, smartphone applications may be practical future platforms for delivery of this technology, with numerous applications for skin cancer screening, education, mole mapping, diagnosis, and research available.^{64,65} Few have been assessed for clinical efficacy, however, and those that have are unreliable and inaccurate with poor diagnostic sensitivity.^{64,66} Although the US Food and Drug Administration proposed recommendations for mobile application regulations in 2015, there is still an alarming lack of regulatory oversight.⁶⁴ Though there is no substitute for in-person skin examinations, reliable smartphone applications and dermoscopy attachments could be combined with AI and used as triaging tools for nondermatologists, improving delivery of

specialized dermatologic care to patients in rural areas. Melanoma incidence and mortality in rural and remote communities is exponentially higher than in urban areas, likely because of limited access to dermatologists and socioeconomic barriers.⁶⁷⁻⁶⁹ Such technological improvements may bridge access gaps and reduce melanoma mortality in remote areas. Although real-life applications still require rigorous study, AI technology is rapidly evolving, and dermatologists should remain cautiously optimistic about its use.

In conclusion, noninvasive diagnostic modalities, such as TBP, SDDI, RCM, and EIS, have helped optimize efficacy of early melanoma diagnosis while minimizing patient morbidity related to obtaining biopsy specimens of benign lesions. CNNs show promise in changing the medical landscape; harnessing this potential may revolutionize melanoma detection efforts and help address disparities in access to care. Still, readers should recognize that these are evolving technologies limited in function by the number of images available for training, and extensive research assessing real-life clinical utility is required before they can be adopted into practice.

REFERENCES

1. Kittler H, Pehamberger H, Wolff K, Binder M. Diagnostic accuracy of dermoscopy. *Lancet Oncol.* 2002;3:159-165.
2. Vestergaard ME, Macaskill P, Holt PE, Menzies SW. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. *Br J Dermatol.* 2008; 159:669-676.
3. Carli P, de Giorgi V, Chiarugi A, et al. Addition of dermoscopy to conventional naked-eye examination in melanoma screening: a randomized study. *J Am Acad Dermatol.* 2004;50:683-689.
4. Carli P, De Giorgi V, Crocetti E, et al. Improvement of malignant/benign ratio in excised melanocytic lesions in the 'dermoscopy era': a retrospective study 1997-2001. *Br J Dermatol.* 2004;150:687-692.
5. Salerni G, Teran T, Puig S, et al. Meta-analysis of digital dermoscopy follow-up of melanocytic skin lesions: a study on behalf of the International Dermoscopy Society. *J Eur Acad Dermatol Venereol.* 2013;27:805-814.
6. Sue W, Kopf AW, Rivers JK. Total-body photographs of dysplastic nevi. *Arch Dermatol.* 1988;124:1239-1243.
7. Waldman RA, Grant-Kels JM, Curiel CN, et al. Consensus recommendations for the use of non-invasive melanoma detection techniques based on results of an international DELPHI process [e-pub ahead of print]. *J Am Acad Dermatol.* 2020. <https://doi.org/10.1016/j.jaad.2019.09.046>. Accessed June 10, 2020.
8. Feit NE, Dusza SW, Marghoob AA. Melanomas detected with the aid of total cutaneous photography. *Br J Dermatol.* 2004; 150:706-714.
9. Lallas A, Apalla Z, Kyrgidis A, et al. Second primary melanomas in a cohort of 977 melanoma patients within the first 5 years of monitoring. *J Am Acad Dermatol.* 2020;82: 398-406.

10. Truong A, Strazzulla L, March J, et al. Reduction in nevus biopsies in patients monitored by total body photography. *J Am Acad Dermatol.* 2016;75:135-143.e5.
11. Moye MS, King SMC, Rice ZP, et al. Effects of total-body digital photography on cancer worry in patients with atypical mole syndrome. *JAMA Dermatol.* 2015;151:137-143.
12. Oliveria SA, Chau D, Christos PJ, Charles CA, Mushlin AI, Halpern AC. Diagnostic accuracy of patients in performing skin self-examination and the impact of photography. *Arch Dermatol.* 2004;140:57-62.
13. Rayner JE, Laino AM, Nufer KL, et al. Clinical perspective of 3D total body photography for early detection and screening of melanoma. *Front Med (Lausanne).* 2018;5:152.
14. Lakdawala N, Bercovitch L, Grant-Kels JM. A picture is worth a thousand words: ethical dilemmas presented by storing digital photographs in electronic health records. *J Am Acad Dermatol.* 2013;69:473-475.
15. Dinnis J, Deeks JJ, Chuchu N, et al. Dermoscopy, with and without visual inspection, for diagnosing melanoma in adults. *Cochrane Database Syst Rev.* 2018;12:CD011902.
16. Altamura D, Avramidis M, Menzies SW. Assessment of the optimal interval for and sensitivity of short-term sequential digital dermoscopy monitoring for the diagnosis of melanoma. *Arch Dermatol.* 2008;144:502-506.
17. Argenziano G, Mordente I, Ferrara G, Sgambato A, Annese P, Zalaudek I. Dermoscopic monitoring of melanocytic skin lesions: clinical outcome and patient compliance vary according to follow-up protocols. *Br J Dermatol.* 2008;159:331-336.
18. Skvara H, Teban L, Fiebiger M, Binder M, Kittler H. Limitations of dermoscopy in the recognition of melanoma. *Arch Dermatol.* 2005;141:155-160.
19. Kittler H, Guitera P, Riedl E, et al. Identification of clinically featureless incipient melanoma using sequential dermoscopy imaging. *Arch Dermatol.* 2006;142:1113-1119.
20. Menzies SW, Gutenev A, Avramidis M, Batrac A, McCarthy WH. Short-term digital surface microscopic monitoring of atypical or changing melanocytic lesions. *Arch Dermatol.* 2001;137:1583-1589.
21. Haenssle HA, Vente C, Bertsch HP, et al. Results of a surveillance programme for patients at high risk of malignant melanoma using digital and conventional dermoscopy. *Eur J Cancer Prev.* 2004;13:133-138.
22. Tromme I, Sacre L, Hammouch F, et al. Availability of digital dermoscopy in daily practice dramatically reduces the number of excised melanocytic lesions: results from an observational study. *Br J Dermatol.* 2012;167:778-786.
23. Menzies SW, Emery J, Staples M, et al. Impact of dermoscopy and short-term sequential digital dermoscopy imaging for the management of pigmented lesions in primary care: a sequential intervention trial. *Br J Dermatol.* 2009;161:1270-1277.
24. Berk-Krauss J, Polksy D, Stein JA. Mole mapping for management of pigmented skin lesions. *Dermatol Clin.* 2017;35:439-445.
25. Gasparini G, Madjlessi N, Delyon J, et al. Usefulness of the "two-step method" of digital follow-up in early stage melanoma detection in at high risk French patients: a retrospective 4-year study. *Br J Dermatol.* 2019;181:415-416.
26. Moloney FJ, Guitera P, Coates E, et al. Detection of primary melanoma in individuals at extreme high risk: a prospective 5-year follow-up study. *JAMA Dermatol.* 2014;150:819-827.
27. Salerni G, Carrera C, Lovatto L, et al. 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. *J Am Acad Dermatol.* 2012;67:e17-e27.
28. Gadens GA. Lack of compliance: a challenge for digital dermoscopy follow-up. *An Bras Dermatol.* 2014;89:242-244.
29. Madigan LM, Treyger G, Kohen LL. Compliance with serial dermoscopic monitoring: an academic perspective. *J Am Acad Dermatol.* 2016;75:1171-1175.
30. Haroon A, Shafi S, Rao BK. Using reflectance confocal microscopy in skin cancer diagnosis. *Dermatol Clin.* 2017;35:457-464.
31. Mandel VD, Bombonato C, Pampena R, et al. Integration of dermoscopy and reflectance confocal microscopy for distinguishing melanomas from nevi of the breast area. *J Eur Acad Dermatol Venereol.* 2018;32:940-946.
32. Gonzalez S, Swindells K, Rajadhyaksha M, Torres A. Changing paradigms in dermatology: confocal microscopy in clinical and surgical dermatology. *Clin Dermatol.* 2003;21:359-369.
33. Calzavara-Pinton P, Longo C, Venturini M, Sala R, Pellacani G. Reflectance confocal microscopy for in vivo skin imaging. *Photochem Photobiol.* 2008;84:1421-1430.
34. Shahriari N, Grant-Kels JM, Rabinovitz H, Oliviero M, Scope A. In vivo reflectance confocal microscopy image interpretation for the dermatopathologist. *J Cutan Pathol.* 2018;45:187-197.
35. Paganelli A, Longo C, Pampena R, Piana S, Borsari S. Early diagnosis of skin melanoma metastasis by means of dermoscopy and confocal microscopy. *JAMA Dermatol.* 2018;154:1482-1485.
36. Lovatto L, Carrera C, Salerni G, Alos L, Malvehy J, Puig S. In vivo reflectance confocal microscopy of equivocal melanocytic lesions detected by digital dermoscopy follow-up. *J Eur Acad Dermatol Venereol.* 2015;29:1918-1925.
37. Xiong YD, Ma S, Li X, Zhong X, Duan C, Chen Q. A meta-analysis of reflectance confocal microscopy for the diagnosis of malignant skin tumours. *J Eur Acad Dermatol Venereol.* 2016;30:1295-1302.
38. Stanganelli I, Longo C, Mazzoni L, et al. Integration of reflectance confocal microscopy in sequential dermoscopy follow-up improves melanoma detection accuracy. *Br J Dermatol.* 2015;172:365-371.
39. Pellacani G, Pepe P, Casari A, Longo C. Reflectance confocal microscopy as a second-level examination in skin oncology improves diagnostic accuracy and saves unnecessary excisions: a longitudinal prospective study. *Br J Dermatol.* 2014;171:1044-1051.
40. Pellacani G, Witkowski A, Cesinaro AM, et al. Cost-benefit of reflectance confocal microscopy in the diagnostic performance of melanoma. *J Eur Acad Dermatol Venereol.* 2016;30:413-419.
41. Yélamos O, Manubens E, Jain M, et al. Improvement of diagnostic confidence and management of equivocal skin lesions by integration of reflectance confocal microscopy in daily practice: prospective study in 2 referral skin cancer centers [e-pub ahead of print]. *J Am Acad Dermatol.* 2020. <https://doi.org/10.1016/j.jaad.2019.05.101>. Accessed June 10, 2020.
42. Alarcon I, Carrera C, Palou J, Alos L, Malvehy J, Puig S. Impact of in vivo reflectance confocal microscopy on the number needed to treat melanoma in doubtful lesions. *Br J Dermatol.* 2014;170:802-808.
43. Guitera P, Menzies SW, Argenziano G, et al. Dermoscopy and in vivo confocal microscopy are complementary techniques for diagnosis of difficult amelanotic and light-coloured skin lesions. *Br J Dermatol.* 2016;175:1311-1319.
44. Borsari S, Pampena R, Lallas A, et al. Clinical indications for use of reflectance confocal microscopy for skin cancer diagnosis. *JAMA Dermatol.* 2016;152:1093-1098.

45. Cinotti E, Labeille B, Debarbieux S, et al. Dermoscopy vs. reflectance confocal microscopy for the diagnosis of lentigo maligna. *J Eur Acad Dermatol Venereol.* 2018;32:1284-1291.
46. Guitera P, Moloney FJ, Menzies SW, et al. Improving management and patient care in lentigo maligna by mapping with in vivo confocal microscopy. *JAMA Dermatol.* 2013;149:692-698.
47. Pellacani G, De Carvalho N, Ciardo S, et al. The smart approach: feasibility of lentigo maligna superficial margin assessment with hand-held reflectance confocal microscopy technology. *J Eur Acad Dermatol Venereol.* 2018;32:1687-1694.
48. Yélamos O, Cordova M, Blank N, et al. Correlation of handheld reflectance confocal microscopy with radial video mosaicing for margin mapping of lentigo maligna and lentigo maligna melanoma. *JAMA Dermatol.* 2017;153:1278-1284.
49. Levine A, Markowitz O. Introduction to reflectance confocal microscopy and its use in clinical practice. *JAAD Case Rep.* 2018;4:1014-1023.
50. Stein JA, Grant-Kels J. Advances in imaging. Presented at the 39th Annual Advances in Dermatology, NYU Langone Health, June 6-7, 2019.
51. Siegel DM. Reflectance confocal microscopy coding. Available at: <https://caliberid.com/vivascope1500-Overview.html#>. Accessed June 10, 2020.
52. Braun RP, Mangana J, Goldinger S, French L, Dummer R, Marghoob AA. Electrical impedance spectroscopy in skin cancer diagnosis. *Dermatol Clin.* 2017;35:489-493.
53. Welzel J, Schuh S. Noninvasive diagnosis in dermatology. *J Dtsch Dermatol Ges.* 2017;15:999-1016.
54. Glickman YA, Filo O, David M, et al. Electrical impedance scanning: a new approach to skin cancer diagnosis. *Skin Res Technol.* 2003;9:262-268.
55. Malvehy J, Hauschild A, Curiel-Lewandrowski C, et al. Clinical performance of the Nevisense system in cutaneous melanoma detection: an international, multicentre, prospective and blinded clinical trial on efficacy and safety. *Br J Dermatol.* 2014;171:1099-1107.
56. Rocha L, Menzies SW, Lo S, et al. Analysis of an electrical impedance spectroscopy system in short-term digital dermoscopy imaging of melanocytic lesions. *Br J Dermatol.* 2017;177:1432-1438.
57. Svoboda RM, Prado G, Mirsky RS, Rigel DS. Assessment of clinician accuracy for diagnosing melanoma on the basis of electrical impedance spectroscopy score plus morphology versus lesion morphology alone. *J Am Acad Dermatol.* 2019;80:285-287.
58. Zakhem GA, Motosko CC, Ho RS. How should artificial intelligence screen for skin cancer and deliver diagnostic predictions to patients? *JAMA Dermatol.* 2018;154:1383-1384.
59. Esteva A, Kuprel B, Novoa RA, et al. Dermatologist-level classification of skin cancer with deep neural networks. *Nature.* 2017;542:115-118.
60. Haenssle HA, Fink C, Schneiderbauer R, et al. Man against machine: diagnostic performance of a deep learning convolutional neural network for dermoscopic melanoma recognition in comparison to 58 dermatologists. *Ann Oncol.* 2018;29:1836-1842.
61. Marchetti MA, Codella NCF, Dusza SW, et al. Results of the 2016 International Skin Imaging Collaboration International Symposium on Biomedical Imaging challenge: comparison of the accuracy of computer algorithms to dermatologists for the diagnosis of melanoma from dermoscopic images. *J Am Acad Dermatol.* 2018;78:270-277.e1.
62. Yu C, Yang S, Kim W, et al. Acral melanoma detection using a convolutional neural network for dermoscopy images. *PLoS One.* 2018;13:e0193321.
63. Adamson AS, Smith A. Machine learning and health care disparities in dermatology. *JAMA Dermatol.* 2018;154:1247-1248.
64. Chao E, Meenan CK, Ferris LK. Smartphone-based applications for skin monitoring and melanoma detection. *Dermatol Clin.* 2017;35:551-557.
65. Marek AJ, Chu EY, Ming ME, Kovarik CL. Assessment of smartphone applications for total body digital photography-guided skin exams by patients. *J Am Acad Dermatol.* 2016;75:1063-1064.e1.
66. Rat C, Hild S, Rault Serandour J, et al. Use of smartphones for early detection of melanoma: systematic review. *J Med Internet Res.* 2018;20:e135.
67. Rollin A, Ridout B, Campbell A. Digital health in melanoma posttreatment care in rural and remote Australia: systematic review. *J Med Internet Res.* 2018;20:e11547.
68. Aneja S, Aneja S, Bordeaux JS. Association of increased dermatologist density with lower melanoma mortality. *Arch Dermatol.* 2012;148:174-178.
69. Stitzenberg KB, Thomas NE, Dalton K, et al. Distance to diagnosing provider as a measure of access for patients with melanoma. *Arch Dermatol.* 2007;143:991-998.



Technological advances for the detection of melanoma

Advances in molecular techniques

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Learning objectives

After completing this learning activity, the participant should be able to describe how the analysis of gene expression from tape stripping (pigmented lesion assay) can risk stratify suspicious pigmented lesions before biopsy; discuss the advantages and limitations of molecular testing on biopsy specimens for melanoma diagnosis and risk stratification; and explain when to counsel patients about genetic testing for familial melanoma.

Disclosures

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The growth of molecular technologies analyzing skin cells and inherited genetic variations has the potential to address current gaps in both diagnostic accuracy and prognostication in patients with melanoma or in individuals who are at risk for developing melanoma. In the second article in this continuing medical education series, novel molecular technologies are reviewed. These have been developed as adjunct tools for melanoma management and include the Pigmented Lesion Assay, myPath Melanoma, and DecisionDx-Melanoma tests, and genetic testing in patients with a strong familial melanoma history. These tests are commercially available and marketed as ancillary tools for clinical decision-making, diagnosis, and prognosis. We review fundamental principles behind each test, discuss peer-reviewed literature assessing their performance, and highlight the utility and limitations of each assay. The goal of this article is to provide a comprehensive, evidence-based foundation for clinicians regarding the management of patients with difficult pigmented lesions. (*J Am Acad Dermatol* 2020;83:996-1004.)

Key words: DecisionDx-Melanoma; gene expression profiles; melanoma; molecular; myPath melanoma; pigmented lesion assay; tape stripping.

Molecular technologies have the potential to improve melanoma management by enhancing diagnostic accuracy and

prognostication. Currently, diagnostic accuracy of the clinical examination is limited, as evidenced by the high proportion of benign lesions from which

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Abbreviations used:

AJCC:	American Joint Committee on Cancer
GEP:	gene expression profile
PLA:	pigmented lesion assay
SLNB:	sentinel lymph node biopsy

biopsy specimens are obtained to rule out melanoma.¹⁻³ In addition, although histopathologic differences between melanoma and nevi are well described, borderline lesions may exhibit characteristics of both; 8% to 20% of pathologist-evaluated lesions are classified as ambiguous or indeterminate.⁴⁻⁶ Studies also demonstrate significant interobserver variability between dermatopathologists regarding severity of atypia.^{2,7,8} As a further challenge, even accurate histologic diagnoses do not always correlate with biologic behavior and prognosis. While Breslow thickness and ulceration are the foundations of tumor staging based on robust associations with patient survival, approximately 15% of melanoma deaths still result from metastases of thin melanomas that lack these features.⁹

Given the current subjective nature of melanoma diagnosis, more objective and accurate methods to guide skin cancer examinations, refine diagnostic classification of borderline lesions, and enhance prognostication could improve patient care. Herein, we review molecular technologies developed to address these issues and present advantages, limitations, and practical applications of each.

These tests are evaluated within the biomarker development paradigm: discovery, validation, and clinical utility.¹⁰ Although validation studies are essential for development and can demonstrate correlation of a biomarker with clinically relevant endpoints, they are generally retrospectively designed and do not reflect actual practice in the intended use population. They are subject to selection bias and often have missing data that may bias the results. Evaluation of biomarker clinical utility requires studies of prospectively collected data from a cohort representative of the intended use population. Ideally, these studies should be replicated in ≥ 1 additional independent patient cohort.¹¹ We will use this lens to examine the available literature on these technologies to best convey their practical applications. Applications of genetic testing for melanoma susceptibility genes will also be described.

PIGMENTED LESION ASSAY/TAPE STRIPPING

Key points

- The pigmented lesion assay is a noninvasive molecular test that determines expression of

2 genes (*PRAME* and *LINC00518*) using RNA from the stratum corneum overlying a suspicious lesion

- Melanoma risk in a lesion positive for *PRAME* is approximately 50%, for *LINC00518* is 7%, and for both *PRAME* and *LINC00518* is 93%
- High negative predictive value (>99%) suggests a role as a rule-out tool for melanoma, reducing biopsy specimens being obtained from benign lesions

Background

The pigmented lesion assay (PLA) is a molecular test developed by DermTech, Inc (La Jolla, CA) to provide a noninvasive, prebiopsy approach to melanoma detection (Table I). Also known as “tape stripping,” it uses proprietary adhesive patches (ie, tapes) to collect stratum corneum overlying a lesion of interest in the office setting.^{12,13} Lesional RNA from the tapes is analyzed to measure levels of 2 genes preferentially identified in melanomas, *LINC00518* and *PRAME*. Clinical utility studies found that the PLA differentiated melanoma from other lesions with 91% to 95% sensitivity, 69% to 91% specificity, and a negative predictive value (NPV) >99%.^{14,15} In 1 study, 93% of assays positive for both *LINC00518* and *PRAME* were diagnosed histopathologically as melanomas.¹⁵ The high NPV was recently supported by a 12-month follow-up study of 734 PLA-negative tests, wherein 98.2% were monitored without biopsy procedures. Of the 13 lesions from which biopsy specimens were obtained (6 at patient request, 7 prompted by clinical change), none received a histopathologic diagnosis of melanoma.¹⁶

Impact on management

In 2 recent studies including nearly 5000 lesions clinically suspicious for melanoma, PLA results impacted clinical decision-making. Approximately 97% of PLA-positive cases had biopsy specimens obtained, while 99.9% of PLA-negative cases were clinically monitored. In both studies, clinicians typically chose to follow-up PLA-negative cases for 6 or 12 months.^{16,17} Clinical application was also demonstrated in a web-based reader study of 45 dermatologists evaluating 60 clinical and dermoscopic images of clinically atypical pigmented lesions. Use of PLA increased sensitivity from 95% to 98% and specificity from 32.1% to 56.9%.¹⁸

Applications and limitations

The PLA can provide clinicians with additional information when deciding whether to obtain a biopsy specimen from a clinically suspicious lesion. The high NPV suggests a role as a noninvasive rule-out test for

Table I. Summary of noninvasive molecular tests

Test	Adjunct test type	Key features and advantages	Limitations	Statistical data from prospective trials*	Financial information
Pigmented Lesion Assay (DermTech Inc, La Jolla, CA)	Diagnostic	Noninvasive risk stratification of suspicious lesions before biopsy procedure; can be used for cosmetically sensitive areas; test takes <5 min to perform using company-provided kits; specimens mailed in preaddressed courier envelopes; results generally available within 1 week	Cannot be used on mucosal or acral surfaces, on lesions <5 mm, in patients <18 years of age, or if blood or hair are present	Sensitivity 91-95%, specificity 69-91%, and NPV >99%	List price: \$1300 Cost to patient: maximum of \$50 if not covered by insurance Insurance coverage: covered by Medicare (\$760 reimbursement) and many commercial insurers; DermTech, Inc submits claims on patient's behalf Cost to clinician: none
myPath Melanoma (Myriad Genetic Laboratories, Salt Lake City, UT)	Diagnostic	Adjunct diagnostic test for dermatopathologists when assessing histopathologically ambiguous melanocytic lesions; tissue block or slides mailed to company using provided kits; cost of shipping reimbursed; results available online in 5-7 days	"Indeterminate" category leads to equivocal results; clinical validation studies used specimens with histopathologic concordance; limited prospective data available	Sensitivity 50%, specificity 96%, 74% agreement between assay result and final histopathologic diagnosis (data for studies of histologically ambiguous cases only)	List price: \$1950 Cost to patient: average patient pays \$95 (fully covered by some insurances; financial assistance offered) Insurance coverage: covered by Medicare and some commercial insurers; Myriad submits claims on patient's behalf Cost to clinician: none (must be ordered by dermatopathologist)
DecisionDx-Melanoma (Castle Biosciences, Friendswood, TX)	Prognostic	Prediction of metastatic risk in lesions diagnosed as melanoma; validated for biopsy-proven, nonmucosal primary melanoma that is beyond <i>in situ</i> depth; results available via fax 5 days after specimen receipt	Test results are not integrated with current AJCC staging and management guidelines; management in cases where test results are discordant with SLNB status is unclear; results of large prospective studies demonstrating prognostic value independent of current staging criteria are lacking	Stage I [†] (n = 96) Sensitivity 0%, specificity 94.6%, PPV 0%, NPV 96.7% Stage II [†] (n = 40) Sensitivity 85.7%, specificity 53.8%, PPV 50%, NPV 87.5% Stage III [†] (n = 23) Sensitivity 91.7%, specificity 81.8%, PPV 84.6%, NPV 90%	List price: \$7900 Cost to patient: patients typically have no copay Insurance coverage: covered by Medicare; covered in part by many commercial insurers (Castle Biosciences covers any remaining cost) Cost to clinician: none

Genetic testing for <i>CDKN2A</i> mutation	Diagnostic identification of individuals at high risk for melanoma who can also be screened for pancreatic cancer; can facilitate appropriate screening in relatives of affected individuals; results available in 2-4 weeks [#]	Applicable only to individuals with strong personal or family history meeting certain criteria	>99% sensitivity for detection of gene variants [#]	List price: \$250-14,000 (self-pay prices typically \$249-399 at most laboratories) [#] Cost to patient: varies between different genetic testing services; most patients pay <\$100 out of pocket [#] Insurance coverage: variable Medicare coverage; covered by many commercial insurers Cost to clinician: none
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AJCC, American Joint Committee on Cancer; NPV, negative predictive value; PPV, positive predictive value; SLNB, sentinel lymph node biopsy.

*Data from the prospective trial on the DecisionDx-Melanoma test by Hsueh et al⁶⁴ were not included in this table because the results are from an interim study at 1.5 years, which may not be a sufficient interval to provide accurate estimations of test performance.

[#]Data reflect 3-year disease-free survival; calculated from outcomes data provided in the study by Keller et al³⁸, which is the only published prospective study to date that provides outcomes by stage.

^aVaries based on laboratory used; data in table are sourced from information provided by GeneDx, Blueprint Genetics, and Invitae melanoma panels and on personal communications with representatives from the NYU High Risk Cancer Genetics Program.

melanoma and the potential to reduce unnecessary biopsy procedures. It may be particularly useful for lesions in cosmetically sensitive areas and in patients who are at risk for poor biopsy procedure outcomes, such as impaired wound healing or exuberant scarring. Tape stripping removes only the outermost layers of the stratum corneum and does not impact future histologic examination of the underlying epidermis.¹⁹

The reduction of unnecessary biopsy procedures not only decreases patient morbidity but also reduces costs to the health care system. An economic impact analysis modeled potential savings of \$447 (47%) per PLA-assessed lesion, mainly attributed to reductions in biopsy/excision procedures and decreased treatment costs from fewer missed melanomas.¹ The selling price used to estimate these savings was \$500; however, the newly issued Centers for Medicare and Medicaid Services reimbursement is \$760, suggesting that the potential cost reduction may be less than previously calculated.²⁰

There is concern that the 91% to 95% sensitivity quoted in validation studies will result in missed melanomas.²¹ If physicians choose to follow-up negative test results in 6 to 12 months as most did in several registry studies, the risks of missed melanomas should be mitigated.

myPath MELANOMA

Key points

- **myPath Melanoma is offered as an adjunct test for dermatopathologists to aid in the assessment of histologically challenging or equivocal melanocytic lesions**
- **A 23-gene expression profile provides a numerical score assessing the likelihood of melanoma**
- **Though the technology holds promise, the collection of long-term outcomes data with rigorous analysis of ambiguous lesions is needed**

Background

Myriad Genetics Laboratories (Salt Lake City, UT) offers myPath Melanoma, a diagnostic test to help dermatopathologists resolve histopathologically ambiguous melanocytic lesions (ie, when pathologists are uncertain whether a specimen constitutes melanoma vs atypical nevus, and might consult colleagues for opinions) (Table 1). RNA from formalin-fixed paraffin-embedded tissue sections is examined for expression of 23 genes whose pattern differs between nevi and melanoma.²² Evaluation of this gene signature produces a numerical score that classifies the lesion as “likely benign,” “likely malignant,” or “indeterminate.” Since the test was developed based

on consensus diagnoses of benign and malignant melanocytic neoplasms, the molecular score essentially approximates the likely histopathologic diagnosis that might be rendered in consensus conference.

Clinical studies

The initial training set included 464 lesions with clearly benign or malignant diagnoses as determined by a panel of 2 to 3 dermatopathologists.²² Subsequent retrospective validation studies including 1355 lesions yielded sensitivities of 91.5% to 94% and specificities of 90% to 96.2% to classify melanomas as “likely malignant” and nonmelanoma lesions as “likely benign” in agreement with dermatopathologists.²²⁻²⁴ These studies notably excluded histopathologically ambiguous lesions and any “indeterminate” 23-gene expression profile (23-GEP) results in sensitivity/specificity calculations.

Studies that did include lesions deemed “histologically equivocal” (with diagnoses subsequently resolved by consensus panel) reported lower sensitivities and specificities with respect to the consensus-determined diagnosis. One retrospective study of 57 equivocal lesions by Minca et al²⁵ reported 52% sensitivity, 80% specificity, and 64% agreement between the 23-GEP result and the final diagnostic interpretation. A prospective study of 53 equivocal lesions collected over 17 months by Reimann et al²⁶ reported 74% overall agreement between 23-GEP result and consensus diagnosis, with 50% sensitivity and 96% specificity. The agreement rate for 81 unequivocal lesions was similar to the rate for the equivocal lesions. In particular, 16 unequivocal invasive and *in situ* melanomas had false negative “likely benign” results.

Impact on management

There are limited data examining how the test results impact treatment recommendations. Cockerell et al²⁷ published a retrospective study where 79 dermatopathologists examined 218 “diagnostically challenging” cases before and after receiving a myPath-melanoma score (gold standard diagnoses subsequently established by a consensus panel). Treatment recommendations were changed correctly (aligning with the consensus-based diagnosis) in 76.7% of cases. However, 9.8% of malignant samples were reassigned a “benign” diagnosis based on a false negative “likely benign” score, and 8.5% of benign samples were upgraded to a “malignant” diagnosis based on a false positive result.

In a prospectively accrued case series including 77 equivocal lesions submitted from 3 academic and community-based dermatopathology practices, recommendations before and after receiving myPath results showed an 80.5% reduction (33/41) in recommended

reexcision of these indeterminate lesions based on “likely benign” myPath Melanoma results.²⁸ However, lack of consensus-based diagnoses or of follow-up patient outcomes limits interpretation of whether these revised treatment decisions may have resulted in missed melanomas or unnecessary excisions.

Applications and limitations

myPath Melanoma is primarily a tool for the dermatopathologist rather than the dermatologist because it is an ancillary test for melanocytic lesions that cannot be confidently diagnosed by histopathology alone. The assay showed promise in using gene signatures to differentiate nevi from melanoma in retrospective validation studies.²²⁻²⁴ However, these and most other studies of assay performance predominantly used samples with clear histopathologic consensus, which differs from the histologically ambiguous lesions for which the tool is marketed.^{22-24,29} There are limited available prospective data to support the routine use of this test to resolve equivocal cases.²⁶ Though the technology holds promise, additional prospective studies of equivocal lesions with long-term outcomes data are needed.

myPath Melanoma is covered under Medicare and some commercial insurers. A 2014 economic impact analysis for US commercial payers modeled potential savings of \$1268 (8.3%) per patient tested over 10 years, mainly attributed to catching missed melanomas at earlier stages.³⁰ Of note, these data are based on 2013 Medicare fee-for-service rates, and calculated savings are based on sensitivity and specificity data from retrospective studies of histologically unequivocal lesions.

DecisionDx-MELANOMA

Key points

- DecisionDx-Melanoma is intended as a prognostic risk stratification test for patients with melanoma to identify a subset that might benefit from closer surveillance
- Using a 31-gene expression profile, lesions are classified as having low risk (class 1A/1B) or high risk (class 2A/2B) for metastasis or locoregional recurrence
- To date, the American Joint Committee on Cancer staging system does not include the results of DecisionDx-Melanoma

Background

Castle Biosciences (Friendswood, TX) offers DecisionDx-Melanoma, a prognostic test for determining the risk of melanoma recurrence or metastasis using measures independent of American Joint Committee on Cancer (AJCC)

Table II. Clinical studies/test metrics for DecisionDx-Melanoma

Melanoma stage(s) studied (n)	Sensitivity of class 2*	Specificity of class 1*	PPV of class 2*	NPV of class 1*	5-year DFS for class 1*	5-year DFS for class 2*
Retrospective studies						
Gerami et al ^{63†} I-IV (104)	88.6%	82.6%	72%	93%	97%	31% ($P < .0001$)
Zager et al ^{34†} I (264) II (93) IIIA (69) I-III (523)	35.3% 76.9% — 70%	86.6% 42.6% — 71% (for recurrence)	15.4% 49.2% — 48% (for recurrence)	95% 71.9% — 87% (for recurrence)	96% 74% 72% 88%	85% ($P = .01$) 55% ($P = .043$) 51% ($P = .015$) 52% ($P < .001$)
Greenhaw et al ^{35‡} I (219) II (37) I-III (256)	0% 83% 77%	91.7% 44% 86.8%	0% 42% 23.8%	99.5% 84.6% 99%	— — 93%	— — 69% ($P < .0001$)
Gastman et al ³⁶ T1 (281)	21%	90%	10%	96%	96.8% (class 1A)	64.6% (class 2B)
Prospective studies						
Hsueh et al ⁶⁴ I-III (322)	80% (1.5 year)	81.8% (1.5-year)	27%	98%	97% (1.5 year)	77% (1.5-year) ($P < .0001$)
Keller et al ³⁸ I (96) II (40) III (23) I-III (159)	0% 85.7% 91.7% 79% (3-year)	94.6% 53.8% 81.8% 85.4% (3-year)	0% 50% 84.6% 54.8%	96.7% 87.5% 90% 94.9%	— 87.5% — 96.6% (3-year)	— 50% — 47.4% (3-year) ($P < .0001$)

Italicized values for sensitivity, specificity, PPV, or NPV were calculated by the authors from outcomes data provided in study results.

DFS, Disease-free survival; NPV, negative predictive value; PPV, positive predictive value.

*For 5-year DFS unless otherwise stated.

†Validation subsets.

‡Calculations are for metastasis/metastasis-free survival.

staging criteria. Using reverse transcription polymerase chain reaction technology on biopsy specimens, lesions are classified as “low risk” (class 1 or 1A/1B) or “high risk” (class 2 or 2A/2B) based on a 31-gene expression profile (31-GEP) signature. This result classification should not be confused with AJCC melanoma stages IA/IB/IIA/IIB or tumor classifications T1a/T1b/T2a/T2, etc. Clinical validation studies were conducted using stage I to III melanomas, but the test is particularly marketed for traditionally low-risk tumors (eg, T1) (Medical Science Liaison at Castle Biosciences, telephone communication, December 4, 2019), which account for >70% of melanomas in the United States.³¹ With a 5-year melanoma-specific survival of 98% in stage 1 melanoma, recurrences are expected to be rare in this subset.³² DecisionDx-Melanoma is intended to help identify those highest risk tumors to help direct increased surveillance and to guide decision for sentinel lymph node biopsy (SLNB) for T1 and T2 tumors.³³

Clinical studies

Stage I melanoma. Retrospective studies currently comprise the majority of published research and show variable performance of the 31-GEP, especially in early-stage disease (Tables I and II).³⁴⁻³⁶ In a retrospective study of 219 patients with stage I melanoma by Greenhaw et al,³⁵ 1 of 201 class 1 (low risk) patients

developed metastases and 0 of 18 class 2 (high risk) samples metastasized. Zager et al³⁴ showed a modest ability of the 31-GEP to predict differences in 5-year disease-free survival (DFS) for stage I patients (96% for a class 1 result and 85% for class 2), with more apparent differences when comparing 1A and 2B subclasses (98% and 73%, respectively). Gastman et al³⁶ reported larger differences in DFS in a study of 281 T1 melanomas (96.8% 5-year DFS for class 1A and 64.6% for class 2B), but an analysis of these data by Marchetti et al³⁷ argued that the low calculated sensitivity and positive predictive value (21% and 10%, respectively) would limit clinical utility.

The only prospective examination of Decision-Dx-Melanoma that reported outcomes by stage is a 2019 study by Keller et al.³⁸ The study included 96 stage I melanomas and also suggested limited sensitivity, with all 3 stage I patients who had recurrences having received class 1 results.³⁸ Also concerning were the 5 of 96 (5%) stage I patients who received a class 2 result but remained disease-free (total study population median follow-up time, 44.9 months).

Stage II/III melanoma. There may be greater utility of the 31-GEP in stage II/III disease, with 2 retrospective studies suggesting higher sensitivity for recurrence.^{34,35} Zager et al³⁴ reported greater ability of the assay to predict 5-year DFS in stage II and III melanomas (74% and 72% for class 1, 55% and 51% for class 2). The prospective study by Keller et al³⁸

supported these findings, with 40 stage II patients demonstrating 87.5% 3-year DFS for class 1 and 50% for class 2.

Applications and limitations

DecisionDx-Melanoma is promoted as an aid to the management of early-stage melanoma, and its potential clinical utility should be evaluated from prospective studies within this intended use population. Currently these data are limited to few studies. The challenge in patients with stage I disease is the low recurrence rate, so large studies will be needed to demonstrate a benefit of 31-GEP use in these patients. For patients with stage II disease, potentially the most promising subset, results from only 40 prospectively studied patients are available, making it difficult to draw firm conclusions on clinical utility at this time.³⁸ Patients with stage III disease are already eligible for adjuvant therapy, and therefore a high-risk test result would not alter patient management.

In summary, as noted by the 2020 National Comprehensive Cancer Network clinical melanoma guidelines, “the currently available prognostic molecular techniques should not replace pathologic staging procedures, and the use of GEP testing according to specific melanoma stage (before or after SLNB) requires further prospective investigation in large, contemporary data sets of unselected patients.”³⁹

For clinicians who are currently using DecisionDx-Melanoma, the integration of results with the new AJCC staging criteria is not clearly defined, particularly if 31-GEP results are discordant with SLNB status. There are no established criteria to guide clinicians on the surveillance and management of patients with melanomas that are SLNB-negative but receive a high-risk 31-GEP score, and additional imaging studies may not be covered by insurance based on current standard of care. If class 2 patients were reliably shown to be at significantly higher risk for recurrence, a randomized clinical trial of more aggressive treatment options versus placebo in the high-risk group would facilitate assessment of clinical utility.

GENETIC TESTING FOR FAMILIAL MELANOMA

Key points

- Individuals with a strong personal or family history of melanoma may possess mutations in melanoma susceptibility genes and may be candidates for genetic testing
- CDKN2A is the most commonly mutated gene associated with familial melanoma and is associated with pancreatic cancer
- Patients with CDKN2A mutations can be screened for pancreatic cancer

Identification of high-risk patients for genetic testing

Most melanomas develop from somatic mutations, but 5% to 10% of melanomas occur in the setting of strong family history and inherited mutations.⁴⁰ Up to 30% to 40% of individuals with a strong personal or family history of melanoma (≥ 3 cases of melanoma in first- or second-degree relatives) carry a melanoma susceptibility gene.⁴⁰ Individuals with a germline mutation may require fewer somatic mutations to reach a critical oncogenic threshold. The most common mutation occurs in *CDKN2A*.⁴¹ Other high-penetrance genes include *CDK4*, *BAP1*, *POT1*, *ACD*, *TERF2IP*, and *TERT*.⁴² Combined, these mutations comprise approximately 50% of familial melanoma cases^{42,43}; causative mutations for the remainder of hereditary melanomas have not yet been identified.

Besides conferring a greater melanoma risk, some predisposition genes are also associated with cancer syndromes, which are either melanoma-predominant (ie, *BAP1* cancer syndrome) or melanoma-including (ie, Li–Fraumeni syndrome).⁴⁰ The 2019 National Comprehensive Cancer Network guidelines recommend referral to a genetic counselor for *p16/CDKN2A* mutation testing if a patient has ≥ 3 invasive melanomas, or a mix of invasive melanoma, pancreatic cancer, or astrocytoma diagnoses in an individual or family.⁴⁴ Other groups have proposed identifying patients who require genetic testing using a “rule of threes” scoring system, with points assigned depending on personal or family history of various cancers, such as melanoma, pancreatic cancer, astrocytoma, and other tumors or cancer syndromes, and accounting for geographic differences in melanoma incidence.^{43,45} Clustering of these cancer types in melanoma families suggests the possibility of common underlying oncogenetic pathways and potential future treatment targets.

CDKN2A and pancreatic cancer

CDKN2A is the gene most commonly implicated in familial melanoma, accounting for 20% to 40% of familial cases.⁴⁶ It encodes 2 tumor suppressor proteins involved in cell cycle regulation, p14^{ARF} and p16^{INK4A}, which regulate the p53 and retinoblastoma pathways. Mutations in *CDKN2A/p14* are potentially associated with risk of central nervous system tumors, such as astrocytomas, though the published literature remains limited.^{46–48}

In contrast, the association between *CDKN2A/p16* and pancreatic cancer is extensively documented.^{46,49–52} The gene confers a 10% to 30% risk of pancreatic cancer, with a relative risk from 22 to

80.8.^{52,53} Large international studies of melanoma-prone families have revealed geographic variations in associations, suggesting involvement of both genetic and environmental factors.^{46,54}

Pancreatic cancer screening in familial high-risk individuals is associated with enhanced detection rate and longer survival.⁵⁵ The optimal screening strategy for these high-risk patients is still evolving, but current recommendations involve yearly pancreatic imaging, alternating between endoscopic ultrasound and magnetic resonance cholangiopancreatography.^{56,57} Multigene panels may also be used for screening.^{43,58,59}

By identifying individuals with a strong personal or family history of melanoma and referring them appropriately for genetic testing, dermatologists may help facilitate early detection of aggressive diseases, such as pancreatic cancer, encourage appropriate screening in relatives of affected individuals, and further advance the understanding of cancer susceptibility genes.

In conclusion, molecular genetic tests have gained momentum in recent years, as evidenced by the availability of commercial tests marketed as ancillary tools for clinical decision-making, diagnosis, and prognosis. Of note, the molecular assays discussed above do not currently require approval from the US Food and Drug Administration. Instead, commercial laboratories may obtain a Clinical Laboratory Improvement Amendments certification, the requirements for which are much less stringent than US Food and Drug Administration approval.⁶⁰ Clinical Laboratory Improvement Amendments certification sets quality control standards for and ensures accuracy, reliability, and timeliness of laboratory testing, but does not take into account the clinical implications of test results for patient management.

Before incorporation into their clinical practices, physicians should maintain a healthy scientific skepticism toward manufacturers' claims. By evaluating the strengths and weaknesses of each study design with a critical eye, physicians can better process conflicting information regarding the utility of these assays.^{61,62}

REFERENCES

1. Hornberger J, Siegel DM. Economic analysis of a noninvasive molecular pathologic assay for pigmented skin lesions. *JAMA Dermatol.* 2018;154:1025-1031.
2. Elmore JG, Barnhill RL, Elder DE, et al. Pathologists' diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study. *BMJ.* 2017;357:j2813.
3. Petty AJ, Ackerson B, Garza R, et al. Meta-analysis of number needed to treat for diagnosis of melanoma by clinical setting. *J Am Acad Dermatol.* 2020;82:1158-1165.
4. Cerroni L, Barnhill R, Elder D, et al. Melanocytic tumors of uncertain malignant potential: results of a tutorial held at the XXIX Symposium of the International Society of Dermatopathology in Graz, October 2008. *Am J Surg Pathol.* 2010;34:314-326.
5. Shoo BA, Sagebiel RW, Kashani-Sabet M. Discordance in the histopathologic diagnosis of melanoma at a melanoma referral center. *J Am Acad Dermatol.* 2010;62:751-756.
6. Veenhuizen KC, De Wit PE, Mooi WJ, Scheffer E, Verbeek AL, Ruiter DJ. Quality assessment by expert opinion in melanoma pathology: experience of the pathology panel of the Dutch Melanoma Working Party. *J Pathol.* 1997;182:266-272.
7. Patrawala S, Maley A, Greskovich C, et al. Discordance of histopathologic parameters in cutaneous melanoma: clinical implications. *J Am Acad Dermatol.* 2016;74:75-80.
8. Farmer ER, Gonin R, Hanna MP. Discordance in the histopathologic diagnosis of melanoma and melanocytic nevi between expert pathologists. *Hum Pathol.* 1996;27:528-531.
9. Gimotty PA, Elder DE, Fraker DL, et al. Identification of high-risk patients among those diagnosed with thin cutaneous melanomas. *J Clin Oncol.* 2007;25:1129-1134.
10. Hunter DJ, Khouri MJ, Drazen JM. Letting the genome out of the bottle—will we get our wish? *N Engl J Med.* 2008;358:105-107.
11. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. *J Natl Cancer Inst.* 2009;101:1446-1452.
12. Wong R, Tran V, Morhenn V, et al. Use of RT-PCR and DNA microarrays to characterize RNA recovered by non-invasive tape harvesting of normal and inflamed skin. *J Investig Dermatol.* 2004;123:159-167.
13. Wong R, Tran V, Talwalker S, Benson NR. Analysis of RNA recovery and gene expression in the epidermis using non-invasive tape stripping. *J Dermatol Sci.* 2006;44:81-92.
14. Gerami P, Yao Z, Polksky D, et al. Development and validation of a noninvasive 2-gene molecular assay for cutaneous melanoma. *J Am Acad Dermatol.* 2017;76:114-120.e2.
15. Ferris LK, Gerami P, Skelsey MK, et al. Real-world performance and utility of a noninvasive gene expression assay to evaluate melanoma risk in pigmented lesions. *Melanoma Res.* 2018;28:478-482.
16. Ferris LK, Rigel DS, Siegel DM, et al. Impact on clinical practice of a non-invasive gene expression melanoma rule-out test: 12-month follow-up of negative test results and utility data from a large US registry study. *Dermatol Online J.* 2019;25:13030/qt61w6h7mn.
17. Brouha B, Ferris LK, Skelsey MK, et al. Real-world utility of a non-invasive gene expression test to rule out primary cutaneous melanoma: a large US registry study. *J Drugs Dermatol.* 2020;19:257-262.
18. Ferris LK, Jansen B, Ho J, et al. Utility of a noninvasive 2-gene molecular assay for cutaneous melanoma and effect on the decision to biopsy. *JAMA Dermatol.* 2017;153:675-680.
19. Wachsmann W, Morhenn V, Palmer T, et al. Noninvasive genomic detection of melanoma. *Br J Dermatol.* 2011;164:797-806.
20. Physician fee schedule search. US Centers for Medicare & Medicaid Services. Available at: <https://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx>. Accessed June 11, 2020.
21. Beatson M, Weinstock MA. Further consideration of the pigmented lesion assay. *JAMA Dermatol.* 2019;155:393.
22. Clarke LE, Warf MB, Flake DD 2nd, et al. Clinical validation of a gene expression signature that differentiates benign nevi from malignant melanoma. *J Cutan Pathol.* 2015;42:244-252.
23. Clarke LE, Flake DD 2nd, Busam K, et al. An independent validation of a gene expression signature to differentiate malignant melanoma from benign melanocytic nevi. *Cancer.* 2017;123:617-628.
24. Ko JS, Matharoo-Ball B, Billings SD, et al. Diagnostic distinction of malignant melanoma and benign nevi by a gene expression signature and correlation to clinical outcomes. *Cancer Epidemiol Biomarkers Prev.* 2017;26:1107-1113.
25. Minca EC, Al-Rohil RN, Wang M, et al. Comparison between melanoma gene expression score and fluorescence in situ

- hybridization for the classification of melanocytic lesions. *Mod Pathol.* 2016;29:832-843.
26. Reimann JDR, Salim S, Velazquez EF, et al. Comparison of melanoma gene expression score with histopathology, fluorescence in situ hybridization, and SNP array for the classification of melanocytic neoplasms. *Mod Pathol.* 2018;31:1733-1743.
 27. Cockerell CJ, Tschen J, Evans B, et al. The influence of a gene expression signature on the diagnosis and recommended treatment of melanocytic tumors by dermatopathologists. *Medicine (Baltimore).* 2016;95:e4887.
 28. Cockerell C, Tschen J, Billings SD, et al. The influence of a gene-expression signature on the treatment of diagnostically challenging melanocytic lesions. *Per Med.* 2017;14:123-130.
 29. Ko JS, Clarke LE, Minca EC, Brown K, Flake DD 2nd, Billings SD. Correlation of melanoma gene expression score with clinical outcomes on a series of melanocytic lesions. *Hum Pathol.* 2019;86:213-221.
 30. Cassarino DS, Lewine N, Cole D, Wade B, Gustavsen G. Budget impact analysis of a novel gene expression assay for the diagnosis of malignant melanoma. *J Med Econ.* 2014;17:782-791.
 31. Shaikh WR, Dusza SW, Weinstock MA, Oliveria SA, Geller AC, Halpern AC. Melanoma thickness and survival trends in the United States, 1989 to 2009. *J Natl Cancer Inst.* 2015;108:dvj294.
 32. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin.* 2017;67:472-492.
 33. Decision-Dx-Melanoma overview. Castle Biosciences, Inc. Available at: <https://castlebiosciences.com/products/decisiondx-melanoma/>. Accessed January 28, 2020.
 34. Zager JS, Gastman BR, Leachman S, et al. Performance of a prognostic 31-gene expression profile in an independent cohort of 523 cutaneous melanoma patients. *BMC Cancer.* 2018;18:130.
 35. Greenhaw BN, Zitelli JA, Brodland DG. Estimation of prognosis in invasive cutaneous melanoma: an independent study of the accuracy of a gene expression profile test. *Dermatol Surg.* 2018;44:1494-1500.
 36. Gastman BR, Gerami P, Kurley SJ, Cook RW, Leachman S, Vetto JT. Identification of patients at risk of metastasis using a prognostic 31-gene expression profile in subpopulations of melanoma patients with favorable outcomes by standard criteria. *J Am Acad Dermatol.* 2019;80:149-157.e4.
 37. Marchetti MA, Bartlett EK, Dusza SW, Bichakjian CK. Use of a prognostic gene expression profile test for T1 cutaneous melanoma: will it help or harm patients? *J Am Acad Dermatol.* 2019;80:e161-e162.
 38. Keller J, Schwartz TL, Lizalek JM, et al. Prospective validation of the prognostic 31-gene expression profiling test in primary cutaneous melanoma. *Cancer Med.* 2019;8:2205-2212.
 39. Coit DG, Thompson JA, Albertini MR, Barker C. NCCN Guidelines Version 1.2020 Cutaneous Melanoma. National Comprehensive Cancer Network. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed February 19, 2020.
 40. Ransohoff KJ, Jaju PD, Tang JY, Carbone M, Leachman S, Sarin KY. Familial skin cancer syndromes: increased melanoma risk. *J Am Acad Dermatol.* 2016;74:423-434.
 41. Kamb A, Gruis NA, Weaver-Feldhaus J, et al. A cell cycle regulator potentially involved in genesis of many tumor types. *Science.* 1994;264:436-440.
 42. Read J, Wadt KA, Hayward NK. Melanoma genetics. *J Med Genet.* 2016;53:1-14.
 43. Leachman SA, Lucero OM, Sampson JE, et al. Identification, genetic testing, and management of hereditary melanoma. *Cancer Metastasis Rev.* 2017;36:77-90.
 44. Coit DG, Thompson JA, Albertini MR, et al. Cutaneous melanoma, version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2019;17:367-402.
 45. Leachman SA, Carucci J, Kohlmann W, et al. Selection criteria for genetic assessment of patients with familial melanoma. *J Am Acad Dermatol.* 2009;61:677.e1-e14.
 46. Goldstein AM, Chan M, Harland M, et al. Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents. *J Med Genet.* 2007;44:99-106.
 47. Randerson-Moor JA, Harland M, Williams S, et al. A germline deletion of p14(ARF) but not CDKN2A in a melanoma-neural system tumour syndrome family. *Hum Mol Genet.* 2001;10:55-62.
 48. Petronzelli F, Sollima D, Coppola G, Martini-Neri ME, Neri G, Genuardi M. CDKN2A germline splicing mutation affecting both p16(ink4) and p14(arf) RNA processing in a melanoma/neurofibroma kindred. *Genes Chromosomes Cancer.* 2001;31:398-401.
 49. Whelan AJ, Bartsch D, Goodfellow PJ. Brief report: a familial syndrome of pancreatic cancer and melanoma with a mutation in the CDKN2 tumor-suppressor gene. *N Engl J Med.* 1995;333:975-977.
 50. Schenck M, Severson RK, Pawlish KS. The risk of subsequent primary carcinoma of the pancreas in patients with cutaneous malignant melanoma. *Cancer.* 1998;82:1672-1676.
 51. Goldstein AM. Familial melanoma, pancreatic cancer and germline CDKN2A mutations. *Hum Mutat.* 2004;23:630.
 52. Vasen H, Ibrahim I, Ponce CG, et al. Benefit of surveillance for pancreatic cancer in high-risk individuals: outcome of long-term prospective follow-up studies from three European expert centers. *J Clin Oncol.* 2016;34:2010-2019.
 53. Goldstein AM, Fraser MC, Struemming JP, et al. Increased risk of pancreatic cancer in melanoma-prone kindreds with p16INK4 mutations. *N Engl J Med.* 1995;333:970-974.
 54. Bishop DT, Demenais F, Goldstein AM, et al. Geographical variation in the penetrance of CDKN2A mutations for melanoma. *J Natl Cancer Inst.* 2002;94:894-903.
 55. Lu C, Xu CF, Wan XY, Zhu HT, Yu CH, Li YM. Screening for pancreatic cancer in familial high-risk individuals: a systematic review. *World J Gastroenterol.* 2015;21:8678-8686.
 56. Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut.* 2013;62:339-347.
 57. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol.* 2015;110:223-262.
 58. Welinsky S, Lucas AL. Familial pancreatic cancer and the future of directed screening. *Gut Liver.* 2017;11:761-770.
 59. Dudley B, Karloski E, Monzon FA, et al. Germline mutation prevalence in individuals with pancreatic cancer and a history of previous malignancy. *Cancer.* 2018;124:1691-1700.
 60. March J, Hand M, Truong A, Grossman D. Practical application of new technologies for melanoma diagnosis: part II. Molecular approaches. *J Am Acad Dermatol.* 2015;72:943-958.
 61. Sominidi-Damodaran S, Pittelkow MR, Meves A. Gene expression profiling in cutaneous melanoma: caveats for clinicians. *Mayo Clin Proc.* 2016;91:1147-1148.
 62. Subramanian J, Simon R. What should physicians look for in evaluating prognostic gene-expression signatures? *Nat Rev Clin Oncol.* 2010;7:327-334.
 63. Gerami P, Cook RW, Wilkinson J, et al. Development of a prognostic genetic signature to predict the metastatic risk associated with cutaneous melanoma. *Clin Cancer Res.* 2015;21:175-183.
 64. Hsueh EC, DeBloom JR, Lee J, et al. Interim analysis of survival in a prospective, multi-center registry cohort of cutaneous melanoma tested with a prognostic 31-gene expression profile test. *J Hematol Oncol.* 2017;10:152.



Immune checkpoint inhibitors to treat cutaneous malignancies

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Learning objectives

After completing this learning activity, participants should be able to describe the mechanism of action of checkpoint inhibitors in their antitumor effects; identify biomarkers associated with response to checkpoint inhibitors; identify the pivotal clinical trials and other data substantiating the use of checkpoint inhibitors in melanoma, cutaneous squamous cell carcinoma, and Merkel cell carcinoma; compare efficacy and safety profiles between checkpoint inhibitors and between tumor types; and recognize active areas of research in checkpoint blockade for cutaneous malignancies.

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As the incidence of cutaneous malignancies continues to rise and their treatment with immunotherapy expands, dermatologists and their patients are more likely to encounter immune checkpoint inhibitors. While the blockade of immune checkpoint target proteins (cytotoxic T-lymphocyte-associated protein-4, programmed cell death-1, and programmed cell death ligand-1) generates an antitumor response in a substantial fraction of patients, there is a critical need for reliable predictive biomarkers and approaches to address refractory disease. The first article of this Continuing Medical Education series reviews the indications, efficacy, safety profile, and evidence supporting checkpoint inhibition as therapeutics for metastatic melanoma, cutaneous squamous cell carcinoma, and Merkel cell carcinoma. Pivotal studies resulting in the approval of ipilimumab, pembrolizumab, nivolumab, cemiplimab, and avelumab by regulatory agencies for various cutaneous malignancies, as well as ongoing clinical research trials, are discussed. (*J Am Acad Dermatol* 2020;83:1239-53.)

Key words: basal cell carcinoma; checkpoint inhibitor; CTLA-4 inhibitor; cutaneous lymphomas; cutaneous malignancies; cutaneous squamous cell carcinoma; immunotherapy; Kaposi sarcoma; melanoma; Merkel cell carcinoma; PD-1 inhibitor; PD-L1 inhibitor; skin cancer.

Immunotherapy has become a cornerstone of advanced tumor management. Via inhibition of the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death-1 (PD-1), and programmed cell death ligand-1 (PD-L1), tumor cells are targeted and destroyed by activated T cells that infiltrate the tumor microenvironment. The first of the immune checkpoint inhibitors (CPIs) approved for cutaneous malignancies was ipilimumab (Yervoy; Bristol-Myers Squibb, New York, NY); an additional 4 CPIs were later approved by regulatory agencies (nivolumab [Opdivo; Bristol-Myers Squibb], pembrolizumab [Keytruda; Merck and Co, Kenilworth, NJ], cemiplimab [Libtayo; Regeneron Pharmaceuticals, Tarrytown, NY], and avelumab [Bavencio; EMD Serono, Rockland, MA]). In addition to melanoma, CPIs are indicated for cutaneous squamous cell carcinoma (cSCC) and Merkel cell carcinoma (MCC). There are currently no CPIs approved for basal cell carcinoma (BCC), cutaneous lymphomas, cutaneous sarcomas, or cutaneous adnexal carcinomas (CACs).

Mechanism of action of immune checkpoint inhibitors

Ipilimumab works by blocking the negative regulator CTLA-4, resulting in increased cytotoxic T cell activation and decreased regulatory T cell immunosuppressive activity.¹ Pembrolizumab and nivolumab selectively block PD-1 receptors and suppress their expression by activated T cells, B cells, monocytes, and natural killer cells.² Atezolizumab, avelumab, and durvalumab inhibit binding of PD-L1 to PD-1 receptors on T cells, thereby resulting in downregulation of T cell quiescence and reinvigoration of the antitumor immune response³ (Fig 1).

Predictive biomarkers of response to immunotherapy

Markers of tumor response to immunotherapy have been investigated,⁴ and while some have been associated with increased overall survival (OS) in patients with melanoma, none have been validated. In accordance with the National Comprehensive Cancer Network (NCCN) Guidelines, PD-L1 has potential utility in identifying patients with melanoma who are more likely to respond to CPIs^{5,6}; however, the routine use of PD-L1 expression is not recommended for treatment decisions.^{5,7} Several additional immunotherapy biomarkers are under development for melanoma, including relative eosinophils, relative basophils, absolute monocytes, lactate dehydrogenase, and neutrophil-to-lymphocyte ratio.⁸⁻¹⁰ The occurrence of immune-related adverse events (irAEs) has also been implicated as potentially useful in tumor response to CPIs.¹¹ In addition, a decrease in regulatory T cells and an increase in activated CD8⁺ T cells have been cited.¹²⁻¹⁴ In advanced cSCC, although PD-L1 appears to be increased in high-risk cSCC specimens compared with normal skin specimens, its levels do not appear to correlate with the antitumor activity of PD-1 blockade.¹⁵⁻¹⁷ However, a higher tumor mutational burden is more commonly observed in immunocompromised cSCC patients.¹⁸⁻²⁰ No predictors of response of MCC to CPIs are available yet.

MELANOMA

Key points

- **Ipilimumab, pembrolizumab, and nivolumab are approved for advanced melanoma**
- **In melanoma, combination therapy with nivolumab and ipilimumab results in higher OS compared with ipilimumab alone**
- **Nivolumab and pembrolizumab have each shown superior OS, with a better safety profile than ipilimumab**

Abbreviations used:

AE:	adverse event
BCC:	basal cell carcinoma
CAC:	cutaneous adnexal carcinoma
CPI:	checkpoint inhibitor
cSCC:	cutaneous squamous cell carcinoma
CTLA-4:	cytotoxic T-lymphocyte-associated protein-4
FDA:	US Food and Drug Administration
irAE:	immune-related adverse event
MCC:	Merkel cell carcinoma
ORR:	objective response rate
PD-1:	programmed cell death-1
PD-L1:	programmed cell death ligand-1
PFS:	progression-free survival

Melanoma of the skin, despite its lower prevalence compared with other cutaneous malignancies, is one of the most aggressive forms of cancer. Noninvasive melanoma (melanoma in situ) has a good surgical prognosis; however, advanced melanoma lacks curative treatment options. Three CPIs are currently available to treat advanced melanoma: ipilimumab, nivolumab, and pembrolizumab.

Ipilimumab: Anti-CTLA-4 therapy for advanced melanoma

Based on the improved OS results of the MDX010-20 phase III trial (Table I), ipilimumab (anti-CTLA-4) was approved in 2011, becoming the first CPI to be indicated for the treatment of nonresectable or metastatic melanoma (Fig 2).²¹ Ipilimumab was found to elicit a dose-dependent effect on efficacy

and safety measures, lending support to further studies at a dose of 10 mg/kg.²² However, while the 10-mg/kg dosing regimen of ipilimumab does result in significantly longer OS than does ipilimumab 3 mg/kg, it also leads to an increased frequency of treatment-related adverse events.²³ In 2015, as significantly improved recurrence-free survival (RFS) for patients with completely resected high-risk stage III melanoma was observed in the European Organisation for Research and Treatment of Cancer (EORTC) 18071 phase III trial, ipilimumab was approved for this indication (Fig 2). Significantly higher rates of RFS, OS, and distant metastasis-free survival compared with placebo were observed,²⁴⁻²⁶ and the frequency of irAEs (Table I) was consistent with that observed in advanced melanoma.^{21,26} However, the adverse event (AE) profile was worse in the EORTC trial than in the MDX010-20 trial, in particular for endocrinopathies.

Pembrolizumab: Anti-PD-1 therapy for advanced melanoma

In September 2014, pembrolizumab was the first PD-1 inhibitor approved for patients with unresectable or ipilimumab-refractory advanced melanoma after treatment with a BRAF inhibitor if positive for the BRAF V600 mutation (Fig 2).²⁷ The phase I trial demonstrated that pembrolizumab was safe and efficacious at both doses of 2 mg/kg and 10 mg/kg every 3 weeks (Table II).²⁸ In December 2015, based on the results of the phase 3 KEYNOTE-006 trial, which showed a substantial prolonged OS,

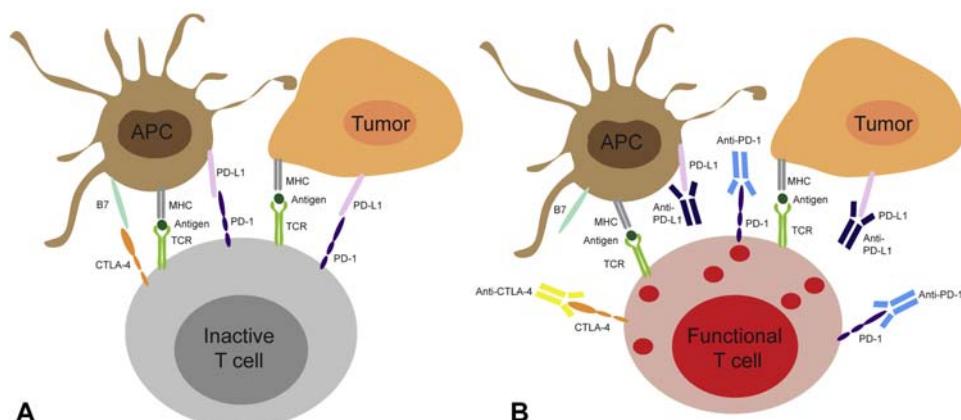


Fig 1. Immune checkpoint inhibitors reinvigorate antitumor immune responses. **A**, Cytotoxic T cells in the tumor microenvironments express high level of inhibitory receptors such as cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death-1 (PD-1). In the absence of immune checkpoint inhibitors, ligation of CTLA-4 and PD-1 by B7 protein or programmed cell death-1 (PD-L1) expressed by antigen-presenting cells (APCs) or tumor cells dampens the cytotoxic functions of T cells and inhibits their antitumor activity. **B**, Anti-CTLA-4, anti-PD-1, and anti-PD-L1 can bind CTLA-4, PD-1, and PD-L1 and prevent the PD-1/PD-L1 and CTLA-4/B7 interactions, which restore the antitumor functions of cytotoxic T cells. *MHC*, Major histocompatibility complex; *TCR*, T-cell receptor.

Table I. Major studies investigating ipilimumab (anti–cytotoxic T-lymphocyte-associated protein-4 immunotherapy) to treat melanoma

Enrollment period	Trial phase/identifier(s)	Patients	Randomization/dosing regimen(s)	Primary endpoint(s)/results	Median follow-up duration	Common severe (grade 3–5) irAEs
2004–2008	Phase III, MDX-010, NCT00094653	Previously treated, unresectable stage III or IV melanoma, n = 676	Ipilimumab 3 mg/kg + gp100 every 3 weeks, for 4 treatments, n = 403 Ipilimumab 3 mg/kg alone every 3 weeks for 4 treatments, n = 137 gp100 alone every 3 weeks for 4 treatments, n = 136	OS: ipilimumab alone, 10.1 months; ipilimumab + gp100, 10 months; gp100 alone, 6.4 months	Ipilimumab alone, 27.8 months; ipilimumab + gp100, 21 months; gp 100 alone, 17.2 months	Ipilimumab (with or without gp100), 10–15%; gp100 alone, 3%
2008–2011	Phase III, EORTC 18071, NCT00636168	Previously untreated resected stage III cutaneous melanoma, n = 951	Ipilimumab, 10 mg/kg every 3 weeks for 4 doses; then every 3 months for up to 3 years, n = 475 Placebo every 3 weeks for 4 doses; then every 3 months for up to 3 years, n = 476	RFS: ipilimumab, 26.1 months; placebo, 17.1 months; 3-year RFS: ipilimumab 46.5% and placebo 34.8%	2.74 years	Ipilimumab vs. placebo: gastrointestinal 16% vs. <1%; hepatic: 11% vs. <1%; endocrine: 8% vs. 0%

EORTC, European Organisation for Research and Treatment of Cancer; gp100, glycoprotein 100 peptide vaccine; OS, overall survival; RFS, recurrence-free survival.

progression-free survival (PFS), and less high-grade toxicity than did ipilimumab (Table II),²⁹ the US Food and Drug Administration (FDA) expanded the approval to include frontline treatment of patients with advanced melanoma with pembrolizumab regardless of *BRAF* status (Fig 2). In February 2019, after impactful results from the EORTC1325/KEYNOTE-054 phase III trial showing improved RFS of pembrolizumab over placebo (Table II),³⁰ pembrolizumab was approved for the adjuvant treatment of patients with high-risk stage III melanoma with resected lymph nodes (Fig 2).

Nivolumab: Anti–PD-1 therapy for advanced melanoma

Following the results of the CheckMate-037 phase III trial³¹ (Table III), in which nivolumab led to a greater proportion of confirmed objective responses and fewer toxic effects compared with chemotherapy in patients with ipilimumab- and *BRAF* inhibitor–refractory melanoma, the FDA granted accelerated approval in December 2014³² (Fig 2). The following year, after a favorable risk/benefit profile associated with significant improvements in OS and PFS (as compared with dacarbazine) was demonstrated by the phase III trial³³ (Table III), nivolumab received additional FDA approval as a first-line single agent treatment of patients with *BRAF* V600 wild-type, unresectable, or metastatic melanoma³⁴ (Fig 2).

In December 2017, as further improvements in RFS and a lower rate of grade 3 or 4 AEs were seen in the CheckMate-238 phase III trial of 906 patients with resectable high-risk and advanced melanoma³⁵ (Table III), nivolumab was approved as adjuvant therapy (Fig 2). Since then, long-term favorable efficacy and tolerability perseveres in patients with advanced or recurrent melanoma who were treated with nivolumab, irrespective of melanoma type,³⁶ with or without *BRAF* mutations.^{37,38}

Nivolumab plus ipilimumab: combination therapy for advanced melanoma

In 2015, the results of the CheckMate-069 phase II trial³⁹ led to accelerated FDA approval of the first ever immunotherapy combination of nivolumab plus ipilimumab for patients with *BRAF* V600 wild-type, unresectable, or metastatic melanoma (Fig 2). Among 109 patients, the combination had a response rate of 60% compared with 11% for ipilimumab alone, and an acceptable safety profile (Table IV).³⁹ Afterward, based on longer PFS rates observed with combination immunotherapy as opposed to ipilimumab alone on the CheckMate-067 phase III trial, ipilimumab plus

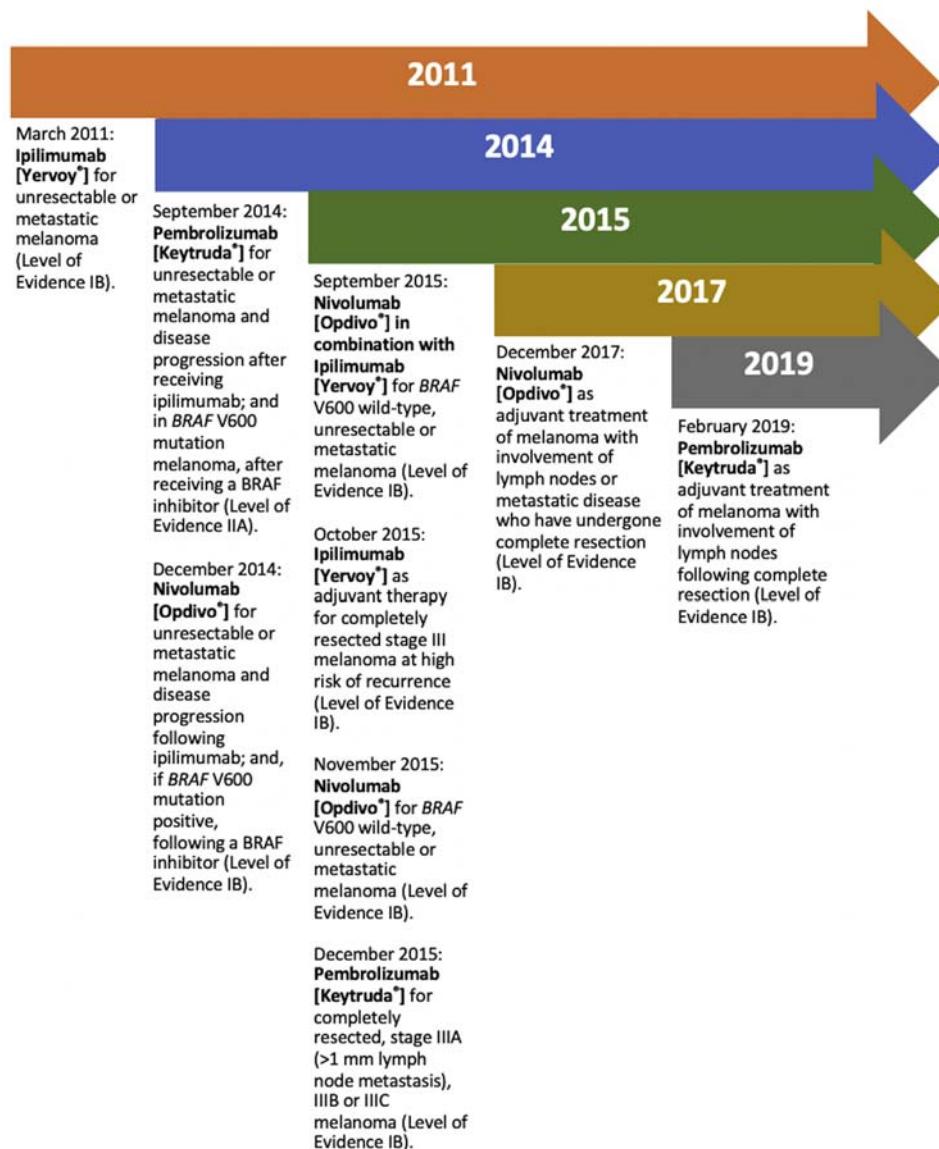


Fig 2. Timeline of approved immune checkpoint inhibitors to treat melanoma. Level IA evidence includes evidence from metaanalysis of randomized controlled trials. Level IB evidence includes evidence from ≥ 1 randomized controlled trial. Level IIA evidence includes evidence from ≥ 1 controlled study without randomization. Level IIB evidence includes evidence from ≥ 1 other type of experimental study. Level III evidence includes evidence from nonexperimental descriptive studies (ie, comparative, correlation, or case-control). Level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

nivolumab was granted accelerated approval in January 2016 for patients with BRAF V600 mutation-positive unresectable or metastatic melanoma (Fig 2).⁴⁰

Among patients with advanced melanoma, therapy with nivolumab plus ipilimumab or nivolumab alone results in longer PFS and OS than with ipilimumab alone^{6,41} (Fig 3); according to the most recently published data, a sustained long-term OS

rate has been observed at 5 years in the nivolumab plus ipilimumab (52%) versus nivolumab (44%) versus ipilimumab group (26%).⁶ However, the nivolumab plus ipilimumab combination results in a high degree of side effects; choosing which patients should receive combination immunotherapy and which patients should receive nivolumab or pembrolizumab alone is a major clinical challenge.

Table II. Major studies investigating pembrolizumab (anti-programmed cell death-1 immunotherapy) to treat melanoma

Enrollment period	Trial phase/identifier	Patients	Randomization/dosing regimen(s)	Primary end-point(s)/results	Median follow-up duration	Common severe (grade 3-5) irAEs
2012-2013	Phase I, KEYNOTE-001, NCT01295827	Previously treated, ipilimumab-refractory advanced melanoma, n = 173	Pembrolizumab 2 mg/kg every 3 weeks, n = 89; pembrolizumab 10 mg/kg every 3 weeks, n = 84	ORR: pembrolizumab 2 mg/kg 26%; pembrolizumab 10 mg/kg 26%	8 months	Pembrolizumab 2 mg/kg 3%; pembrolizumab 10 mg/kg 0%
2013-2014	Phase III, KEYNOTE-006, NCT01866319	Previously treated and untreated (65.8%) advanced melanoma, n = 834	Pembrolizumab 10 mg/kg every 2 weeks, n = 279; pembrolizumab 10 mg/kg every 3 weeks, n = 277; ipilimumab 3 mg/kg (4 doses) every 3 weeks, n = 278	6 month-PFS, 12-month OS, RR: Pembrolizumab 10 mg/kg every 2 weeks: 47.3%, 74.1%, and 33.7%; Pembrolizumab ipilimumab 10 mg/kg every 3 weeks: 46.4%, 68.4%, and 32.9%; Ipilimumab 3 mg/kg (4 doses) every 3 weeks: 26.5%, 58.2%, and 11.9%	7.9 months	Pembrolizumab 10 mg/kg every 2 weeks 13.3%; pembrolizumab 10 mg/kg every 3 weeks 10.1%; ipilimumab 3 mg/kg (4 doses) every 3 weeks 19.9%
2015-2016	Phase III, EORTC132, KEYNOTE-054, NCT02362594	Previously treated, completely resected stage III melanoma patients, n = 1019; PD-L1 ⁺ subgroup, n = 853	Pembrolizumab 200 mg every 3 weeks for a total of 18 doses Placebo (~1 year), n = 514; placebo every 3 weeks for a total of 18 doses (~1 year), n = 505	RFS in overall intention to treat group: Pembrolizumab 75.4% Placebo 61.0% 1-year rate of RFS in PD-L1 ⁺ subgroup: Pembrolizumab 77.1% Placebo 62.6%	15 months	Pembrolizumab 14.7%; placebo 3.4%

EORTC, European Organisation for Research and Treatment of Cancer; irAE, immune-related adverse event; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; RR, response rate.

CUTANEOUS SQUAMOUS CELL CARCINOMA

Key points

- Cemiplimab is the only approved CPI for cSCC
- Pembrolizumab demonstrated antitumor activity against cSCC in a phase II trial
- Most patients with cSCC do not respond to immunotherapy

cSCC is the second most common cutaneous malignancy.⁴² Despite excellent prognosis, 4% of

cSCCs are unresectable and 1.5% of patients die from the disease.⁴³ Until recently, there was no accepted standard of care for advanced cSCC. The use of CPIs in cSCC has attracted considerable interest because cSCC has high mutational burden and is more commonly observed in immunosuppressed patients.¹⁸⁻²⁰

In 2018, based on the results of the EMPOWER-CSCC-1 and NCT02383212 trials (Table V), cemiplimab, an anti-PD-1 agent, became the first approved CPI for cSCC (Fig 4). The most recent update of the EMPOWER-CSCC-1 phase 2 trial⁴⁴ reports a long-

Table III. Major studies investigating nivolumab (anti-programmed cell death-1 immunotherapy) to treat melanoma

Enrollment period	Trial phase/ identifier	Patients	Randomization/dosing regimen(s)	Primary endpoint(s)/results	Median follow-up	Common severe (grade 3-5) irAEs
2012-2014	Phase III, CheckMate 037, NCT01721746	Previously treated, unresectable or metastatic ipilimumab-refractory melanoma; or (if <i>BRAF</i> V600 mutation-positive) ipilimumab plus <i>BRAF</i> inhibitor-refractory melanoma, n = 631	Nivolumab 3 mg/kg every 2 weeks, n = 272; ORR: nivolumab chemotherapy (dacarbazine 1000 mg/m ² every 3 weeks or paclitaxel 175 mg/m ² combined with carboplatin area under the curve 6 every 3 weeks), n = 133	ORR: nivolumab (n = 120) 37.1%; chemotherapy (n = 47) 10.6%	8.4 months	Nivolumab 5%; chemotherapy 9%
2013-2014	Phase III, Checkmate 066, NCT01721772	Previously untreated melanoma without <i>BRAF</i> mutation, n = 418	Nivolumab 3 mg/kg every 2 weeks and dacarbazine-matched placebo every 3 weeks, n = 210; dacarbazine 1000 mg/m ² BSA every 3 weeks and nivolumab-matched placebo every 2 weeks, n = 208	1-year OS: nivolumab 72.9%; dacarbazine 42.1%	Nivolumab 8.9 months; dacarbazine 6.8 months	Nivolumab 11.7%; dacarbazine 17.6%
2015	Phase III, Checkmate 238, NCT02388906	Completely resected, advanced (stage IIb, IIIc, or IV) melanoma patients, n = 906	Nivolumab 3 mg/kg every 2 weeks, n = 453; ipilimumab, 10 mg/kg every 3 weeks for 4 doses; then every 12 weeks, n = 453	RFS in overall intention to treat group: nivolumab 70.5%; ipilimumab 60.8%	18 months	Nivolumab 14.4%; ipilimumab 45.9%

BSA, Body surface area; IC, investigator's choice of chemotherapy; irAE, immune-related adverse event; ORR, objective response rate; OS, overall survival; RFS, recurrence-free survival.

Table IV. Major studies investigating combination of nivolumab plus ipilimumab (anti-programmed cell death-1 plus anti-cytotoxic T-lymphocyte-associated protein-4 immunotherapy) to treat melanoma

Enrollment period	Trial phase/ identifier	Patients	Randomization/dosing regimen(s)	Primary endpoint(s)/results	Median follow-up	Grade 3-4 irAEs
2013-2014	Phase II, CheckMate-069, NCT01927419	Untreated metastatic melanoma, n = 142	Ipilimumab 3 mg/kg plus nivolumab 1 mg/kg (combination group) once every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg every 3 weeks for 4 doses or placebo every 2 weeks, n = 95; ipilimumab 3 mg/kg plus placebo, followed by nivolumab 3 mg/kg every 3 weeks for 4 doses or placebo every 2 weeks, n = 47	ORR among patients with <i>BRAF</i> V600 wild-type tumors: ipilimumab plus nivolumab (n = 72), 61%; ipilimumab plus placebo (n = 37), 11%	11 months	Combination group 54%; ipilimumab monotherapy 24%
2013-2014	Phase III, CheckMate-067, NCT01844505	Untreated, unresectable stage III or IV melanoma patients, n = 945	Nivolumab alone, n = 316; nivolumab plus ipilimumab, n = 314; ipilimumab alone, n = 315	PFS: nivolumab plus ipilimumab 11.5 months; nivolumab alone, 6.9 months; ipilimumab alone, 2.9 months	12.2-12.5 months	Nivolumab alone 16.3%; nivolumab plus ipilimumab 55%; ipilimumab alone 27.3%

irAE, Immune-related adverse event; ORR, objective response rate; PFS, progression-free survival.

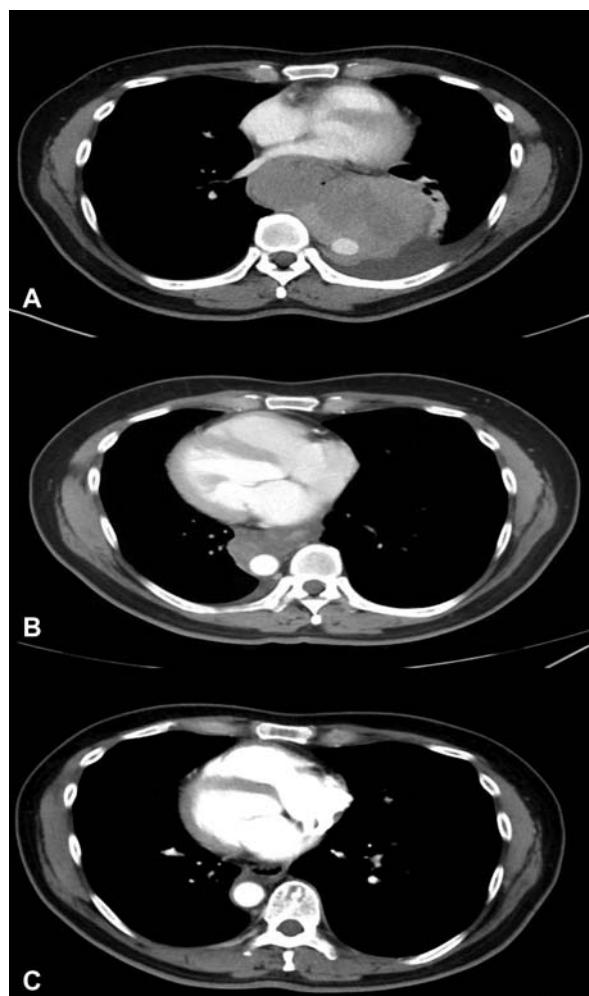


Fig 3. Durable antitumor response after treatment with ipilimumab and nivolumab in a patient with *BRAF* wild-type melanoma, metastatic to the lungs. Computerized tomography scan of metastatic disease in **(A)** February 2016, **(B)** May 2016, and **(C)** January 2018. Adverse events affecting multiple organs were observed and successfully managed with corticosteroids.

lasting antitumor effect and favorable safety profiles in patients with metastatic cSCC.⁴⁵ The NCT02383212 phase 1 trial has also demonstrated a positive risk/benefit ratio with durable antitumor response in advanced cSCC (Table V).⁴⁶

Pembrolizumab is being evaluated as first-line therapy in patients with unresectable cSCC in the NCT02883556 trial.¹⁷ Initial results showed a promising objective response rate (ORR) of 38.5% at 15 weeks with a median PFS of 8.4 months. AEs occurred in 67% of patients and caused discontinuation in 10% of patients. Eight percent of patients had severe AEs, including cholestasis and colitis. Retrospective studies and case reports of pembrolizumab for cSCC have shown varying responses.^{15,47-52}

The use of CPIs in immunosuppressed patients is not well studied.⁵³ Favorable responses to CPIs have been reported in transplant recipients either with or without graft rejection.^{47,48} Optimal immunosuppressive regimens that promote graft preservation without dampening CPI antitumor activity would greatly benefit this group of patients.

Nivolumab for cSCC has only been studied in case reports, showing benefit in recurrent cSCC. AEs include weight loss, nausea, fatigue, hyponatremia, hip pain, and hyperglycemia, with 1 death caused by arrhythmia.^{50,51,54,55} Data on ipilimumab for cSCC are limited, with 1 case report showing some efficacy when used in conjunction with radiotherapy in a patient with metastatic cSCC and metastatic melanoma.⁵⁶ Chemotherapy and radiotherapy used concurrently with CPIs have shown efficacy in refractory cSCC^{55,57} and could be used to further improve the antitumor activities of immunotherapy.

MERKEL CELL CARCINOMA

Key points

- Avelumab and pembrolizumab are approved for MCC
- Nivolumab showed efficacy against MCC with favorable safety profile in an ongoing trial
- The NCCN recommends avelumab, pembrolizumab, and nivolumab as first-line therapies for advanced MCC before chemotherapy

MCC is a rare and aggressive neuroendocrine skin cancer associated with Merkel cell polyomavirus, ultraviolet radiation exposure, immunosuppression, and advanced age.⁵⁸ Excision followed by radiotherapy is considered the first-line treatment for primary MCC. Before immunotherapy, chemotherapy was the only systemic treatment available for advanced MCC,⁵⁸ which despite a good initial response in nearly 90% of patients, has a short-lived efficacy (approximately 90 days). Currently, CPIs have emerged as front-line therapies for advanced MCC with about 50% of patients demonstrating a durable response, although not without considerable toxicity.

In 2017, on the basis of durable responses and favorable safety profiles observed in the JAVELIN Merkel 200 trial part A, avelumab became the first approved treatment for metastatic MCC (Table V)^{59,60}; part B of this trial recently showed good tolerance of the anti-PD-L1 agent as a first-line therapy for metastatic MCC (Table V).⁶¹ In 2018, pembrolizumab was approved for first-line treatment of advanced MCC in the KEYNOTE-017 trial⁶²

Table V. Major studies investigating immune checkpoint inhibitors to treat cutaneous malignancy

Type of cutaneous malignancy	Investigating agent/regimen	Trial identifier/current phase	Patient population	Median follow-up	Adverse event(s)	
					Common	Rare/serious
Cutaneous squamous cell carcinoma	Cemiplimab, 3 mg/kg every 2 weeks	EMPOWER-cSCC-1, NCT02760498/phase II trial	59 patients with metastatic cSCC	16.5 months	ORR 49.2%; CR 6.8%; PR 42.4%; SD 13.5%; PD 37.3%; PFS 18.4 months	Diarrhea (28.8%), fatigue (25.4%), and nausea (23.7%)
Cutaneous squamous cell carcinoma	Cemiplimab, 3 mg/kg every 2 weeks	NCT02383212/phase I trial with expansion cohort	26 patients with locally advanced or metastatic cSCC	11.0 months	ORR 50.0%; CR 0.0%; PR 50.0%; SD 25.0%; PD 27.0%; PFS not reported	Fatigue (26.9%), constipation (15%), decreased appetite (15%), diarrhea (15%), nausea (15%), constipation (15%), hypercalcemia (15%), hypophosphatemia (15%), and urinary tract infection (15%)
Merkel cell carcinoma	Avelumab, 10 mg/kg every 2 weeks	JAVELIN Merkel 200 NCT02155647/phase II (part A) trial	88 patients with stage IV MCC that is refractory to chemotherapy	16.4 months	ORR 33.0%; CR 11.4%; PR 21.6%; SD 10.2%; PD 36.4%; PFS 2.7 months	Fatigue (24%), infusion-related reactions (17%), diarrhea (9%), nausea (9%), asthenia (9%), rash (7%) and decreased appetite (6%)
Merkel cell carcinoma	Avelumab, 10 mg/kg every 2 weeks	JAVELIN Merkel 200 NCT02155647/phase II (part B) trial	39 patients with metastatic MCC who had not received prior systemic treatment	5.1 months	ORR 62.1%; CR 13.8%; PR 48.3%; SD 10.3%; PD 27.6%; PFS 9.1 months	Infusion-related reactions (23.1%)
Pembrolizumab, 2 mg/kg every 3 weeks	KEYNOTE-017 NCT02267603/phase II trial	50 patients (26 from original cohort and 24 from expansion cohort) with advanced MCC who had not received systemic treatment	14.9 months	ORR 56.0%; CR 24.0%; PR 32.0%; SD 10.0%; PD 32%; PFS 16.8 months	Fatigue and laboratory abnormalities	
						Cholangitis, elevated aspartate and alanine aminotransferase levels, paraneoplastic syndrome, gait disturbance, paraneoplastic encephalomyelitis, and polyneuropathy
						Myocarditis, elevated liver enzymes, and death

CR, Complete response; cSCC, cutaneous squamous cell carcinoma; MCC, Merkel cell carcinoma; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

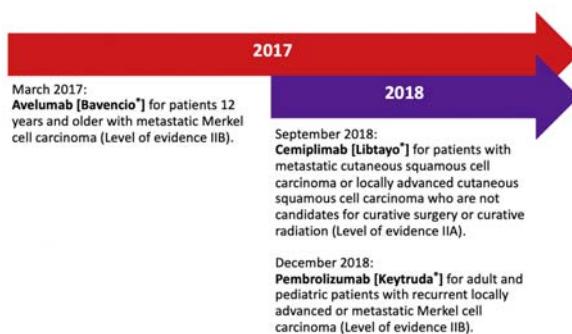


Fig 4. Timeline of approved immune checkpoint inhibitors to treat cutaneous squamous cell carcinoma and Merkel cell carcinoma. Level IA evidence includes evidence from metaanalysis of randomized controlled trials. Level IB evidence includes evidence from ≥ 1 randomized controlled trial. Level IIA evidence includes evidence from ≥ 1 controlled study without randomization. Level IIB evidence includes evidence from ≥ 1 other type of experimental study. Level III evidence includes evidence from nonexperimental descriptive studies (ie, comparative, correlation, or case-control). Level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

(Table V), which in addition to positive CPI-associated antitumor efficacy and safety outcomes also showed glucocorticoids having no effect on tumor response among patients with severe AEs.⁶² The expanded NCT02267603 trial further strengthened the efficacy of pembrolizumab as first-line treatment for advanced MCC (Fig 5).⁶³ The CheckMate 358 trial with 25 patients investigated nivolumab for advanced MCC, resulting in a 68% ORR and more than two-thirds with AEs.⁶⁴ In the above studies, PD-L1 expression and Merkel cell polyomavirus status did not appear to correlate with clinical responses.^{59,60,62,64}

The use of avelumab, pembrolizumab, and nivolumab for advanced metastatic MCC has also been reported in cases studies, with varying responses.⁶⁵⁻⁷⁴ Serious AEs included central diabetes insipidus,⁶⁶ pneumonia, autoimmune hepatitis,⁶⁸ cytokine release syndrome,⁷⁴ and thrombocytopenia.⁷⁵ Ipilimumab has been studied less frequently against MCC, with inconclusive antitumor activity.⁷⁶ In addition, ipilimumab did not demonstrate activity as adjuvant therapy for resected MCC.⁷⁷ Despite the success of CPIs in treating MCC, many patients do not respond to or develop resistant disease after an initial response; however, the use of combinatorial or sequential CPIs has shown activation of antitumor immunity in a subset of nonresponders,⁷⁸ which represents a promising therapeutic approach for patients who do not persistently benefit from CPI treatment in this population.

OTHER CUTANEOUS NEOPLASMS

Key points

- There is no CPI approved for BCC, cutaneous lymphoma, cutaneous sarcoma, or CAC
- In small studies and case reports, anti-PD-1 therapy appears to be efficacious in BCC, certain subsets of cutaneous lymphoma, and cutaneous sarcoma

Basal cell carcinoma

BCC is the most common human cancer with increasing incidence. A small subset of BCC progresses to locally advanced and metastatic tumors and requires aggressive systemic treatments.^{79,80} Immunotherapy is anticipated to be effective in BCC because it bears the highest mutational burden of any human cancer.⁸¹

Pembrolizumab showed antitumor activity against advanced BCC in a phase Ib trial, in which 9 patients received pembrolizumab monotherapy and 7 patients received pembrolizumab plus vismodegib.⁸² The ORRs at 18 weeks were 44% and 29%, and the 1-year PFSs were 62% and 83% for the monotherapy versus dual therapy group, respectively. Thus, the response rate of the dual therapy was not superior to the monotherapy group. Pembrolizumab was well tolerated with dermatitis and fatigue being the most common AEs.⁸² The use of pembrolizumab in BCC has also been reported in 5 case reports with clinical responses ranging from disease progression⁸³ to partial response^{16,84,85} and complete response.^{83,86} There was only 1 report of subclinical hypothyroidism⁸⁴ and sarcoid-like lymph node reaction.¹⁶ Cemiplimab⁸⁷ and nivolumab^{88,89} have also shown efficacy against advanced BCC without serious AEs.

Cutaneous lymphomas

Cutaneous T cell lymphomas (CTCLs) involve extensive infiltration of malignant T cells into the skin and lack effective treatment for advanced disease.⁹⁰ Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common CTCL subtypes, with cells expressing high level of PD-1, PD-L1, and CTLA-4, suggesting a role of CPIs in targeting the disease.^{91,92}

As demonstrated by a 15% ORR in 13 patients with MF and 0% ORR in 2 patients with SS in a phase Ib trial, nivolumab has a limited antitumor activity against CTCL.⁹³ AEs occurred in 65% of patients, with 15% discontinuing treatment because of severe AEs, including pneumonitis, sepsis, and myositis. A phase II study of pembrolizumab for 24 patients with advanced CTCL demonstrated a 38% ORR.^{94,95} While



Fig 5. Complete clinicopathologic response in a patient with Merkel cell carcinoma who was treated with pembrolizumab. **A** and **B**, Clinical images of a patient with Merkel cell carcinoma pre-treatment and 3 weeks after the first dose of pembrolizumab. **C**, Findings on histopathology reveal dermal fibrosis and a mixed lymphocytic inflammation with negative synaptophysin and chromogranin stains (not shown), both of which were expressed pre-treatment with pembrolizumab.

there was no significant association between tumor response and the expression of PD-1, PD-L1, or infiltrating CD8⁺ T cells, pembrolizumab was well-tolerated; serious AEs included grade 2 pneumonitis and grade 3 diarrhea caused by steroid-refractory duodenitis.⁹⁴ Curiously, 53% patients with SS experienced skin flare reactions, characterized by a transient worsening of erythroderma and pruritus.⁹⁵ This reaction correlated with PD-1 expression on Sézary cells but did not associate with subsequent clinical responses. The use of ipilimumab for CTCL has been reported in only 2 case reports with conflicting responses and requires additional investigation.^{96,97}

Cutaneous sarcomas

Cutaneous sarcomas are a rare and heterogeneous group of skin mesenchymal spindle cell tumors with good prognosis for early disease. There is a lack of effective therapy for patients with advanced diseases.⁹⁸ In a phase II trial,⁹⁹ pembrolizumab did not show benefit in patients with undifferentiated pleomorphic sarcoma. In the NCT01295827 trial with 10 patients with undifferentiated pleomorphic sarcoma, there was 10% complete response, 30% partial response, 30% stable disease, and 30% progressive disease.¹⁰⁰ Among the 10 patients with liposarcoma in the same trial, there was 0% complete response, 2% partial response, 40% stable disease, and 40% progressive disease. The most frequent grade 3 or worse AEs were anemia and other hematologic abnormalities, and 6% of patients discontinued

therapy because of toxicity, including nephritis and pneumonitis.

Kaposi sarcoma (KS) is often observed in immunosuppressed patients, suggesting that it might be a good target for CPIs. In a series of 9 HIV-positive patients with KS who received nivolumab ($n = 8$) or pembrolizumab ($n = 1$), the ORR was 66%. The most common AEs were fatigue, pruritus, muscle/joint ache, abdominal discomfort, and onycholysis.¹⁰¹ Pembrolizumab also has antitumor activity against HIV-negative, classic KS.^{69,102} Nivolumab is also effective in HIV-negative patients with KS with the only notable AE being hyponatremia because of low cortisol level.¹⁰³ Pembrolizumab has also been attempted in 2 separate cases of angiosarcoma in which the patients either achieved a complete response¹⁰⁴ or durable partial response with autoimmune hepatitis that required prednisone treatment.¹⁰⁵ There are no data regarding the efficacy of CPIs against dermatofibrosarcoma protuberans or cutaneous leiomyosarcoma.

Cutaneous adnexal carcinomas

CACs are a heterogeneous group of malignant neoplasms that display differentiation toward skin-primary adnexal structures and which currently have limited effective treatment for metastasis.¹⁰⁶ High expression levels of PD-L1 have been reported in sebaceous carcinoma.^{73,107} In 2 case reports, the use of pembrolizumab with or without chemotherapy demonstrated clinical efficacy against metastatic sebaceous

carcinoma.^{108,109} One patient remained on pembrolizumab despite requiring systemic corticosteroids because of secondary adrenal insufficiency.¹⁰⁸

FUTURE DIRECTIONS AND CONCLUSIONS

As the field of immunotherapeutics continues to revolutionize the treatment of cutaneous malignancies, blocking antibodies to CTLA-4 and PD-1/PD-L1 have improved survival for many patients. For melanoma, ipilimumab in combination with nivolumab or either nivolumab or pembrolizumab alone are standard front-line treatment options. Several trials are in development to investigate the role of anti-PD-L1 agents in metastatic melanoma,^{110,111} including atezolizumab and avelumab.

Cemiplimab is the only approved CPI for cSCC, and there is a critical need for improved therapies that can better target the advanced stage of this cutaneous malignancy. Although pembrolizumab has demonstrated antitumor activity against cSCC in a phase II trial, most patients do not respond to immunotherapy. For MCC, the NCCN guidelines recommend avelumab, pembrolizumab, and nivolumab as first-line therapies, ahead of chemotherapy. Although the data are limited and there is no CPI approved for BCC, cutaneous lymphoma, cutaneous sarcoma, or CACs,¹¹² evidence from small observational studies and case reports suggest the potential utility of anti-PD-1 therapy in BCC and certain subsets of cutaneous lymphoma and cutaneous sarcoma.

Despite exceptional clinical benefits observed with CPIs in cutaneous malignancies, their associated irAEs require careful monitoring. As such, expanding immunotherapy clinical research efforts can lead to identifying new CPI regimens that improve antitumor responses and reduce the incidence and severity of irAEs. Furthermore, striving to achieve a more concrete understanding of predictive markers of response and mechanisms of resistance to anti-CTLA-4 and anti-PD-1/PD-L1 therapies may help identify subsets of patients who are more likely to respond to therapy with these agents.

REFERENCES

- Ribas A. Tumor immunotherapy directed at PD-1. *N Engl J Med.* 2012;366:2517-2519.
- Alsaab HO, Sau S, Alzhrani R, et al. PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome. *Front Pharmacol.* 2017;8:561.
- Boussioutis VA. Molecular and biochemical aspects of the PD-1 checkpoint pathway. *N Engl J Med.* 2016;375:1767-1778.
- Kluger HM, Zito CR, Turcu G, et al. PD-L1 studies across tumor types, its differential expression and predictive value in patients treated with immune checkpoint inhibitors. *Clin Cancer Res.* 2017;23:4270-4279.
- Coit DG, Thompson JA, Albertini MR, et al. Cutaneous melanoma, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2019;17:367-402.
- Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med.* 2019;381:1535-1546.
- Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncol.* 2018;19:1480-1492.
- Zaragoza J, Caille A, Beneton N, et al. High neutrophil to lymphocyte ratio measured before starting ipilimumab treatment is associated with reduced overall survival in patients with melanoma. *Br J Dermatol.* 2016;174:146-151.
- Kelderman S, Heemskerk B, van Tinteren H, et al. Lactate dehydrogenase as a selection criterion for ipilimumab treatment in metastatic melanoma. *Cancer Immunol Immunother.* 2014;63:449-458.
- Rosner S, Kwong E, Shoushtari AN, et al. Peripheral blood clinical laboratory variables associated with outcomes following combination nivolumab and ipilimumab immunotherapy in melanoma. *Cancer Med.* 2018;7:690-697.
- de Coana YP, Wolodarski M, Poschke I, et al. Ipilimumab treatment decreases monocytic MDSCs and increases CD8 effector memory T cells in long-term survivors with advanced melanoma. *Oncotarget.* 2017;8:21539-21553.
- Ouwerkerk W, van den Berg M, van der Niet S, Limpens J, Luiten RM. Biomarkers, measured during therapy, for response of melanoma patients to immune checkpoint inhibitors: a systematic review. *Melanoma Res.* 2019;29:453-464.
- Byrne EH, Fisher DE. Immune and molecular correlates in melanoma treated with immune checkpoint blockade. *Cancer.* 2017;123(suppl 11):2143-2153.
- Weber JS, Hamid O, Chasalow SD, et al. Ipilimumab increases activated T cells and enhances humoral immunity in patients with advanced melanoma. *J Immunother.* 2012;35:89-97.
- Stevenson ML, Wang CQ, Abikhair M, et al. Expression of programmed cell death ligand in cutaneous squamous cell carcinoma and treatment of locally advanced disease with pembrolizumab. *JAMA Dermatol.* 2017;153:299-303.
- Winkler JK, Schneiderbauer R, Bender C, et al. Anti-programmed cell death-1 therapy in nonmelanoma skin cancer. *Br J Dermatol.* 2017;176:498-502.
- Maubec E, Boubaya M, Petrow P, et al. Pembrolizumab as first-line therapy in patients with unresectable cutaneous squamous cell carcinoma (cSCC): phase 2 results from CARSKIN [abstract]. *J Clin Oncol.* 2019;37(15 suppl):9547.
- Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med.* 2017;9:34.
- Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med.* 2003;348:1681-1691.
- Pickering CR, Zhou JH, Lee JJ, et al. Mutational landscape of aggressive cutaneous squamous cell carcinoma. *Clin Cancer Res.* 2014;20:6582-6592.
- Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010;363:711-723.
- Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. *Lancet Oncol.* 2010;11:155-164.

23. Ascierto PA, Del Vecchio M, Robert C, et al. Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol.* 2017;18:611-622.
24. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2015;16:522-530.
25. Eggermont AM, Chiarion-Sileni V, Grob JJ. Correction to *Lancet Oncol* 2015; 16: 522-30. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2015;16:e262.
26. Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of stage III melanoma: long-term follow-up results of the European Organisation for Research and Treatment of Cancer 18071 double-blind phase 3 randomised trial. *Eur J Cancer.* 2019; 119:1-10.
27. Raedler LA. Keytruda (pembrolizumab): first PD-1 inhibitor approved for previously treated unresectable or metastatic melanoma. *Am Health Drug Benefits.* 2015;8(spec feature):96-100.
28. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet.* 2014;384: 1109-1117.
29. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med.* 2015;372: 2521-2532.
30. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med.* 2018;378:1789-1801.
31. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol.* 2015;16:375-384.
32. Hazarika M, Chuk MK, Theoret MR, et al. U.S. FDA approval summary: nivolumab for treatment of unresectable or metastatic melanoma following progression on ipilimumab. *Clin Cancer Res.* 2017;23:3484-3488.
33. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med.* 2015;372:320-330.
34. Beaver JA, Theoret MR, Mushti S, et al. FDA approval of nivolumab for the first-line treatment of patients with BRAF(V600) wild-type unresectable or metastatic melanoma. *Clin Cancer Res.* 2017;23:3479-3483.
35. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med.* 2017;377:1824-1835.
36. Yamazaki N, Kiyohara Y, Uhara H, et al. Long-term follow up of nivolumab in previously untreated Japanese patients with advanced or recurrent malignant melanoma. *Cancer Sci.* 2019;110:1995-2003.
37. Yamazaki N, Kiyohara Y, Uhara H, et al. Efficacy and safety of nivolumab in Japanese patients with previously untreated advanced melanoma: a phase II study. *Cancer Sci.* 2017;108: 1223-1230.
38. Ascierto PA, Long GV, Robert C, et al. Survival outcomes in patients with previously untreated BRAF wild-type advanced melanoma treated with nivolumab therapy: three-year follow-up of a randomized phase 3 trial. *JAMA Oncol.* 2019;5:187-194.
39. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med.* 2015;372:2006-2017.
40. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med.* 2015;373:23-24.
41. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med.* 2017;377:1345-1356.
42. Que SKT, Zwald FO, Schmuls CD. Cutaneous squamous cell carcinoma: incidence, risk factors, diagnosis, and staging. *J Am Acad Dermatol.* 2018;78:237-247.
43. Karia PS, Han J, Schmuls CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. *J Am Acad Dermatol.* 2013;68:957-966.
44. Migden MR, Rischin D, Schmuls CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Engl J Med.* 2018;379:341-351.
45. Guminiski AD, Lim AML, Khushalani NI, et al. Phase 2 study of cemiplimab, a human monoclonal anti-PD-1, in patients (pts) with metastatic cutaneous squamous cell carcinoma (mCSCC; Group 1): 12-month follow-up [abstract]. *J Clin Oncol.* 2019;37(15 suppl):9526.
46. Owonikoko TK, Papadopoulos KP, Johnson ML, et al. Phase 1 study of cemiplimab, a human monoclonal anti-PD-1, in patients with unresectable locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC): final efficacy and safety data [abstract]. *J Clin Oncol.* 2018;36(15 suppl):9557.
47. Lipson EJ, Bagnasco SM, Moore J Jr, et al. Tumor regression and allograft rejection after administration of anti-PD-1. *N Engl J Med.* 2016;374:896-898.
48. Sadaat M, Jang S. Complete tumor response to pembrolizumab and allograft preservation in renal allograft recipient on immunosuppressive therapy. *J Oncol Pract.* 2018;14:198-199.
49. Assam JH, Powell S, Spanos WC. Unresectable cutaneous squamous cell carcinoma of the forehead with MLH1 mutation showing dramatic response to programmed cell death protein 1 inhibitor therapy. *Clin Skin Cancer.* 2016;1:26-29.
50. Tran DC, Colevas AD, Chang AL. Follow-up on programmed cell death 1 inhibitor for cutaneous squamous cell carcinoma. *JAMA Dermatol.* 2017;153:92-94.
51. Borradori L, Sutton B, Shayesteh P, Daniels GA. Rescue therapy with anti-programmed cell death protein 1 inhibitors of advanced cutaneous squamous cell carcinoma and basosquamous carcinoma: preliminary experience in five cases. *Br J Dermatol.* 2016;175:1382-1386.
52. Chang AL, Kim J, Luciano R, Sullivan-Chang L, Colevas AD. A case report of unresectable cutaneous squamous cell carcinoma responsive to pembrolizumab, a programmed cell death protein 1 inhibitor. *JAMA Dermatol.* 2016;152:106-108.
53. Cippa PE, Schiesser M, Ekberg H, et al. Risk stratification for rejection and infection after kidney transplantation. *Clin J Am Soc Nephrol.* 2015;10:2213-2220.
54. Blum V, Muller B, Hofer S, et al. Nivolumab for recurrent cutaneous squamous cell carcinoma: three cases. *Eur J Dermatol.* 2018;28:78-81.
55. Chen A, Ali N, Boasberg P, Ho AS. Clinical remission of cutaneous squamous cell carcinoma of the auricle with cetuximab and nivolumab. *J Clin Med.* 2018;7:10.
56. Day F, Kumar M, Fenton L, Gedye C. Durable response of metastatic squamous cell carcinoma of the skin to ipilimumab immunotherapy. *J Immunother.* 2017;40:36-38.
57. Vaidya P, Mehta A, Ragab O, Lin S, In GK. Concurrent radiation therapy with programmed cell death protein 1 inhibition

- leads to a complete response in advanced cutaneous squamous cell carcinoma. *J AAD Case Rep.* 2019;5:763-766.
58. Bichakjian CK, Olencki T, Aasi SZ, et al. Merkel cell carcinoma, version 1.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2018;16:742-774.
 59. Kaufman HL, Russell J, Hamid O, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncol.* 2016;17:1374-1385.
 60. Kaufman HL, Russell JS, Hamid O, et al. Updated efficacy of avelumab in patients with previously treated metastatic Merkel cell carcinoma after $>/=1$ year of follow-up: JAVELIN Merkel 200, a phase 2 clinical trial. *J Immunother Cancer.* 2018;6:7.
 61. D'Angelo SP, Russell J, Lebbe C, et al. Efficacy and safety of first-line avelumab treatment in patients with stage IV metastatic Merkel cell carcinoma: a preplanned interim analysis of a clinical trial. *JAMA Oncol.* 2018;4:e180077.
 62. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. *N Engl J Med.* 2016;374:2542-2552.
 63. Nghiem P, Bhatia S, Lipson EJ, et al. Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. *J Clin Oncol.* 2019;37:693-702.
 64. Topalian SL, Bhatia S, Hollebecque A, et al. Non-comparative, open-label, multiple cohort, phase 1/2 study to evaluate nivolumab (NIVO) in patients with virus-associated tumors (CheckMate 358): efficacy and safety in Merkel cell carcinoma (MCC) [abstract]. *Cancer Res.* 2017;77(13 suppl):CT074.
 65. Eshghi N, Lundein TF, MacKinnon L, Avery R, Kuo PH. 18F-FDG PET/CT for monitoring response of Merkel cell carcinoma to the novel programmed cell death ligand 1 inhibitor avelumab. *Clin Nucl Med.* 2018;43:e142-e144.
 66. Zhao C, Tella SH, Del Rivero J, et al. Anti-PD-L1 treatment induced central diabetes insipidus. *J Clin Endocrinol Metab.* 2018;103:365-369.
 67. Mantripragada K, Birnbaum A. Response to anti-PD-1 therapy in metastatic Merkel cell carcinoma metastatic to the heart and pancreas. *Cureus.* 2015;7:e403.
 68. Walocko FM, Scheier BY, Harms PW, Fecher LA, Lao CD. Metastatic Merkel cell carcinoma response to nivolumab. *J Immunother Cancer.* 2016;4:79.
 69. Patnaik A, Kang SP, Rasco D, et al. Phase I study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. *Clin Cancer Res.* 2015; 21:4286-4293.
 70. Cugley DR, Roberts-Thomson SJ, McNab AA, Pick Z. Biopsy-proven metastatic Merkel cell carcinoma to the orbit: case report and review of literature. *Ophthalmic Plast Reconstr Surg.* 2018;34:e86-e88.
 71. Winkler JK, Bender C, Kratochwil C, Enk A, Hassel JC. PD-1 blockade: a therapeutic option for treatment of metastatic Merkel cell carcinoma. *Br J Dermatol.* 2017;176:216-219.
 72. Haug V, Behle V, Benoit S, et al. Pembrolizumab-associated mucous membrane pemphigoid in a patient with Merkel cell carcinoma. *Br J Dermatol.* 2018;179:993-994.
 73. Xu MJ, Wu S, Daud Al, Yu SS, Yom SS. In-field and abscopal response after short-course radiation therapy in patients with metastatic Merkel cell carcinoma progressing on PD-1 checkpoint blockade: a case series. *J Immunother Cancer.* 2018;6:43.
 74. Barker CA, Kim SK, Budhu S, Matsoukas K, Daniyan AF, D'Angelo SP. Cytokine release syndrome after radiation therapy: case report and review of the literature. *J Immunother Cancer.* 2018;6:1.
 75. Kratzsch D, Simon JC, Ponitzsch I, Ziemer M. Lethal thrombocytopenia in a patient treated with avelumab for metastatic Merkel cell carcinoma. *J Dtsch Dermatol Ges.* 2019;17: 73-75.
 76. Winkler JK, Dimitrakopoulou-Strauss A, Sachpekidis C, Enk A, Hassel JC. Ipilimumab has efficacy in metastatic Merkel cell carcinoma: a case series of five patients. *J Eur Acad Dermatol Venereol.* 2017;31:e389-e391.
 77. Becker JC, Hassel JC, Menzer C, et al. Adjuvant ipilimumab compared with observation in completely resected Merkel cell carcinoma (ADMEC): a randomized, multicenter DeCOG/ADO study [abstract]. *J Clin Oncol.* 2018;36(15 suppl):9527.
 78. LoPiccolo J, Schollenberger MD, Dakhil S, et al. Rescue therapy for patients with anti-PD-1-refractory Merkel cell carcinoma: a multicenter, retrospective case series. *J Immunother Cancer.* 2019;7:170.
 79. Cameron MC, Lee E, Hibler BP, et al. Basal cell carcinoma: epidemiology; pathophysiology; clinical and histological subtypes; and disease associations. *J Am Acad Dermatol.* 2019;80: 303-317.
 80. Cameron MC, Lee E, Hibler BP, et al. Basal cell carcinoma: contemporary approaches to diagnosis, treatment, and prevention. *J Am Acad Dermatol.* 2019;80:321-339.
 81. Jayaraman SS, Rayhan DJ, Hazany S, Kolodney MS. Mutational landscape of basal cell carcinomas by whole-exome sequencing. *J Invest Dermatol.* 2014;134:213-220.
 82. Chang ALS, Tran DC, Cannon JGD, et al. Pembrolizumab for advanced basal cell carcinoma: an investigator-initiated, proof-of-concept study. *J Am Acad Dermatol.* 2019;80:564-566.
 83. Cannon JGD, Russell JS, Kim J, Chang ALS. A case of metastatic basal cell carcinoma treated with continuous PD-1 inhibitor exposure even after subsequent initiation of radiotherapy and surgery. *JAAD Case Rep.* 2018; 4:248-250.
 84. Lipson EJ, Lilo MT, Ogurtsova A, et al. Basal cell carcinoma: PD-L1/PD-1 checkpoint expression and tumor regression after PD-1 blockade. *J Immunother Cancer.* 2017;5:23.
 85. Fischer S, Hasan Ali O, Jochum W, Kluckert T, Flatz L, Siano M. Anti-PD-1 therapy leads to near-complete remission in a patient with metastatic basal cell carcinoma. *Oncol Res Treat.* 2018;41:391-394.
 86. Moreira A, Kirchberger MC, Toussaint F, Erdmann M, Schuler G, Heinzerling L. Effective anti-programmed death-1 therapy in a SUFU-mutated patient with Gorlin-Goltz syndrome. *Br J Dermatol.* 2018;179:747-749.
 87. Falchook GS, Leidner R, Stankevich E, et al. Responses of metastatic basal cell and cutaneous squamous cell carcinomas to anti-PD1 monoclonal antibody REGN2810. *J Immunother Cancer.* 2016;4:70.
 88. Cohen PR, Kato S, Goodman AM, Ikeda S, Kurzrock R. Appearance of new cutaneous superficial basal cell carcinomas during successful nivolumab treatment of refractory metastatic disease: implications for immunotherapy in early versus late disease. *Int J Mol Sci.* 2017;18:1663.
 89. Ikeda S, Goodman AM, Cohen PR, et al. Metastatic basal cell carcinoma with amplification of PD-L1: exceptional response to anti-PD1 therapy. *NPJ Genom Med.* 2016;1:16037.
 90. Wilcox RA. Cutaneous T-cell lymphoma: 2017 update on diagnosis, risk-stratification, and management. *Am J Hematol.* 2017;92:1085-1102.

91. Dai J, Almazan T, Kim Y, Khodadoust M. Pembrolizumab in systemic and cutaneous T-cell lymphoma. *Ann Lymphomad.* 2018;2:3.
92. Wong HK, Wilson AJ, Gibson HM, et al. Increased expression of CTLA-4 in malignant T-cells from patients with mycosis fungoides—cutaneous T cell lymphoma. *J Invest Dermatol.* 2006;126:212-219.
93. Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase I study. *J Clin Oncol.* 2016;34: 2698-2704.
94. Khodadoust M, Rook AH, Porcu P, et al. Pembrolizumab for treatment of relapsed/refractory mycosis fungoides and Sézary syndrome: clinical efficacy in a Citt multicenter phase 2 study. *Blood.* 2016;128:181.
95. Khodadoust MS, Rook AH, Porcu P, et al. Pembrolizumab in relapsed and refractory mycosis fungoides and Sézary syndrome: a multicenter phase II study. *J Clin Oncol.* 2020;38:20-28.
96. Bar-Sela G, Bergman R. Complete regression of mycosis fungoides after ipilimumab therapy for advanced melanoma. *JAAD Case Rep.* 2015;1:99-100.
97. Sekulic A, Liang WS, Tembe W, et al. Personalized treatment of Sezary syndrome by targeting a novel CTLA4:CD28 fusion. *Mol Genet Genomic Med.* 2015;3:130-136.
98. Kohlmeyer J, Steimle-Grauer SA, Hein R. Cutaneous sarcomas. *J Dtsch Dermatol Ges.* 2017;15:630-648.
99. Toulmonde M, Penel N, Adam J, et al. Use of PD-1 targeting, macrophage infiltration, and IDO pathway activation in sarcomas: a phase 2 clinical trial. *JAMA Oncol.* 2018;4:93-97.
100. Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol.* 2017;18:1493-1501.
101. Galanina N, Goodman AM, Cohen PR, Frampton GM, Kurzrock R. Successful treatment of HIV-associated Kaposi sarcoma with immune checkpoint blockade. *Cancer Immunol Res.* 2018;6:1129-1135.
102. Saller J, Walko CM, Millis SZ, Henderson-Jackson E, Makani R, Brohl AS. Response to checkpoint inhibitor therapy in advanced classic kaposi sarcoma: a case report and immunogenomic study. *J Natl Compr Canc Netw.* 2018;16:797-800.
103. Delyon J, Bizot A, Battistella M, Madelaine I, Vercellino L, Lebbe C. PD-1 blockade with nivolumab in endemic Kaposi sarcoma. *Ann Oncol.* 2018;29:1067-1069.
104. Hamacher R, Kämpfe D, Ahrens M, et al. 1506PPD-L1 inhibition – a new therapeutic opportunity in cutaneous angiosarcoma? *Ann Oncol.* 2017;28(suppl 5).
105. Sindhu S, Gimber LH, Cranmer L, McBride A, Kraft AS. Angiosarcoma treated successfully with anti-PD-1 therapy - a case report. *J Immunother Cancer.* 2017;5:58.
106. Martinez SR, Barr KL, Canter RJ. Rare tumors through the looking glass: an examination of malignant cutaneous adnexal tumors. *Arch Dermatol.* 2011;147:1058-1062.
107. Kandl TJ, Sagiv O, Curry JL, et al. High expression of PD-1 and PD-L1 in ocular adnexal sebaceous carcinoma. *Oncoimmunology.* 2018;7:e1475874.
108. Domingo-Musibay E, Murugan P, Giubellino A, et al. Near complete response to pembrolizumab in microsatellite-stable metastatic sebaceous carcinoma. *J Immunother Cancer.* 2018;6:58.
109. Kodali S, Tipirneni E, Gibson PC, Cook D, Verschraegen C, Lane KA. Carboplatin and pembrolizumab chemoimmunotherapy achieves remission in recurrent, metastatic sebaceous carcinoma. *Ophthalmic Plast Reconstr Surg.* 2018;34: e149-e151.
110. Hamid O, Molinero L, Bolen CR, et al. Safety, clinical activity, and biological correlates of response in patients with metastatic melanoma: results from a phase I trial of atezolizumab. *Clin Cancer Res.* 2019;25:6061-6072.
111. Keilholz U, Mehrt JM, Bauer S, et al. Avelumab in patients with previously treated metastatic melanoma: phase 1b results from the JAVELIN Solid Tumor trial. *J Immunother Cancer.* 2019;7:12.
112. Choi FD, Kraus CN, Elsensohn AN, et al. Programmed cell death 1 protein and programmed death-ligand 1 inhibitors in the treatment of nonmelanoma skin cancer: a systematic review. *J Am Acad Dermatol.* 2020;82: 440-459.

Answers to CME examination

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Immune checkpoint inhibitor–related dermatologic adverse events

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Learning objectives

After completing this learning activity, participants should be able to identify the significance of dermatologic reactions to immune checkpoint inhibitors to cancer outcomes; recognize the clinical and histological features of dermatologic reactions to immune checkpoint inhibitors; distinguish primary autoimmune/autoinflammatory conditions from immune-related dermatologic adverse events; describe appropriate management of immune-related dermatologic adverse events to immune checkpoint inhibitors; and identify novel or emerging strategies of managing immune checkpoint inhibitor-related dermatologic adverse events.

Disclosures

Editors

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Immune checkpoint inhibitors have emerged as a pillar in the management of advanced malignancies. However, nonspecific immune activation may lead to immune-related adverse events, wherein the skin and its appendages are the most frequent targets. Cutaneous immune-related adverse events include a diverse group of inflammatory reactions, with maculopapular rash, pruritus, psoriasiform and lichenoid eruptions being the most prevalent subtypes. Cutaneous immune-related adverse events occur early, with maculopapular rash presenting within the first 6 weeks after the initial immune checkpoint inhibitor

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dose. Management involves the use of topical corticosteroids for mild to moderate (grades 1-2) rash, addition of systemic corticosteroids for severe (grade 3) rash, and discontinuation of immunotherapy with grade 4 rash. Bullous pemphigoid eruptions, vitiligo-like skin hypopigmentation/depigmentation, and psoriasiform rash are more often attributed to programmed cell death-1/programmed cell death ligand-1 inhibitors. The treatment of bullous pemphigoid eruptions is similar to the treatment of maculopapular rash and lichenoid eruptions, with the addition of rituximab in grade 3-4 rash. Skin hypopigmentation/depigmentation does not require specific dermatologic treatment aside from photoprotective measures. In addition to topical corticosteroids, psoriasiform rash may be managed with vitamin D₃ analogues, narrowband ultraviolet B light phototherapy, retinoids, or immunomodulatory biologic agents. Stevens-Johnson syndrome and other severe cutaneous immune-related adverse events, although rare, have also been associated with checkpoint blockade and require inpatient care as well as urgent dermatology consultation. (J Am Acad Dermatol 2020;83:1255-68.)

Key words: checkpoint inhibitor; CTLA-4 inhibitor; dermatologic adverse event; immune-related cutaneous adverse event; lichenoid eruption; maculopapular rash; PD-1 inhibitor; PD-L1 inhibitor; pruritus; vitiligo.

EPIDEMIOLOGY

Key points

- Immune-related adverse events are less frequent and less severe in patients treated with anti-programmed cell death-1/programmed cell death ligand-1 than with cytotoxic T-lymphocyte-associated protein-4 inhibitors
- Cutaneous immune-related adverse events are the most common and usually manifest first
- Multiple studies have suggested an association between cutaneous immune-related adverse events and tumor response

Immunotherapy has emerged as a dominant paradigm in the management of advanced malignancies. Checkpoint inhibitors (CPIs) have shown dramatic efficacy; however, their use can be accompanied by nonspecific immune activation leading to a myriad of autoimmune and autoinflammatory phenomena termed immune-related adverse events (irAEs). These irAEs profoundly impact patient quality of life and may impact CPI treatment efficacy through CPI dose-limiting effects. Immune-related cutaneous adverse events (irCAEs) are the most frequent and earliest irAEs to arise in patients receiving CPIs; thus, understanding their clinicopathologic features and crafting targeted and effective management strategies is paramount to a successful oncidermatologic practice.

irAEs affecting a variety of organ systems occur in $\leq 90\%$ of patients treated with cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) inhibitors, 70% of patients treated with programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) inhibitors, and almost all patients receiving combined therapies.¹ irAEs are generally mild to

moderate, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, with severe (grade 3-4) toxicity (Table I) observed in $\leq 25\%$ of patients treated with CTLA-4 inhibitor monotherapy and $<20\%$ of patients treated with PD-1/PD-L1 inhibitor monotherapy.^{2,3} Severe irAEs may lead to death in $<2\%$ of cases.¹ Whereas colitis complicated by bowel perforation represents the majority of life-threatening events under CTLA-4 inhibition, pneumonitis represents the majority of life-threatening events under PD-1/PD-L1 blockade.^{2,4}

Typically, mild to moderate irAEs (CTCAE grades 1-2) are largely reversible within 2 weeks when adequately treated.^{2,5,6} With prompt recognition and management, $<5\%$ of irAEs require discontinuation of CPI therapy.⁷⁻¹⁰ For patients treated with CTLA-4 inhibitors, irAEs mostly involve the skin (44%), gastrointestinal tract (35%), endocrine system (6%), and liver (5%).^{2,11} Not only are irCAEs the most common, but they also occur earliest, at an average of 3.6 weeks after treatment initiation versus a 6- to 7-week latency for gastrointestinal toxicities and a 9-week latency for endocrine toxicity.^{2,5,7,8,12,13} irCAEs occur before systemic irAEs, and therefore it is important to identify them early in the course of treatment.^{2,5,7,8,12,13}

Combination therapy using the CPIs ipilimumab and nivolumab has been approved for the treatment of patients with advanced melanoma.¹⁴⁻¹⁶ Studies evaluating the concurrent use of a CTLA-4 inhibitor and PD-1 inhibitor versus CTLA-4 inhibition alone showed a superior response rate ($>50\%$) and increased incidence of irAEs ($>50\%$) in the combination.^{2,7,8,14,17-29} As early as 2005, an association between irAEs and tumor response to an anti-CTLA-4 peptide vaccination was observed.^{30,31} This association is supported by a meta-analysis demonstrating statistically significant

Abbreviations used:

AE:	adverse event
BP:	bullous pemphigoid
BSA:	body surface area
CPI:	checkpoint inhibitor
CTLA-4:	cytotoxic T-lymphocyte-associated protein-4
DIF:	direct immunofluorescence
DRESS:	drug reaction with eosinophilia and systemic symptoms
irAE:	immune-related adverse event
irCAE:	immune-related cutaneous adverse event
LP:	lichen planus
MPR:	maculopapular rash
PD-1:	programmed cell death protein-1 receptor
PD-L1:	programmed cell death protein-1 ligand
SCAR:	severe cutaneous adverse reaction
SJS:	Stevens-Johnson syndrome
TCS:	topical corticosteroids
TEN:	toxic epidermal necrolysis

overall survival benefit and longer progression-free survival.^{30,31}

The most common irCAEs include nonspecific maculopapular rash (MPR), pruritus, psoriasiform, eczematous, and lichenoid dermatoses.^{32,33} Other less frequent irCAEs include bullous pemphigoid, vitiligo-like skin hypopigmentation/depigmentation, and alopecia.^{7,8} Cutaneous complications are usually self-limiting, but severe irCAEs may also rarely occur, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS).^{2,7,8} Treatment algorithms for irCAEs center around early recognition and the use of corticosteroids or anti-tumor necrosis factor- α agents.^{2,34} However, the early use of corticosteroids immediately before or after CPI initiation may lead to decreased tumor efficacy.^{28,35-40} It is thought that CTLA-4 downregulates T cell activation primarily in lymphoid tissue, whereas PD-1/PD-L1 inhibitors act primarily in the tumor microenvironment, resulting in distinct irAE spectra between CPI classes.^{2,7,8,18,41-46} Because of their differing mechanisms, it can be hypothesized that in the case of severe toxicity with a CPI, rechallenge with

an agent of a different class may be a safe treatment strategy.⁴⁷ Given the diverse inflammatory eruptions observed in CPI recipients, tailored management strategies have been developed through expert consensus and retrospective analyses from supportive oncologic and dermatologic perspectives.

CUTANEOUS ERUPTIONS

Key points

- MPR, pruritus, psoriasiform rash, eczema, and lichenoid eruptions represent the most common irCAEs
- Less common irCAEs include bullous pemphigoid, skin hypopigmentation/depigmentation, alopecia, SJS, TEN, and DRESS
- Whereas moderate- to high-potency topical corticosteroids are first-line treatment for mild to moderate irCAEs, systemic corticosteroids may be indicated for widespread or severe disease
- Although an area of ongoing investigation, consideration should be given to phenotype-directed therapies (ie, specific biologics in psoriasiform rash)

Maculopapular rash

A pruritic maculopapular rash (MPR) represents the most prevalent irCAE induced by CTLA-4 inhibition.^{7,8} There is a predilection for the MPR phenotype under CTLA-4 blockade compared with PD-1/PD-L1 monotherapy.⁴³ MPR of any grade is observed in 49% to 68% of patients treated with anti-CTLA-4 therapy versus 20% of patients treated with anti-PD-1/PD-L1 therapy.⁴⁸⁻⁵⁰ The rash occurs early in treatment, usually 3 to 6 weeks after the initial dose, and appears to be dose dependent (Fig 1).^{7,8,14,49,51} MPR most commonly affects the trunk and extensor surfaces of the extremities (Fig 2).^{2,7,8,14,50-52} A typical rash consists of faint erythematous macules and papules coalescing into plaques.^{2,7,8,14,50-52} The body surface area (BSA) involved varies, but MPR is usually self-limiting (grade 1-2), covering <30% BSA. In 4% of patients, rash is considered severe (grade 3-4).⁴⁹ External trauma

Table I. Common Terminology Criteria for Adverse Events Version 5.0

CTCAE grade	Description
1	Lesions covering <10% BSA with or without symptoms (ie, pruritus, burning, or tightness)
2	Lesions covering 10-30% BSA with or without symptoms (ie, pruritus, burning, or tightness); OR limiting instrumental ADL; OR lesions covering >30% BSA with or without mild symptoms, without limiting self-care ADL
3	Lesions covering >30% BSA with moderate or severe symptoms; limiting self-care ADL
4+	Life-threatening consequences, urgent intervention needed

irCAE Time to Onset (weeks)					
0-3	4-6	7-9	10-12	13-15	16+
Psoriasisiform rash	Maculopapular rash		Lichenoid eruption	Bullous pemphigoid	
	Pruritus				
SJS					
TEN					
DRESS					
			Vitiligo-like skin hypopigmentation or depigmentation		Alopecia

Fig 1. Time to onset of immune-related cutaneous adverse events. *DRESS*, Drug reaction with eosinophilia and systemic symptoms; *irCAE*, immune-related cutaneous adverse event; *SJS*, Stevens–Johnson syndrome; *TEN*, toxic epidermal necrolysis.

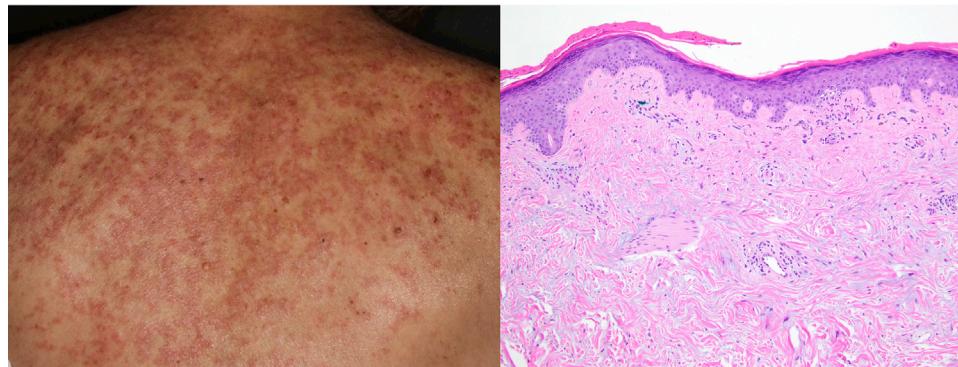


Fig 2. Maculopapular rash, grade 2. Patient receiving pembrolizumab for stage IV lung adenocarcinoma. Histopathology reveals interface dermatitis with increased dermal mucin. There are many features, including interface changes, mucin and increased basement membrane suggestive of connective tissue disease, and also the possibility of a drug reaction resembling connective tissue disease.

(ie, excoriation) may lead to new lesion formation (ie, Koebner phenomenon).⁵²

Histopathologic features include a superficial, perivascular CD4-predominant T cell infiltrate with eosinophils^{25,7,8,43,49,52} with or without a mild epidermal spongiosis, papillary dermal edema, and rare dyskeratotic cells.^{5,7,8,43,52} Management of CPI-related MPR (grade 1-2) includes either superpotent or midpotent topical corticosteroids (TCS) (as the former is not superior to the latter [$P = .07$]),^{2,7,8,49-51,53} and continuation of immunotherapy.^{7,8,14} Grade 3 rash is treated with TCS plus a 4-week tapering course of systemic corticosteroids, starting with prednisone 1 mg/kg/day and increasing the dose up to 2 mg/kg/day if needed.^{2,14,49} In addition, immunotherapy should be withheld until rash is grade 1 or less.^{14,49,51} In grade 4 rash, immunotherapy should be discontinued and methylprednisolone 2 mg/kg/day should be administered (Table II).^{14,49}

Lichenoid/lichen planus–like eruption

The incidence of CPI-related lichenoid or lichen planus (LP)-like eruption is sporadically reported and probably underestimated.^{7,8,54} One study suggested that lichenoid eruptions occur more frequently than MPR, with an incidence of 26 in 103 patients as opposed to 18 in 103 patients.³³ Lichenoid eruption is associated with anti–PD-1/PD-L1 therapy.^{48,53} Clinically, lichenoid eruptions have been reported in 0.5% to 6% of patients.^{48,53,55} The onset of lichenoid eruptions is delayed compared with MPR, with a mean time to onset of 6 to 12 weeks (Fig 1).^{7,8,48,51,56} Lichenoid eruptions present as multiple, discrete, erythematous, violaceous papules and plaques on the chest and back, but may rarely involve the limbs, palmoplantar surfaces, and oral mucosa (Fig 3).^{7,8,14,56,57}

Histopathologic features include a dense superficial dermal band–like lymphocytic infiltrate

Table II. Immune-related cutaneous adverse events: Management and recommendations

CTCAE grade	MPR*	Lichenoid eruption*	Bullous pemphigoid eruption	Psoriasisiform rash	SJS/TEN/DRESS	Pruritus	Vitiligo-like skin hypopigmentation/depigmentation	Alopecia	Mucosal toxicity
1	Moderate- to high-potency TCS twice a day	High-potency TCS twice a day	High-potency TCS twice a day	High-potency TCS twice a day	N/A	High-potency TCS twice a day	Photoprotection	Moderate- to high-potency TCS	TCS, lidocaine
2	Moderate- to high-potency TCS twice a day or systemic corticosteroids (prednisone 0.5-1 mg/kg/day)	High-potency TCS twice a day or systemic corticosteroids (prednisone 0.5-1 mg/kg/day)	Hold CPI until grade 0-1; high-potency TCS twice a day and systemic corticosteroids (prednisone 0.5-1 mg/kg/day)	High-potency TCS twice a day and systemic corticosteroids (prednisone 0.5-1 mg/kg/day)	N/A	High-potency TCS twice a day and GABA analogs	Photoprotection	Moderate- to high-potency TCS	TCS, lidocaine
3+	Hold CPI until grade 0-1; systemic corticosteroid (prednisone 0.5-1 mg/kg/day with dose increase up to 2 mg/kg/day if no improvement) or biologics (infliximab or tocilizumab)	Hold CPI until grade 0-1; systemic corticosteroid (prednisone 0.5-1 mg/kg/day with dose increase up to 2 mg/kg/day if no improvement) or biologics (infliximab or tocilizumab)	Hold CPI until grade 0-1; systemic corticosteroid (prednisone 0.5-1 mg/kg/day with dose increase up to 2 mg/kg/day if no improvement) and rituximab	Hold CPI until grade 0-1; biologics (ustekinumab, guselkumab, infliximab, adalimumab, or apremilast) or retinoids	Discontinue CPI, hospitalization, intravenous corticosteroid, cyclosporine, and close monitoring	Hold CPI until grade 0-1; oral antihistamines and GABA analogs; and omalizumab or dupilumab	N/A	N/A	Hold CPI until grade 0-1; TCS, lidocaine

The level of evidence for all management recommendations is III-IV. Level IA evidence includes evidence from meta-analysis of randomized controlled trials. Level IB evidence includes evidence from ≥ 1 randomized controlled trial. Level IIA evidence includes evidence from ≥ 1 controlled study without randomization. Level IIB evidence includes evidence from ≥ 1 other type of experimental study. Level III evidence includes evidence from nonexperimental descriptive studies (ie, comparative, correlation, or case-control). Level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

CPI, Checkpoint inhibitor; DRESS, drug reaction with eosinophilia and systemic symptoms; GABA, gamma-aminobutyric acid; irCAE, immune-related cutaneous adverse event; IV, intravenous; MPR, maculopapular rash; NBUVB, narrowband ultraviolet B light; SJS, Stevens-Johnson syndrome; TCS, topical corticosteroids; TEN, toxic epidermal necrolysis.

*For corticosteroid-resistant MPR or lichenoid eruption, preliminary success has been shown with targeted biologic monoclonal antibody therapy (infliximab or omalizumab).

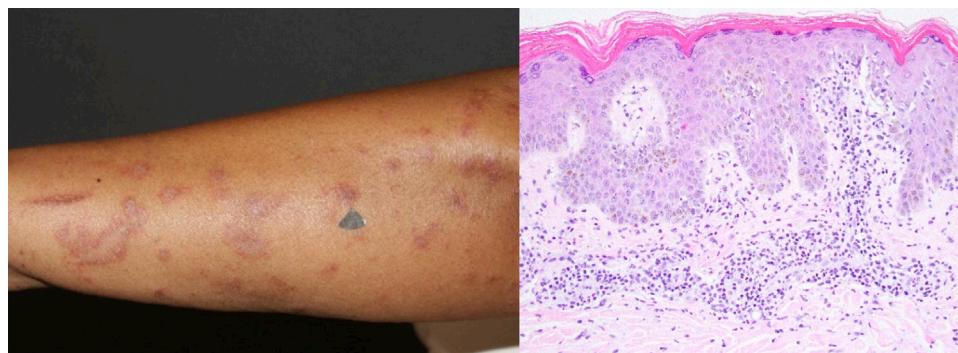


Fig 3. Lichenoid eruption, grade 2. Patient receiving atezolizumab for multifocal muscle invasive bladder carcinoma. Histopathology reveals interface and perivascular lymphocytic dermatitis with rare eosinophils and evidence of minor vascular damage, consistent with a reaction to treatment.

with vacuolar degeneration and scattered apoptotic keratinocytes in the basal layer of the epidermis; occasional eosinophils, parakeratosis, and slight spongiosis may be present.^{7,8,56} Compared with idiopathic LP, CPI-related lichenoid eruptions have an increased abundance of CD163⁺ cells, indicating a macrophage-monocyte lineage.^{51,58,59} These lesions are managed with high-potency TCS without CPI dose interruption, but may require systemic corticosteroids and CPI treatment cessation in high-grade toxicity (Table II).^{7,8,51,56} Alternative treatment options for high-grade toxicity include phototherapy and acitretin.⁸

Bullous pemphigoid eruption

Both lichenoid and bullous pemphigoid (BP) eruptions are associated with PD-1/PD-L1 inhibitors and primary tumor types including melanoma, non-small cell lung carcinoma, urothelial carcinoma, and head and neck squamous cell carcinoma.^{48,53} More than twenty cases of BP eruptions with PD-1/PD-L1 inhibitor therapy have been reported.⁶⁰ Compared with other irCAEs, BP eruptions have a delayed mean onset of 14 weeks after treatment initiation (Fig 1)⁴⁸ and present with a prodromal nonbullous phase of pruritus followed by the development of generalized or localized tense blisters filled with serous or hemorrhagic fluid (Fig 4); the oral mucosa is involved in 10% to 30% of cases.^{61,62} A high suspicion for BP eruptions should be maintained when patients with pruritus or rash are refractory to TCS.⁶⁰ Distribution is mostly typified by involvement of the trunk and extremities.^{48,63}

Pathologic autoantibody production has been identified in patients with CPI-related BP eruptions, and therefore a humoral component to its development is hypothesized because of T cell activation. Serologic testing by enzyme-linked immunosorbent assay for circulating antibodies against the basement membrane

components BP180 and BP230 (expressed in melanoma, basement membrane of the skin, and non–small cell lung carcinomas) is helpful in confirming the diagnosis, correlating with disease severity, and monitoring treatment response.⁶³ In addition to serologic testing, the standard diagnostic workup comprises obtaining biopsy specimens of lesional skin and normal-appearing perilesional tissue for routine dermatopathologic evaluation and direct immunofluorescence (DIF), respectively. Histopathologic features include a subepidermal cleft with eosinophilic infiltrate. The presence of linear deposits of immunoglobulin G and complement component C3 at the dermoepidermal junction on DIF is characteristic, although not entirely specific for BP because it is seen in cicatricial pemphigoid and epidermolysis bullosa acquisita; thus, DIF on salt-split skin can be performed to differentiate BP from these entities, showing immunoglobulin G deposition on the blister roof. Indirect immunofluorescence could be performed to test for circulating immunoglobulin G autoantibodies targeting the roof of the blister on salt-split skin.

Although grade 1 BP eruptions may respond to TCS, the addition of systemic corticosteroids in grade 2 and the addition of rituximab in grades 3-4 is often warranted (Table II).^{53,62,64} In contrast to traditional drug-induced BP, CPI-related BP may persist for several months after discontinuation of immunotherapy, consistent with an enduring state of immune activation that contributes to the maintenance of tumor response.⁶³

PRURITUS

Key points

- Pruritus is the second most common irCAE
- CPI-related pruritus may occur with and without cutaneous eruption
- Pruritus can be managed with TCS, oral antihistamines, and oral neuromodulators

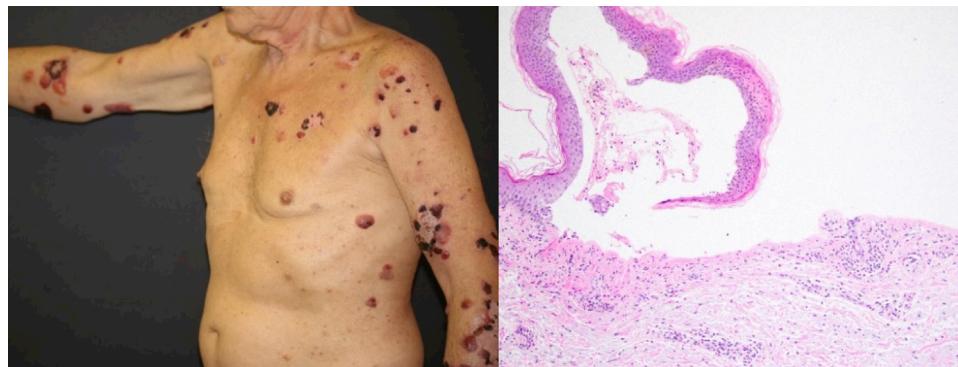


Fig 4. Bullous pemphigoid eruption, grade 3. Patient receiving pembrolizumab for stage IV sarcomatoid lung carcinoma. Histopathology shows a subepidermal blister with a superficial dermal lymphocytic infiltrate and scattered eosinophils.



Fig 5. Skin hypopigmentation/depigmentation, grade 2. Patient receiving pembrolizumab for metastatic melanoma.

Pruritus is second to MPR as the most common irCAE.^{7,8} However, the two often coexist.^{43,51} As with MPR, pruritus is most frequently encountered in patients receiving the anti-CTLA-4 agent ipilimumab.^{7,8} Pruritus also occurs in $\leq 21\%$ of patients treated with anti-PD-1/PD-L1 therapy.^{7,8,44,65} Symptoms are usually grade 1-2 in severity, with high-grade pruritus occurring in $< 1\%$ of cases.^{7,8} Pruritus is usually managed with emollients and oral antihistamines (ie, hydroxyzine), with or without the addition of TCS (Table II).^{7,8,18,44,53} Gamma-aminobutyric acid analogs (ie, pregabalin) have also been used, resulting in moderate to significant improvement in 17 of 17 patients (compared to oral antihistamines, which have demonstrated benefit in 13 of 16 patients).^{51,53} Based on its success in epidermal growth factor receptor inhibitor (EGFRi) and tyrosine kinase inhibitor

(TKI)-related pruritus and uremic pruritus, the neurokinin receptor inhibitor aprepitant could be considered for patients who are refractory to other treatments.⁶⁶ In a trial of 45 patients with EGFRi and TKI-related pruritus, every other day aprepitant dosing for a total of 3 doses yielded a $> 50\%$ reduction in pruritus intensity, with pruritus recurring in only 13% of those treated.^{51,66}

VITILIGO-LIKE SKIN HYPOPIGMENTATION/DEPIGMENTATION

Key points

- The risk of CPI-related skin hypopigmentation/depigmentation among patients with melanoma is 10-fold higher than in the general population
- Vitiligo has been shown to be a positive predictive factor for tumor response to CPIs

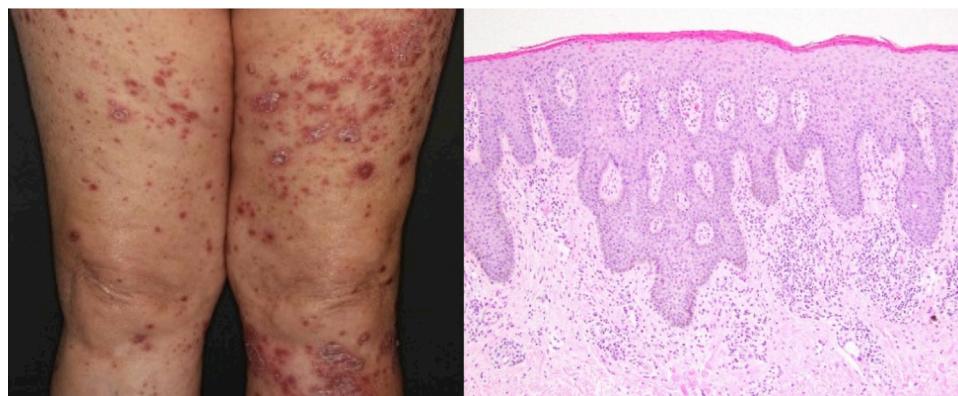


Fig 6. Psoriasisiform rash, grade 3. Patient receiving pembrolizumab for metastatic non–small cell lung cancer. Histopathology reveals epidermal hyperplasia with elongation of rete ridges, overlying parakeratosis and hypogranulosis, and a superficial perivascular lymphocytic infiltrate.

- **The development of vitiligo-like skin hypopigmentation/depigmentation has been associated with greater anticancer benefit from CPIs in patients with melanoma**

Vitiligo is an autoimmune disorder characterized by depigmented macules or patches originating from the loss of functional melanocytes in the epidermis, which can be delineated with a Wood's lamp (Fig 5).^{51,67,68} Vitiligo incidence reaches 11% in anti–CTLA-4 therapy and 25% in anti–PD-1 therapy.^{7,8,51} Vitiligo does not appear until months after CPI initiation and does not seem to be dose related (Fig 1).^{7,8,50} In anti–PD-1 treatment, CD8⁺ cytotoxic T cells are activated against melanoma-associated antigens (MART-1/MelanA, gp100, and tyrosinase-related proteins 1 and 2) shared by normal melanocytes and melanomas.^{7,8,67,69} Immunohistochemical staining done after treatment with anti–CTLA-4 has shown CD4 and MelanA-specific CD8⁺ T cells in close proximity to apoptotic melanocytes, suggesting that anti–CTLA-4 antibodies stimulate an immune response against melanocytes.⁴⁹

Although CPI-related skin hypopigmentation/depigmentation has been observed in 2.0% to 8.3% of melanoma patients by meta-analysis,^{2,7,67–74} its incidence in nonmelanoma patients is not known. Immune-related depigmentation has been reported in 8 patients with non–small cell lung cancer, 3 patients with renal cell carcinoma, 1 patient with hepatocellular carcinoma, 1 patient with cholangiocarcinoma, 1 patient with acute myelogenous leukemia, and 1 patient with soft tissue sarcoma.^{53,71–73,75–100} CPI-related vitiligo appears to have a distinct phenotype, characterized by multiple flecked macules of depigmentation evolving into large plaques on

photoexposed skin.⁷¹ The development of CPI-related vitiligo in patients with melanoma portends a favorable response to therapy, demonstrating the correlation of irAEs with enhanced antitumor response.^{51,67,68} Those who develop vitiligo have 2 to 4 times prolonged progression-free survival and overall survival, respectively.⁶⁸ Vitiligo-like skin hypopigmentation/depigmentation does not resolve after immunotherapy cessation^{7,8,51} and does not require specific treatment aside from photoprotective measures and camouflaging to limit its psychosocial impact (Table II).^{7,8}

OTHER CUTANEOUS ERUPTIONS

Key points

- **Psoriasisiform rash has been reported after the use of PD-1/PD-L1 inhibitors**
- **Although severe cutaneous adverse reactions, such as SJS, TEN, and DRESS, have rarely been reported with the use of CPIs, these may be life threatening, and management includes discontinuation of immunotherapy and administration of systemic treatment**

A broad spectrum of CPI-related cutaneous eruptions has been reported, representing the potential for varied autoinflammatory and autoimmune phenomena in the setting of nonspecific immune activation. Psoriasisiform rash, either de novo or reactivated, has been reported after the use of a PD-1/PD-L1 inhibitor for melanoma and the eruption correlates strongly with tumor response.^{53,101–105} Lesions appear after about 3 weeks of treatment (Fig 1) and present as sharply bordered, scaly, erythematous plaques on the trunk and extremities (Fig 6).^{102,103} Skin biopsy



Fig 7. Stevens–Johnson syndrome, grade 4. Patient receiving combination therapy with ipilimumab plus nivolumab for melanoma.

specimens reveal parakeratosis, hypogranulosis, acanthosis with elongation of rete ridges, and a perivascular lymphocytic infiltration.^{102–104} CPIs augment helper T cell 1 as well as helper T cell 17 activity, which produces interleukin-17 and plays a pivotal role in the pathogenesis of psoriasis.^{7,8,101,103} Treatment for CPI-related psoriasiform rash includes high-potency TCS, vitamin D₃ analogues, narrowband ultraviolet B phototherapy; and if lesions persist, retinoids or biologics (Table II).^{7,8,53,102,104}

While severe cutaneous adverse reactions (SCARs) including SJS, TEN, and DRESS have rarely been reported (Fig 7),^{2,7,8,48,49,63,106–108} these reactions are potentially life threatening. However, they are usually reversible upon the discontinuation of immunotherapy and administration of systemic immunomodulatory treatment.^{49,60} The mortality rate is 10% for SJS, 30% for SJS-TEN overlapping, and 50% for TEN.¹⁰⁶ The latency from the start of CPI treatment to the onset of SCAR varies from 1 to 20 weeks (Fig 1).¹⁰⁶ SCARs may manifest as MPR initially and develop clinical symptoms suggestive of a potentially life-threatening skin reaction (eg, blister formation, Nikolsky sign, mucosal ulcerations, fever, or skin pain).^{7,8} Biopsy specimens show full-thickness epidermal necrosis with minimal inflammatory infiltrate. Immunohistochemical studies show increased expression of PD-L1 on both lymphocytes and keratinocytes at the dermoepidermal junction. Although PD-L1 is not usually detectable in skin, the use of anti–PD-1 therapy increases the expression of PD-L1 in keratinocytes, leading to the targeting and apoptosis of cells by activated cytotoxic CD8⁺ T cells.^{106–109} CPI-related skin eruptions share similar gene expression profiles with SCARs, such as the upregulation of major inflammatory chemokines (CXCL9, CXCL10, and CXCL11), cytotoxic mediators (PRF1 and GZMB),

and proapoptotic molecules (FASLG).^{106,110} The management of SCARs includes immunotherapy discontinuation, hospitalization, intravenous corticosteroids, and cyclosporine (Table II).^{2,49,108,109}

HAIR AND MUCOSAL TOXICITIES

Key points

- The most common CPI-related hair toxicity is alopecia, with an incidence of 1% to 2%
- CPI-related alopecia has a phenotype similar to alopecia areata, although cases of telogen effluvium have also been reported
- Xerostomia and lichenoid reactions are the most common oral mucosal toxicities

Hair and mucosal irAEs represent a significant, albeit small, portion of CPI toxicity profiles. The most common hair toxicity of CPI is alopecia areata, with an incidence of 1% to 2%,^{52,111,112} and some cases of telogen effluvium (Fig 8). Evidence shows that PD-L1 is expressed on the hair follicle dermal sheath and PD-1 inhibitors directly induce alopecia areata or universalis through a CD4⁺ and CD8⁺ T cell-mediated immune response.⁵⁸ The onset is within 3 to 6 months (Fig 1) and histopathology is significant for perifollicular lymphocytic inflammation.¹¹¹ Diagnostic workup includes clinical evaluation of the scalp, a hair pull test, obtaining a biopsy specimen of the scalp, and laboratory testing for other causes of alopecia (thyroid dysfunction and deficiencies of zinc, vitamin D, or iron). Treatment includes intralesional triamcinolone and clobetasol foam (Table II). Hair regrowth in the alopecic areas manifesting with poliosis is a well-recognized feature.¹¹¹ Hair depigmentation may also be observed in the context of CPI-related skin hypopigmentation/depigmentation.^{7,8}

[F8-4/C]



Fig 8. Alopecia and telogen effluvium. Patient receiving combination therapy with ipilimumab plus nivolumab for metastatic melanoma.

Although CPI-related mucosal toxicities have not emerged as treatment-limiting AEs in key clinical trials, they nevertheless impact patient quality of life.^{2,50,58,113,114} Nonspecific stomatitis, mucosal inflammation, periodontal disease, and lichenoid reactions have been described with both anti–PD-1 and anti–PD-L1 therapy.^{2,7,8,58,113} The incidence of oral complications with anti–CTLA-4 therapy is not well defined.^{2,113} Periodontal disease represents a chronic infectious/inflammatory condition modulated by T cell dysregulation, resulting in periodontal pocket formation, alveolar bone resorption, and tooth loss.¹¹³ Lichenoid reactions present as reticulated white streaks consistent with Wickham striae and whitish confluent papules, sometimes with plaque-like, ulcerative, atrophic, erythematous lesions. The lesions may affect dorsal or lateral sides of the tongue, the lips, gingivae, hard palate, buccal mucosa, or perianal and vulvar areas. Patients may report pain or soreness, but the lesions can be asymptomatic.^{7,8,14,58} Histologic analysis shows a patchy or florid lichenoid interface lymphocytic infiltrate in the upper lamina propria, composed of an admixture of CD4⁺ and CD8⁺ T cells.⁵⁷ These lesions are reversible and can be treated with TCS and lidocaine in order to maintain immunotherapy dose intensity (Table II).⁵⁸ However, candidiasis should always be kept in the differential diagnosis for these patients who may be treated with corticosteroids for the management of other irAEs.^{2,50,113}

FUTURE DIRECTIONS AND CONCLUSIONS

Key points

- As CPIs become the mainstay of cancer treatment, a better understanding of their irAEs is warranted

- **Management of corticosteroid-resistant CPI treatment-related irCAEs is being actively investigated**

The advent of CPIs has challenged the medical community to redefine the fundamental aspects of melanoma and other solid tumor treatments, including prognostication, monitoring, and toxicity management.⁴² Clinicians and patients must be well-educated regarding irAEs; yet, in the published literature, there is substantial variability in the reporting of these toxicities.⁴² In addition, patients may develop distinct irAEs when transitioned between classes of CPIs.¹⁰⁴ As CPIs transition to the forefront of cancer treatment, standardization of irAE reporting will be vital in promoting safe clinical practice. Traditional cytotoxic chemotherapy toxicity is usually temporally related to drug administration and self-limited in duration. Conversely, CPI-related irAEs may have a delayed and refractory course.⁴² Therefore, consideration should be given to developing a unique toxicity monitoring, grading, and reporting framework specifically designed to tackle the dynamic challenges posed by irAEs.⁴²

A subset of irCAEs appear to be corticosteroid-refractory, persisting or worsening despite CPI discontinuation and systemic corticosteroids. These cases present a management challenge without clear therapeutic recourse. As immunotherapies become the mainstay of metastatic malignancy management, ongoing studies will be critical for understanding the incidence, phenotype, and management of irAEs.^{104,115,116}

REFERENCES

1. Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer*. 2017;5:95.

2. Inno A, Metro G, Bironzo P, et al. Pathogenesis, clinical manifestations and management of immune checkpoint inhibitors toxicity. *Tumori*. 2017;103:405-421.
3. Shoushtari AN, Friedman CF, Navid-Azarbaijani P, et al. Measuring toxic effects and time to treatment failure for nivolumab plus ipilimumab in melanoma. *JAMA Oncol*. 2018;4:98-101.
4. Wang DY, Salem JE, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. *JAMA Oncol*. 2018;4:1721-1728.
5. Lacouture ME, Wolchok JD, Yosipovitch G, Kahler KC, Busam KJ, Hauschild A. Ipilimumab in patients with cancer and the management of dermatologic adverse events. *J Am Acad Dermatol*. 2014;71:161-169.
6. Weber JS, Dummer R, de Pril V, Lebbe C, Hodi FS. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. *Cancer*. 2013;119:1675-1682.
7. Sibaud V, Meyer N, Lamant L, Vigarios E, Mazieres J, Delord JP. Dermatologic complications of anti-PD-1/PD-L1 immune checkpoint antibodies. *Curr Opin Oncol*. 2016;28:254-263.
8. Sibaud V. Dermatologic reactions to immune checkpoint inhibitors: skin toxicities and immunotherapy. *Am J Clin Dermatol*. 2018;19:345-361.
9. Eigentler TK, Hassel JC, Berking C, et al. Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. *Cancer Treat Rev*. 2016;45:7-18.
10. Champiat S, Lambotte O, Barreau E, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. *Ann Oncol*. 2016;27:559-574.
11. Habre M, Habre SB, Kourie HR. Dermatologic adverse events of checkpoint inhibitors: what an oncologist should know. *Immunotherapy*. 2016;8:1437-1446.
12. Sosa A, Lopez Cadena E, Simon Olive C, Karachaliou N, Rosell R. Clinical assessment of immune-related adverse events. *Ther Adv Med Oncol*. 2018;10:1758835918764628.
13. Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev*. 2016;44:51-60.
14. Collins LK, Chapman MS, Carter JB, Samie FH. Cutaneous adverse effects of the immune checkpoint inhibitors. *Curr Probl Cancer*. 2017;41:125-128.
15. Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol*. 2016;13:473-486.
16. Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. *Transl Lung Cancer Res*. 2015;4:560-575.
17. Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G, Weber JS. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. *Clin Cancer Res*. 2016;22:886-894.
18. Attia P, Phan GQ, Makar AV, et al. Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4. *J Clin Oncol*. 2005;23:6043-6053.
19. Lo JA, Fisher DE, Flaherty KT. Prognostic significance of cutaneous adverse events associated with pembrolizumab therapy. *JAMA Oncol*. 2015;1:1340-1341.
20. Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. *Lancet Oncol*. 2010;11:155-164.
21. Ascierto PA, Del Vecchio M, Robert C, et al. Overall survival (OS) and safety results from a phase 3 trial of ipilimumab (IPI) at 3 mg/kg vs 10 mg/kg in patients with metastatic melanoma (MEL). *Ann Oncol*. 2016;27(suppl 6):379-400.
22. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med*. 2018;378:2093-2104.
23. Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. *Lancet Oncol*. 2017;18:31-41.
24. Judd J, Zibelman M, Handorf E, et al. Immune-related adverse events as a biomarker in non-melanoma patients treated with programmed cell death 1 inhibitors. *Oncologist*. 2017;22:1232-1237.
25. Sznojol M, Ferrucci PF, Hogg D, et al. Pooled analysis safety profile of nivolumab and ipilimumab combination therapy in patients with advanced melanoma. *J Clin Oncol*. 2017;35:3815-3822.
26. Weber JS, Hodi FS, Wolchok JD, et al. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. *J Clin Oncol*. 2017;35:785-792.
27. Grangeon M, Tomasini P, Chaleat S, et al. Association between immune-related adverse events and efficacy of immune checkpoint inhibitors in non-small-cell lung cancer. *Clin Lung Cancer*. 2019;20:201-207.
28. Cousin S, Italiano A. Molecular pathways: immune checkpoint antibodies and their toxicities. *Clin Cancer Res*. 2016;22:4550-4555.
29. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. *JAMA Oncol*. 2016;2:1346-1353.
30. Cortellini A, Buti S, Agostinelli V, Bersanelli M. A systematic review on the emerging association between the occurrence of immune-related adverse events and clinical outcomes with checkpoint inhibitors in advanced cancer patients. *Semin Oncol*. 2019;46:362-371.
31. Das S, Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. *J Immunother Cancer*. 2019;7:306.
32. Minkis K, Garden BC, Wu S, Pulitzer MP, Lacouture ME. The risk of rash associated with ipilimumab in patients with cancer: a systematic review of the literature and meta-analysis. *J Am Acad Dermatol*. 2013;69:e121-e128.
33. Coleman E, Ko C, Dai F, Tomayko MM, Kluger H, Leventhal JS. Inflammatory eruptions associated with immune checkpoint inhibitor therapy: a single-institution retrospective analysis with stratification of reactions by toxicity and implications for management. *J Am Acad Dermatol*. 2019;80:990-997.
34. Kumar V, Chaudhary N, Garg M, Floudas CS, Soni P, Chandra AB. Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. *Front Pharmacol*. 2017;8:49.
35. Ricciuti B, Dahlberg SE, Adeni A, Sholl LM, Nishino M, Awad MM. Immune checkpoint inhibitor outcomes for patients with non-small-cell lung cancer receiving baseline corticosteroids for palliative versus nonpalliative indications. *J Clin Oncol*. 2019;37:1927-1934.
36. Faje AT, Lawrence D, Flaherty K, et al. High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma. *Cancer*. 2018;124:3706-3714.
37. Della Corte CM, Morgillo F. Early use of steroids affects immune cells and impairs immunotherapy efficacy. *ESMO Open*. 2019;4:e000477.
38. Arbour KC, Mezquita L, Long N, et al. Impact of baseline steroids on efficacy of programmed cell death-1 and programmed

- death-ligand 1 blockade in patients with non-small-cell lung cancer. *J Clin Oncol.* 2018;36:2872-2878.
39. Horvat TZ, Adel NG, Dang TO, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. *J Clin Oncol.* 2015;33:3193-3198.
 40. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur J Cancer.* 2016;54:139-148.
 41. Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. *Ann Oncol.* 2017;28:2377-2385.
 42. Levine O, Devji T, Xie F. A new frontier in treatment of advanced melanoma: redefining clinical management in the era of immune checkpoint inhibitors. *Hum Vaccin Immunother.* 2017;13:1765-1767.
 43. Phan GQ, Yang JC, Sherry RM, et al. Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. *Proc Natl Acad Sci U S A.* 2003;100:8372-8377.
 44. Sanlorenzo M, Vujic I, Daud A, et al. Pembrolizumab cutaneous adverse events and their association with disease progression. *JAMA Dermatol.* 2015;151:1206-1212.
 45. Liu J, Blake SJ, Harjunpaa H, et al. Assessing immune-related adverse events of efficacious combination immunotherapies in preclinical models of cancer. *Cancer Res.* 2016;76:5288-5301.
 46. Oh DY, Cham J, Zhang L, et al. Immune toxicities elicited by CTLA-4 blockade in cancer patients are associated with early diversification of the T-cell repertoire. *Cancer Res.* 2017;77:1322-1330.
 47. Santini FC, Rizvi H, Plodkowski AJ, et al. Safety and efficacy of re-treating with immunotherapy after immune-related adverse events in patients with NSCLC. *Cancer Immunol Res.* 2018;6:1093-1099.
 48. Curry JL, Tetzlaff MT, Nagarajan P, et al. Diverse types of dermatologic toxicities from immune checkpoint blockade therapy. *J Cutan Pathol.* 2017;44:158-176.
 49. Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol.* 2012;30:2691-2697.
 50. Postow MA. Managing immune checkpoint-blocking antibody side effects. *Am Soc Clin Oncol Educ Book.* 2015;76-83.
 51. de Golian E, Kwong BY, Swetter SM, Pugliese SB. Cutaneous complications of targeted melanoma therapy. *Curr Treat Options Oncol.* 2016;17:57.
 52. Jaber SH, Cowen EW, Haworth LR, et al. Skin reactions in a subset of patients with stage IV melanoma treated with anti-cytotoxic T-lymphocyte antigen 4 monoclonal antibody as a single agent. *Arch Dermatol.* 2006;142:166-172.
 53. Phillips GS, Wu J, Hellmann MD, et al. Treatment outcomes of immune-related cutaneous adverse events. *J Clin Oncol.* 2019;37:2746-2758.
 54. Min Lee CK, Li S, Tran DC, et al. Characterization of dermatitis after PD-1/PD-L1 inhibitor therapy and association with multiple oncologic outcomes: a retrospective case-control study. *J Am Acad Dermatol.* 2018;79:1047-1052.
 55. Kaunitz GJ, Loss M, Rizvi H, et al. Cutaneous eruptions in patients receiving immune checkpoint blockade: clinicopathologic analysis of the nonlichenoid histologic pattern. *Am J Surg Pathol.* 2017;41:1381-1389.
 56. Tetzlaff MT, Nagarajan P, Chon S, et al. Lichenoid dermatologic toxicity from immune checkpoint blockade therapy: a detailed examination of the clinicopathologic features. *Am J Dermatopathol.* 2017;39:121-129.
 57. Shi VJ, Rodic N, Gettinger S, et al. Clinical and histologic features of lichenoid mucocutaneous eruptions due to anti-programmed cell death 1 and anti-programmed cell death ligand 1 immunotherapy. *JAMA Dermatol.* 2016;152:1128-1136.
 58. Lacouture M, Sibaud V. Toxic side effects of targeted therapies and immunotherapies affecting the skin, oral mucosa, hair, and nails. *Am J Clin Dermatol.* 2018;19(suppl 1):31-39.
 59. Schaberg KB, Novoa RA, Wakelee HA, et al. Immunohistochemical analysis of lichenoid reactions in patients treated with anti-PD-L1 and anti-PD-1 therapy. *J Cutan Pathol.* 2016;43:339-346.
 60. Lopez AT, Geskin L. A case of nivolumab-induced bullous pemphigoid: review of dermatologic toxicity associated with programmed cell death protein-1/programmed death ligand-1 inhibitors and recommendations for diagnosis and management. *Oncologist.* 2018;23:1119-1126.
 61. Lopez AT, Khanna T, Antonov N, Audrey-Bayan C, Geskin L. A review of bullous pemphigoid associated with PD-1 and PD-L1 inhibitors. *Int J Dermatol.* 2018;57:664-669.
 62. Siegel J, Totonych M, Damsky W, et al. Bullous disorders associated with anti-PD-1 and anti-PD-L1 therapy: a retrospective analysis evaluating the clinical and histopathologic features, frequency, and impact on cancer therapy. *J Am Acad Dermatol.* 2018;79:1081-1088.
 63. Naidoo J, Schindler K, Querfeld C, et al. Autoimmune bullous skin disorders with immune checkpoint inhibitors targeting PD-1 and PD-L1. *Cancer Immunol Res.* 2016;4:383-389.
 64. Sowerby L, Dewan AK, Granter S, Gandhi L, LeBoeuf NR. Rituximab treatment of nivolumab-induced bullous pemphigoid. *JAMA Dermatol.* 2017;153:603-605.
 65. Phillips GS, Freites-Martinez A, Wu J, et al. Clinical characterization of immunotherapy-related pruritus among patients seen in 2 oncodermatology clinics. *JAMA Dermatol.* 2019;155:249-251.
 66. Santini D, Vincenzi B, Guida FM, et al. Aprepitant for management of severe pruritus related to biological cancer treatments: a pilot study. *Lancet Oncol.* 2012;13:1020-1024.
 67. Hua C, Boussemart L, Mateus C, et al. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. *JAMA Dermatol.* 2016;152:45-51.
 68. Teulings HE, Limpens J, Jansen SN, et al. Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. *J Clin Oncol.* 2015;33:773-781.
 69. Quaglini P, Mareno F, Osella-Abate S, et al. Vitiligo is an independent favourable prognostic factor in stage III and IV metastatic melanoma patients: results from a single-institution hospital-based observational cohort study. *Ann Oncol.* 2010;21:409-414.
 70. Belum VR, Benhuri B, Postow MA, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. *Eur J Cancer.* 2016;60:12-25.
 71. Larsabal M, Marti A, Jacquemin C, et al. Vitiligo-like lesions occurring in patients receiving anti-programmed cell death-1 therapies are clinically and biologically distinct from vitiligo. *J Am Acad Dermatol.* 2017;76:863-870.
 72. Liu RC, Consuegra G, Chou S, Fernandez Penas P. Vitiligo-like depigmentation in oncology patients treated with immunotherapies for nonmelanoma metastatic cancers. *Clin Exp Dermatol.* 2019;44:643-646.

73. Lolli C, Medri M, Ricci M, et al. Vitiligo-like lesions in a patient treated with nivolumab for renal cell carcinoma. *Medicine (Baltimore)*. 2018;97:e13810.
74. Hasan Ali O, Diem S, Markert E, et al. Characterization of nivolumab-associated skin reactions in patients with metastatic non-small cell lung cancer. *Oncimmunology*. 2016;5:e123129.
75. Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol*. 2016;17:883-895.
76. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373:1627-1639.
77. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol*. 2010;28:3167-3175.
78. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078-2092.
79. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372:2018-2028.
80. Goldberg SB, Gettinger SN, Mahajan A, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol*. 2016;17:976-983.
81. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387:1540-1550.
82. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol*. 2016;17:1497-1508.
83. Nishio M, Takahashi T, Yoshioka H, et al. KEYNOTE-025: phase 1b study of pembrolizumab in Japanese patients with previously treated programmed death ligand 1-positive advanced non-small-cell lung cancer. *Cancer Sci*. 2019;110:1012-1020.
84. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379:2040-2051.
85. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823-1833.
86. Rizvi NA, Hellmann MD, Brahmer JR, et al. Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol*. 2016;34:2969-2979.
87. Kosche C, Mohindra N, Choi JN. Vitiligo in a patient undergoing nivolumab treatment for non-small cell lung cancer. *JAAD Case Rep*. 2018;4:1042-1044.
88. Nishino K, Ohe S, Kitamura M, et al. Nivolumab induced vitiligo-like lesions in a patient with metastatic squamous cell carcinoma of the lung. *J Thorac Dis*. 2018;10:E481-E484.
89. Uenami T, Hosono Y, Ishijima M, et al. Vitiligo in a patient with lung adenocarcinoma treated with nivolumab: a case report. *Lung Cancer*. 2017;109:42-44.
90. Yin ES, Totonchy MB, Leventhal JS. Nivolumab-associated vitiligo-like depigmentation in a patient with acute myeloid leukemia: a novel finding. *JAAD Case Rep*. 2017;3:90-92.
91. Zarogoulidis P, Huang H, Tsiodra T, et al. Immunotherapy "shock" with vitiligo due to nivolumab administration as third line therapy in lung adenocarcinoma. *Respir Med Case Rep*. 2017;22:283-286.
92. Zhao ZM, Liu SC, Xu XJ, Zhang ZF, Nie KK, Ji YX. Treatment of skin reaction induced by nivolumab combined with radiotherapy in non-small cell lung cancer: a case report. *Chin Med Sci J*. 2018;33:183-187.
93. Rodriguez-Lomba E, Molina-Lopez I, Suarez-Fernandez R, Baniandres-Rodriguez O. Vitiligo-like lesions and immune checkpoint inhibition therapy: is it truly an adverse event exclusive to patients with melanoma? *Clin Exp Dermatol*. 2018;43:598-599.
94. Salati M, Baldessari C, Calabrese F, et al. Nivolumab-induced impressive response of refractory pulmonary sarcomatoid carcinoma with brain metastasis. *Case Rep Oncol*. 2018;11:615-621.
95. Dumbrava El, Ivan D, Subbiah V. Hypopigmented skin lesions after immunotherapy. *JAMA Oncol*. 2018;4:1118-1119.
96. Atkins MB, Plimack ER, Puzanov I, et al. Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial. *Lancet Oncol*. 2018;19:405-415.
97. Hammers HJ, Plimack ER, Infante JR, et al. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: the CheckMate 016 study. *J Clin Oncol*. 2017;35:3851-3858.
98. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373:1803-1813.
99. Motzer RJ, Rini Bl, McDermott DF, et al. Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. *J Clin Oncol*. 2015;33:1430-1437.
100. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378:1277-1290.
101. Matsumura N, Otsuka M, Kikuchi N, Yamamoto T. Exacerbation of psoriasis during nivolumab therapy for metastatic melanoma. *Acta Derm Venereol*. 2016;96:259-260.
102. Kato Y, Otsuka A, Miyachi Y, Kabashima K. Exacerbation of psoriasis vulgaris during nivolumab for oral mucosal melanoma. *J Eur Acad Dermatol Venereol*. 2016;30:e89-e91.
103. Ohtsuka M, Miura T, Mori T, Ishikawa M, Yamamoto T. Occurrence of psoriasisiform eruption during nivolumab therapy for primary oral mucosal melanoma. *JAMA Dermatol*. 2015;151:797-799.
104. Totonchy MB, Ezaldein HH, Ko CJ, Choi JN. Inverse psoriasisiform eruption during pembrolizumab therapy for metastatic melanoma. *JAMA Dermatol*. 2016;152:590-592.
105. Bonigen J, Raynaud-Donzel C, Hureaux J, et al. Anti-PD1-induced psoriasis: a study of 21 patients. *J Eur Acad Dermatol Venereol*. 2017;31:e254-e257.
106. Chen CB, Wu MY, Ng CY, et al. Severe cutaneous adverse reactions induced by targeted anticancer therapies and immunotherapies. *Cancer Manag Res*. 2018;10:1259-1273.
107. Vivar KL, Deschaine M, Messina J, et al. Epidermal programmed cell death-ligand 1 expression in TEN associated with nivolumab therapy. *J Cutan Pathol*. 2017;44:381-384.
108. Nayar N, Briscoe K, Fernandez Penas P. Toxic epidermal necrolysis-like reaction with severe satellite cell necrosis associated with nivolumab in a patient with ipilimumab refractory metastatic melanoma. *J Immunother*. 2016;39:149-152.

109. Saw S, Lee HY, Ng QS. Pembrolizumab-induced Stevens-Johnson syndrome in non-melanoma patients. *Eur J Cancer*. 2017;81:237-239.
110. Goldinger SM, Steiger P, Meier B, et al. Cytotoxic cutaneous adverse drug reactions during anti-PD-1 therapy. *Clin Cancer Res*. 2016;22:4023-4029.
111. Zarbo A, Belum VR, Sibaud V, et al. Immune-related alopecia (areata and universalis) in cancer patients receiving immune checkpoint inhibitors. *Br J Dermatol*. 2017;176:1649-1652.
112. Guidry J, Brown M, Medina T. PD-1 inhibitor induced alopecia areata. *Dermatol Online J*. 2018;24.
113. Jackson LK, Johnson DB, Sosman JA, Murphy BA, Epstein JB. Oral health in oncology: impact of immunotherapy. *Support Care Cancer*. 2015;23:1-3.
114. Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol*. 2014;32:1020-1030.
115. Perez-Ruiz E, Minute L, Otano I, et al. Prophylactic TNF blockade uncouples efficacy and toxicity in dual CTLA-4 and PD-1 immunotherapy. *Nature*. 2019;569:428-432.
116. Gao L, Yang X, Yi C, Zhu H. Adverse events of concurrent immune checkpoint inhibitors and antiangiogenic agents: a systematic review. *Front Pharmacol*. 2019;10:1173.

Prurigo nodularis



Epidemiology and clinical features

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Learning objectives

After completing this learning activity participants should be able to describe patient populations commonly affected by prurigo nodularis and recognize clinical signs and symptoms of prurigo nodularis, as well as associated co-morbid conditions.

Disclosures

Editors

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Prurigo nodularis (PN) is a chronic inflammatory skin disease characterized by intensely pruritic, hyperkeratotic nodules that favor the extensor surfaces of the extremities and the trunk. In addition to its significant impact on quality of life, many patients with PN are recalcitrant to therapy because there are currently no therapies approved by the US Food and Drug Administration. In the first article of this 2-part continuing medical education series, we describe the broader epidemiology, patient demographics, physical examination findings, and symptoms to aid in the timely recognition and diagnosis of PN. Furthermore, we quantify the burden of comorbidities in PN by discussing the broad spectrum of systemic diseases and mental health conditions that have been associated with this condition. The second article of this 2-part series focuses on the pathogenesis of PN and provides detailed algorithms for comprehensive work-up and management. (J Am Acad Dermatol 2020;83:1559-65.)

Key words: clinical features; comorbidities; epidemiology; itch; physical examination; prurigo nodularis; pruritus; symptoms.

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CLINICAL FEATURES OF PRURIGO NODULARIS

Key points

- Prurigo nodularis is a chronic, pruritic inflammatory skin disease characterized by numerous symmetrically distributed hyperkeratotic nodules most commonly on the extensor surfaces of the extremities and trunk
- Prurigo nodularis is diagnosed clinically, although biopsy specimens of lesional skin can show thickened, hyperplastic dermal nerve fibers with decreased density of intraepidermal nerve fibers

Prurigo nodularis (PN) was first described by Hyde in 1909,¹ who detailed the hyperkeratotic nodules and intractable pruritus experienced by patients with this chronic dermatosis. With no targeted therapies approved by the US Food and Drug Administration available to date and many patients refractory to off-label treatments, PN exerts a significant burden on quality of life.²⁻⁴ Increased rates of mental health conditions including depression and anxiety have been reported in PN, as well as various systemic comorbidities that will be discussed later.^{5,6} Whether these conditions contribute directly to PN or are the result of a shared systemic process that also causes the skin lesions of PN is not known.

The number of nodules in PN can range from several to >100, and they are often grouped and symmetrically distributed on the extensor surfaces of the extremities and trunk (Fig 1). Nodules can affect any area of the body, although patients typically display the “butterfly sign” where skin on the upper aspect of the back is spared.⁷ Most lesions of PN measure between several millimeters up to 2 cm in diameter. Accompanying excoriation and crusting are common secondary signs of an intractable itch-scratch cycle, with pruritus so severe in some patients that bleeding can also result (Fig 2).⁸ While the skin between nodules is often normal, it can also be dry, lichenified, or show signs of postinflammatory pigmentary changes.⁹ Pruritus is a necessary feature in PN, although some patients may also have burning or stinging pain.¹⁰

To date, PN remains a clinical diagnosis.^{4,7} Though not necessary for diagnosis, skin biopsy specimens of nodules in PN often show thickened, hyperplastic dermal nerve fibers along with decreased density of intraepidermal nerve fibers.^{3,9} In addition, PN has also been associated with peripheral neuropathies in an epidemiologic study.¹¹ However, recent studies suggest that intraepidermal structural alterations may be the result of mechanical damage from chronic scratching.¹² Updates in the literature regarding the pathogenesis of PN will be

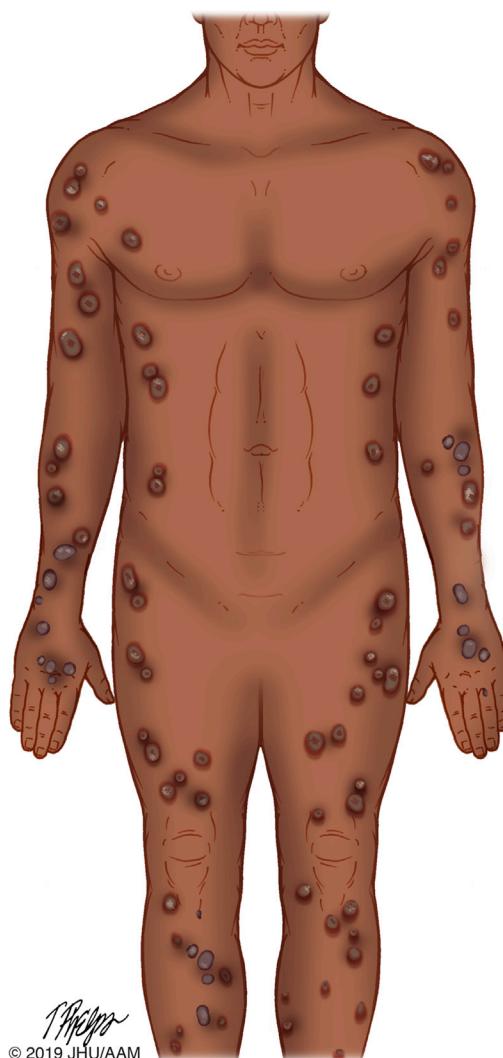


Fig 1. Prurigo nodularis clinical presentation. Figure courtesy of Tim Phelps © 2019 JHU AAM, Department of Art as Applied to Medicine, The Johns Hopkins University School of Medicine.

discussed in the second article in this continuing medical education series.

PATIENT DEMOGRAPHICS AND EPIDEMIOLOGY

Key points

- Prurigo nodularis most commonly affects middle-aged adults and tends to be diagnosed more frequently in females compared with males
- Patients with skin of color, including African Americans, are also at increased risk

Prevalence

PN is a relatively rare condition, with an estimated prevalence of 72 per 100,000 individuals in an epidemiologic study of US adults 18 to 64 years of



Fig 2. Clinical photograph of prurigo nodularis. Intense itching experienced by patients can perpetuate the chronic itch–scratch cycle and lead to bleeding from excoriations.

age who have health care insurance.¹³ Given the variability in the coding of PN in medical claims data, this figure may be a conservative estimate. More research is needed quantify the prevalence of PN in the pediatric population and in adults ≥ 65 years of age.

Age

The mean and median ages of patients with PN ($N = 7095$) identified in the epidemiologic study were 50.9 and 54 years, respectively.¹³ A separate study conducted at a single institution in the United States found that among 909 patients with PN the relative majority was between 51 and 65 years of age.¹⁴ Analysis of the National Inpatient Sample 2016 dataset found that the mean age of patients hospitalized with PN was 55.2 years.¹⁵ Although PN is a condition that most commonly affects middle-aged adults in the fifth and sixth decades of life, small case series have also reported PN in pediatric patients and in older adults.^{16,17}

Gender

PN was first characterized in a cohort of exclusively female patients in the early 20th century.¹ While clinical experience since then has shown that PN affects both genders, there is some evidence that PN is slightly more common in females. In an epidemiologic study of 7095 adult patients with PN in the United States, 53.1% were female while 46.9% were male.¹³ In addition, there may also be differences in the gender distribution of PN by race. A single-center study found that 54.6% of African American patients with PN were female compared with 50.5% of whites with PN and 41.9% of Asians with PN.¹⁴ Further research is needed to elucidate any gender differences in PN and how race may serve as an effect modifier.

Race

Both single-institution and national database research suggests that PN is more common in patients with skin of color. Boozalis et al¹⁴ reported a 3.4-fold increased odds (95% confidence interval [CI] 2.9–3.9, $P < .001$) of PN in African Americans compared with whites in the ambulatory and inpatient setting.¹⁴ Analysis of the National Inpatient Sample 2016 data also showed increased odds of patients hospitalized with PN being black (odds ratio [OR] 4.43, $P < .001$), Asian (OR 3.44, $P = .003$), or Hispanic (OR 1.77, $P = .02$) respectively, compared with being white.¹⁵ In addition to being at higher risk for PN, patients with atopic dermatitis who are African American can present with more numerous PN lesions compared with other racial groups.¹⁸ Barriers to access and suboptimal care for atopic dermatitis in African American patients may contribute to a higher prevalence of moderate-to-severe atopic dermatitis and increase the risk of concomitant PN in this population.¹⁹ Recognizing the disproportionate burden of PN in patients with skin of color may help mitigate disparities in health outcomes for these patients.

Health care setting

Analysis of patients with PN who were hospitalized in 2016 showed that these patients were more likely to have Medicare (OR 2.81, $P < .001$) or Medicaid (OR 2.24, $P < .001$) compared with private insurance.¹⁵ Furthermore, patients with PN were more likely to receive care at teaching hospitals (OR 2.60, $P < .001$) compared with nonteaching hospitals.

Other demographic variables

In an analysis of insurance claims data from 2016–2017, regional distribution (eg, Northeast, North Central, South, and West) and industry of employment of patients with PN were similar to age- and sex-matched control subjects.¹³

ASSOCIATED COMORBID CONDITIONS

Key points

- Prurigo nodularis is associated with increased rates of mental health, endocrine, cardiovascular, and renal disorders, as well as HIV and malignancy
- The burden of systemic comorbidities in prurigo nodularis often exceeds that of other inflammatory skin disorders (ie, atopic dermatitis or psoriasis)

A variety of comorbidities associated with PN have been identified through case series and

epidemiologic studies. Knowledge of associated comorbidities can help guide the provider in the comprehensive work-up and management of patients with PN.

Mental health

PN is associated with an increased rate of psychiatric conditions, including anxiety and depression.²⁰ A Danish study of 877 patients with PN identified from the national registry demonstrated increased odds of depression (adjusted OR 2.82 [95% CI 2.14-3.72]) and anxiety (adjusted OR 2.06 [95% CI 1.23-3.44]) compared with age- and sex-matched control subjects.⁵ The depression and anxiety experienced by patients with PN are often severe enough to warrant pharmaceutical intervention, with increased use of both antidepressants (adjusted OR 2.60 [95% CI 2.24-3.01]) and anxiolytics (adjusted OR 4.64 [95% CI 3.97-5.43]) in PN compared with matched control subjects. No statistically significant difference in the rate of completed suicides was seen in patients with PN compared with control subjects.

Corroborating the Danish study, an epidemiologic study using health care claims within the United States of 7095 adults with PN showed increased rates of mood (OR 2.24 [95% CI 2.05-2.46]) and anxiety (OR 1.93 [95% CI 1.78-2.09]) disorders compared with age- and sex-matched control subjects.¹³ Furthermore, odds of mood and anxiety disorders were also increased in patients with PN compared with those with other inflammatory skin disorders (ie, atopic dermatitis and psoriasis, respectively).

While several studies have examined anxiety and depression in patients with PN, fewer studies have examined other mental health disorders in patients with PN. However, a large US epidemiologic study also found significantly increased odds of eating disorders, self-harm, attention-deficit/hyperactivity disorder, and schizophrenia in patients with PN compared with age- and sex-matched control subjects.¹³ Many of these mental health conditions (eg, psychotic, mood, and substance use disorders) have also been reported in lichen simplex chronicus, a condition similarly characterized by intense pruritus and scratching.²¹ One study of patients with PN/lichen simplex chronicus using the National Inpatient Sample database found increased rates of hospitalization for mental health concerns as well as longer inpatient stays in this population.²¹ Given the scarcity of clinical data confirming these epidemiologic associations, more research is needed to quantify the full burden of mental health conditions in the PN population. Whether mental health conditions contribute to disease pathogenesis in PN or

become exacerbated by chronic symptoms of intense refractory pruritus also deserve further study.²²

Infectious

PN has been associated with multiple infectious agents, among which HIV has been particularly well-studied.²³⁻²⁶ Although patients with HIV are affected by a variety of chronic pruritic dermatoses, PN in particular has been associated with severe itch and significantly lower quality of life in this population.²³ In a US-based study, patients with PN had 2.68 higher odds (95% CI 1.66-4.33) of HIV infection compared with age- and sex-matched control subjects. In areas with high endemic levels of HIV infection, such as French Guyana, PN has also been noted to have a high positive predictive value of 72% for poorly controlled HIV and advanced immunosuppression (ie, CD4 count <200 cells/mm³).^{23,24} Interestingly, lesions of PN in HIV-infected individuals may be responsive to treatment of HIV with antiretroviral therapy (ie, raltegravir).^{26,27} The successful use of immunomodulatory agents such as thalidomide for treatment of patients with PN both with and without HIV further suggests the important role of the immune response in PN.²⁸ In addition, thalidomide's established anxiolytic properties may augment its efficacy for treatment of PN given the significant burden of mental health comorbidities experienced by these patients.²⁹

Apart from HIV, PN has also been associated with other viral infections, including hepatitis C in clinical case series.³⁰⁻³² Although the relationship between hepatitis C infection and PN has yet to be demonstrated on a larger epidemiologic level, it has been hypothesized that immunologic dysregulation and circulating immune complexes in the context of persistent hepatitis C virus infection may also be implicated in the pathogenesis of PN.^{31,32}

Autoimmune and autoinflammatory

Patients with PN have been reported to have increased rates of celiac disease and thyroid disease (eg, Hashimoto thyroiditis).³³⁻³⁵ An epidemiologic study from the United States corroborated an increased odds of celiac disease in patients with PN compared with control subjects (OR 2.70 [95% CI 1.43-5.08]) but also implicated other conditions, including inflammatory bowel diseases and type 1 diabetes mellitus.¹³ Patients with PN had an increased odds of Crohn's disease (OR 2.40 [95% CI 1.51-3.81]), ulcerative colitis (OR 1.64 [95% CI 1.13-2.37]), and type 1 diabetes mellitus (OR 2.23 [95% CI 1.72-2.90]). Given the hypothesized influence of the immune response in PN pathogenesis discussed earlier in the infectious comorbidity section, more

research is needed to understand the link between autoimmune/autoinflammatory processes and PN.

Dermatologic and allergic

The presence of other dermatologic diseases is common in PN, with the majority of patients with PN also affected by another skin condition.^{17,36} Among dermatologic conditions associated with PN, atopic dermatitis has been the most widely reported in both case series and epidemiologic studies.^{2,14,18} The prevalence of atopic dermatitis in patients with PN has been increased compared with control subjects, with evidence that patients with PN may also be more likely to have an atopic disposition.^{2,37} In line with this hypothesis, a large-scale epidemiologic study in the United States also found increased odds of allergic comorbidities including asthma and urticaria in patients with PN compared with age- and sex-matched controls.¹³

In addition to atopic dermatitis, other dermatologic conditions have also been associated with PN. One epidemiologic study demonstrated over 4 times increased odds of psoriasis and over 70 times increased odds of neurotic excoriations in patients with PN compared with matched control subjects.¹³ Case reports and series have also highlighted other skin diseases associated with PN, including keratoacanthomas, bullous pemphigoid, and linear immunoglobulin A disease.³⁸⁻⁴¹

Malignancies

PN has also been documented arising in association with cancer, most notably hematologic malignancies such as non-Hodgkin and Hodgkin lymphoma.⁴²⁻⁴⁴ Not only can PN be the presenting symptom of lymphoma, treatment of the underlying lymphoma can lead to improvement or resolution of PN lesions in some patients.^{42,43} Compared with control subjects, patients with PN had a 2-5 times increased odds of non-Hodgkin lymphoma according to 2 US-based epidemiologic studies.^{13,45} In addition, PN has also been linked to primary cutaneous lymphoma, mycosis fungoides, and multiple myeloma.^{45,46}

With regard to solid tumors, patients with PN may have increased odds of some cancers such as those of the gastrointestinal tract.^{45,47} However, additional research is needed to verify these associations in large, multi-institutional studies.

Endocrine

Endocrine and metabolic dysfunction are common in patients with PN, affecting over half of patients with PN in some cohorts.^{2,48} The association of PN with type 1 and 2 diabetes mellitus has

been particularly notable.^{2,14,18,48} Compared with matched control subjects, patients with PN had a 2.23 times increased odds (95% CI 1.72-2.90) of type 1 diabetes mellitus and a 1.42 times increased odds (95% CI 1.30-1.55) of type 2 diabetes mellitus.¹³ In addition, increased odds of hypertension, hyperlipidemia, and obesity have been shown in patients with PN relative to control subjects from the general population.^{13,14} It has been hypothesized that pruritus caused by underlying metabolic dysregulation may contribute to the development of PN, although this process is still not well understood.⁴⁸

Other systemic diseases

Finally, PN has been also been associated with additional systemic diseases that involve various organ systems including renal, hematologic, pulmonary, and cardiovascular.

The association of PN with kidney dysfunction, especially end-stage renal disease, is consistent throughout the published literature.⁴⁹⁻⁵¹ Although less common than anemia in terms of absolute prevalence, chronic kidney disease was found to be increased in patients with PN in 2 separate epidemiologic studies conducted in the United States.^{13,14} Compared with age- and sex-matched control subjects, patients with PN had a 1.85 times increased odds of chronic kidney disease (95% CI 1.52-2.25) and a 4.88 times increased odds of requiring dialysis (95% CI 2.40-9.92).¹³ Increased pruritus experienced by patients with chronic kidney disease caused by increased systemic inflammation, metabolic/electrolyte dysregulation, and neuropathic abnormalities may increase the risk of PN in this population.^{52,53}

Anemia, most commonly iron deficiency anemia, has been reported in both case reports and small case series of patients with PN.^{54,55} In the latter, the reported prevalence of anemia in patients with PN has been as high as 27.5%.^{17,36} However, a more recent epidemiologic study has not reported a statistically significant odds of anemia in PN compared with matched control subjects (OR 1.37 [95% CI 0.93-2.03]).¹³ Whether anemia is independently linked with PN deserves further investigation because patients with PN are also more likely to have conditions that increase risk of anemia (eg, renal failure, as discussed previously).

In addition, chronic obstructive pulmonary disease may be more common among patients with PN compared with the general population.^{13,14} Although data on tobacco use and smoking in patients with PN are lacking, further investigation into this modifiable risk factor for chronic obstructive pulmonary disease is key.

Finally, there is evidence of increased cardiovascular and cerebrovascular disease in patients with PN. Compared with age- and sex-matched control subjects, patients with PN had roughly double the odds of heart failure, cerebrovascular disease, and coronary heart disease according to one epidemiologic study.¹³ Moreover, the odds of cerebrovascular and coronary heart disease in patients with PN was increased even compared with patients with psoriasis after adjusting for age and sex. This is notable because patients with psoriasis are known to have an increased risk of atherosclerotic conditions (including cerebrovascular and coronary heart disease) that are linked to increased mortality compared with the general population.⁵⁶ The heavy burden of comorbidities in PN even compared to other inflammatory skin disorders such as psoriasis highlights the need for epidemiologic evaluation of mortality in patients with PN.

In conclusion, it is notable that despite the diverse range of comorbidities in PN many of them share an association with chronic pruritus. Although the etiology of PN is still under active investigation, chronic itch in the setting of these conditions (eg, atopic dermatitis, HIV, end-stage renal disease, Hodgkin lymphoma, and others) may promote and perpetuate the itch–scratch cycle that is central to PN. This is supported by data showing an increased prevalence of PN in populations with poor control of pruritic conditions, such as in African Americans who have higher rates of moderate-to-severe atopic dermatitis. Given that not all patients with chronic pruritus will develop PN and that some patients with PN do not have an identifiable underlying cause, the pathogenesis of disease is likely multifactorial and influenced by individual patient characteristics. Key areas of future research include understanding how the severity and duration of chronic pruritus may affect the development of PN and exploring the causal links between PN and associated comorbidities.

REFERENCES

1. Tan WS, Tey HL. Extensive prurigo nodularis: characterization and etiology. *Dermatology*. 2014;228:276-280.
2. Ilking A, Grundmann S, Chatzigeorgakidis E, Phan N, Klein D, Ständer S. Prurigo as a symptom of atopic and non-atopic diseases: aetiological survey in a consecutive cohort of 108 patients. *J Eur Acad Dermatol Venereol*. 2013;27:550-557.
3. Zeidler C, Ständer S. The pathogenesis of prurigo nodularis - "Super-Itch" in exploration. *Eur J Pain*. 2016;20:37-40.
4. Pereira MP, Basta S, Moore J, Ständer S. Prurigo nodularis: a physician survey to evaluate current perceptions of its classification, clinical experience and unmet need. *J Eur Acad Dermatol Venereol*. 2018;32:2224-2229.
5. Jørgensen KM, Egeberg A, Gislason GH, Skov L, Thyssen JP. Anxiety, depression and suicide in patients with prurigo nodularis. *J Eur Acad Dermatol Venereol*. 2017;31:e106-e107.
6. Lotti T, Buggiani G, Prignano F. Prurigo nodularis and lichen simplex chronicus. *Dermatol Ther*. 2008;21:42-46.
7. Fostini AC, Girolomoni G, Tessari G. Prurigo nodularis: an update on etiopathogenesis and therapy. *J Dermatolog Treat*. 2013;24:458-462.
8. Kwatra SG. Breaking the itch–scratch cycle in prurigo nodularis. *N Engl J Med*. 2020;382:757-758.
9. Lee MR, Shumack S. Prurigo nodularis: a review. *Australas J Dermatol*. 2005;46:211-220.
10. Kwon CD, Khanna R, Williams KA, Kwatra MM, Kwatra SG. Diagnostic workup and evaluation of patients with prurigo nodularis. *Medicines (Basel)*. 2019;6:97.
11. Hughes J-DM, Woo TE, Belzberg M, et al. Association between prurigo nodularis and etiologies of peripheral neuropathy: suggesting a role for neural dysregulation in pathogenesis. *Medicines (Basel)*. 2020;7:4.
12. Pereira MP, Pogatzki-Zahn E, Snels C, et al. There is no functional small-fibre neuropathy in prurigo nodularis despite neuroanatomical alterations. *Exp Dermatol*. 2017;26:969-971.
13. Huang AH, Canner JK, Khanna R, Kang S, Kwatra SG. Real-world prevalence of prurigo nodularis and burden of associated diseases. *J Invest Dermatol*. 2020;140:480-483.e4.
14. Boozalis E, Tang O, Patel S, et al. Ethnic differences and comorbidities of 909 prurigo nodularis patients. *J Am Acad Dermatol*. 2018;79:714-719.
15. Whang KA, Kang S, Kwatra SG. Inpatient burden of prurigo nodularis in the United States. *Medicines (Basel)*. 2019;6:88.
16. Amer A, Fischer H. Prurigo nodularis in a 9-year-old girl. *Clin Pediatr (Phila)*. 2009;48:93-95.
17. Payne CMER, Wilkinson JD, McKeef PH, Jureckail W, Black MM. Nodular prurigo — a clinicopathological study of 46 patients. *Br J Dermatol*. 1985;113:431-439.
18. Zeidler C, Tsianakas A, Pereira M, Ständer H, Yosipovitch G, Ständer S. Chronic prurigo of nodular type: a review. *Acta Derm Venereol*. 2018;98:173-179.
19. Silverberg JL. Racial and ethnic disparities in atopic dermatitis. *Curr Dermatol Rep*. 2015;4:44-48.
20. Dazzi C, Erma D, Piccinno R, Veraldi S, Caccialanza M. Psychological factors involved in prurigo nodularis: a pilot study. *J Dermatolog Treat*. 2011;22:211-214.
21. Singam V, Patel KR, Silverberg JL. Association of prurigo nodularis and lichen simplex chronicus with hospitalization for mental health disorders in US adults. *Arch Dermatol Res*. 2020;312:587-593.
22. Schneider G, Hockmann J, Ständer S, Luger TA, Heuft G. Psychological factors in prurigo nodularis in comparison with psoriasis vulgaris: results of a case-control study. *Br J Dermatol*. 2006;154:61-66.
23. Kaushi SB, Cerci FB, Miracle J, et al. Chronic pruritus in HIV-positive patients in the southeastern United States: its prevalence and effect on quality of life. *J Am Acad Dermatol*. 2014;70:659-664.
24. Magand F, Nacher M, Cazorla C, Cambazard F, Sainte D, Couppié P. Predictive values of prurigo nodularis and herpes zoster for HIV infection and immunosuppression requiring HAART in French Guiana. *Trans R Soc Trop Med Hyg*. 2011;105:401-404.
25. Matthews SN, Cockerell CJ. Prurigo nodularis in HIV-infected individuals. *Int J Dermatol*. 1998;37:401-409.
26. Motegi SI, Kato M, Uchiyama A, et al. Persistent prurigo nodularis in HIV-infected patient responsive to antiretroviral therapy with raltegravir. *J Dermatol*. 2014;41:272-273.
27. Unemori P, Leslie KS, Maurer T. Persistent prurigo nodularis responsive to initiation of combination therapy with raltegravir. *Arch Dermatol*. 2010;146:682-683.

28. Sharma D, Kwatra SG. Thalidomide for the treatment of chronic refractory pruritus. *J Am Acad Dermatol.* 2016;74:363-369.
29. Mujagić H, Chabner BA, Mujagić Z. Mechanisms of action and potential therapeutic uses of thalidomide. *Croat Med J.* 2002;43:274-285.
30. Weisshaar E, Ständer S. Prurigo nodularis in hepatitis C infection: result of an occupational disease? *Acta Derm Venereol.* 2012;92:532-533.
31. Neri S, Raciti C, D'Angelo G, Ierna D, Bruno CM. Hyde's prurigo nodularis and chronic HCV hepatitis. *J Hepatol.* 1998;28:161-164.
32. Kanazawa K, Hideo Y, Tsuda F, Murata K, Okamoto H. Association of prurigo with hepatitis C virus infection. *Arch Dermatol.* 1995;131:852-853.
33. Francesco Stefanini G, Resta F, Marsigli L, et al. Prurigo nodularis (Hyde's prurigo) disclosing celiac disease. *Hepato-gastroenterology.* 1999;46:2281-2284.
34. McKenzie A, Stubbing D, Elvy B. Prurigo nodularis and gluten enteropathy. *Br J Dermatol.* 1976;95:89-92.
35. Goodwin P. Nodular prurigo associated with gluten enteropathy. *Proc Roy Soc Med.* 1977;70:140-141.
36. Akarsu S, Ozbagcivan O, Ilknur T, Semiz F, Inci BB, Fetil E. Xerosis cutis and associated co-factors in women with prurigo nodularis. *An Bras Dermatol.* 2018;93:671-679.
37. Tanaka M, Aiba S, Matsumura N, Aoyama H, Tagami H. Prurigo nodularis consists of two distinct forms: early-onset atopic and late-onset non-atopic. *Dermatology.* 1995;190:269-276.
38. Xu Q, Li C, Zhang J, Ling B, Yu H, Yao Z. Generalized eruptive keratoacanthoma with vitiligo followed by the development of prurigo nodularis: a case report and published work review. *J Dermatol.* 2018;45:211-215.
39. Wu TP, Miller K, Cohen DE, Stein JA. Keratoacanthomas arising in association with prurigo nodules in pruritic, actinically damaged skin. *J Am Acad Dermatol.* 2013;69:426-430.
40. Roenigk RK, Dahl MV. Bullous pemphigoid and prurigo nodularis. *J Am Acad Dermatol.* 1986;14:944-947.
41. Torchia D, Caproni M, Del Bianco E, Cozzani E, Ketabchi S, Fabbri P. Linear IgA disease presenting as prurigo nodularis. *Br J Dermatol.* 2006;155:479-480.
42. Schweda K, Hainz M, Loquai C, Grabbe S, Saloga J, Tuettnerberg A. Prurigo nodularis as index symptom of (non-Hodgkin) lymphoma: ultrasound as a helpful diagnostic tool in dermatological disorders of unknown origin. *Int J Dermatol.* 2015;54:462-464.
43. Shelnitz LS, Paller AS. Hodgkin's disease manifesting as prurigo nodularis. *Pediatr Dermatol.* 1990;7:136-139.
44. Rubenstein M, Duvic M. Cutaneous manifestations of Hodgkin's disease. *Int J Dermatol.* 2006;45:251-256.
45. Larson VA, Tang O, Stander S, Miller LS, Kang S, Kwatra SG. Association between prurigo nodularis and malignancy in middle-aged adults. *J Am Acad Dermatol.* 2019;81:1198-1201.
46. Gulin SJ, Ćeović R, Lončarić D, Ilić I, Radman I. Nodular prurigo associated with mycosis fungoides – case report. *Acta Dermatovenerol Croat.* 2015;23:203-207.
47. Funaki M, Ohno T, Dekio S, et al. Prurigo nodularis associated with advanced gastric cancer: report of a case. *J Dermatol.* 1996;23:703-707.
48. Winhoven S, Gawkroger D. Nodular prurigo: metabolic disease are a common association. *Clin Exp Dermatol.* 2007;32:201-226.
49. Kowalski EH, Kneiber D, Valdebran M, Amber KT. Treatment-resistant prurigo nodularis: challenges and solutions. *Clin Cosmet Investig Dermatol.* 2019;12:163-172.
50. Swarna SS, Aziz K, Zubair T, Qadir N, Khan M. Pruritus associated with chronic kidney disease: a comprehensive literature review. *Cureus.* 2019;11:e5256.
51. Shirazian S, Aina O, Park Y, et al. Chronic kidney disease-associated pruritus: impact on quality of life and current management challenges. *Int J Nephrol Renovasc Dis.* 2017;10:11-26.
52. Combs SA, Teixeria JP, Germain MJ. Pruritus in kidney disease. *Semin Nephrol.* 2015;35:383-391.
53. Mettang T. Pruritus in renal disease. In: Carstens E, Akiyama T, eds. *Itch: Mechanisms and Treatment.* Boca Raton, FL: CRC Press/Taylor & Francis; 2014:47-60.
54. Winhoven S, Gawkroger D. Nodular prurigo - a retrospective analysis [abstract]. *J Am Acad Dermatol.* 2005;52(suppl):S2.
55. Lezcano L, Ortiz BDM, Masi MR, Knopfelmacher O, De Lezcano LB. Prurigo nodularis. *Med J Armed Forces India.* 1996;52:258-259.
56. Prodanovich S, Kirsner RS, Kravetz JD, Ma F, Martinez L, Federman DG. Association of psoriasis with coronary artery, cerebrovascular, and peripheral vascular diseases and mortality. *Arch Dermatol.* 2009;145:700-703.

Answers to CME examination

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Prurigo nodularis



Pathogenesis and management

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Learning objectives

After completing this learning activity participants should be able to discuss the pathogenesis of prurigo nodularis and describe current management practices and approaches for treating patients with prurigo nodularis.

Disclosures

Editors

The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Authors

Dr Kwatra is an advisory board member for Pfizer Inc, Regeneron Pharmaceuticals, and Menlo Therapeutics and has received grant funding from Pfizer and Kiniksa Pharmaceuticals. The other authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Planners

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Prurigo nodularis is a chronic skin condition characterized by severely pruritic nodules that cause a profound negative impact on quality of life. The second article in this 2-part continuing medical education series focuses on reviewing the pathogenesis of prurigo nodularis and exploring management algorithms for this condition. In addition, we discuss some emerging and novel therapies for treating prurigo nodularis. The first article in this 2-part series describes the broader epidemiology, patient demographics, physical examination findings, and symptoms to aid in the timely recognition and diagnosis of prurigo nodularis. (*J Am Acad Dermatol* 2020;83:1567-75.)

Key words: antipruritic; clinical features; itch; management; pathogenesis; prurigo nodularis; pruritus; therapeutics.

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PATHOGENESIS OF PRURIGO NODULARIS

Key points

- Immune and neural dysregulation are implicated in the pathogenesis of prurigo nodularis
- Immune cells and neuropeptides play an important role in cutaneous inflammation and altered neural circuitry that drives pruritus associated with prurigo nodularis

Prurigo nodularis (PN) is a chronic, inflammatory skin condition characterized by severely pruritic nodules that cause a profound negative impact on quality of life.¹ The pathogenesis of PN is thought to be a cutaneous reaction pattern caused by vicious cycles of chronic itch followed by repeated scratching.^{1,2} The exact pathogenesis of PN remains unknown. However, previous studies show that significant interaction and dysregulation between immune cells and neuronal circuitry play important roles in the pathogenesis of PN.

Immune dysregulation

Histopathologic studies show dense dermal, interstitial, and perivascular infiltrates in the dermis of PN lesions, primarily consisting of increased numbers of T lymphocytes, mast cells, and eosinophilic granulocytes.^{3,4} Immune cells in the skin generate a robust inflammatory response and intense itch by releasing mediators such as interleukin (IL)-31, tryptase, eosinophil cationic protein, histamine, prostaglandins, and neuropeptides.^{3,4} This immune response is central to the pathogenesis of PN.

Eosinophils play a role in the cutaneous inflammation and pruritus associated with PN. There is an accumulation of eosinophils in the dermis of PN lesional skin. Granules released by eosinophils include neuropeptides and eosinophil cationic protein, eosinophil-derived neurotoxin, eosinophil protein X, and major basic protein.⁵⁻⁷ Eosinophil cationic protein and eosinophil-derived neurotoxin are of particular interest because they have a neurotoxic effect and are both significantly increased in the skin of patients with PN.^{5,6,8}

T cells and their cytokines, particularly IL-31, are also involved in the pathogenesis of PN. Messenger RNA for the T cell–derived cytokine IL-31 is more abundant in PN lesional skin when compared with healthy skin.^{4,9} IL-31 propagates itch via binding to the heterodimeric IL-31A and oncostatin M receptor.^{4,5} This mechanism is supported by transgenic mouse studies showing that IL-31 expression was associated with significant skin inflammation and severe itch, while the use of anti-IL-31 monoclonal antibodies led to a significant reduction in scratch activity.^{5,10,11} Finally, subsets of T_H2 cytokines such

as IL-4 have also been found to be increased in prurigo-like skin lesions.

Neural dysregulation

Multiple studies have investigated the architecture and distribution of nerve fibers in the lesional and nonlesional dermis of patients with PN.⁵ In 1934, Pautrier described neuronal hyperplasia (Pautrier neuroma) within the dermis of a patient with PN.^{4,12} Several studies have verified this by staining for the panneuronal marker protein gene product-9.5 and nerve growth factor receptor within lesional PN skin.⁶ One study showed that the nerve growth factor receptor– and protein gene product–immunoreactive structures in the dermis of PN patients are present at a significantly greater density compared with healthy control subjects. In contrast, the epidermis of patients with PN lack nerve growth factor receptor–immunoreactive nerve fibers and far fewer PGP-9.5⁺ nerve fibers.⁶ Despite this difference in nerve fiber density between the dermis and epidermis, a functional small fiber neuropathy in patients with PN has not been identified.^{4,13} This finding argues against intrinsic neuropathy as the cause of reduced intraepidermal nerve fiber density in patients with PN, which may be secondary to repeated mechanical scratching. However, increased dermal nerve fiber density seen in patients with PN and its association with peripheral neuropathies warrants further investigation.¹⁴

Dysregulation of several neuropeptides, particularly calcitonin gene-related peptide and substance P (SP) have been implicated in the pathogenesis of PN. SP is a neurotransmitter secreted by neurons that binds to the neurokinin-1 receptor in the skin and in the central nervous system.^{3,4} One study found an increased number of SP⁺ nerve fibers and increased expression of SP in dermal PN skin.^{4,5,15} Calcitonin gene-related peptide is another neuropeptide with a similar mechanism to SP that is also upregulated in PN and may contribute to disease pathogenesis. Calcitonin gene-related peptide can be secreted into cutaneous tissue via nerve fibers causing neurogenic inflammation through the regulation of eosinophils and mast cells.^{4,6} CGRP can also affect endorphin levels and cause dysregulated expression of mu and kappa opioid receptors, both of which may contribute to pruritus in PN.

MANAGEMENT OF PRURIGO NODULARIS

Key points

- The diagnostic workup for prurigo nodularis includes a complete blood cell count with differential, liver and renal function tests, and a thorough

review of systems to guide evaluation for associated systemic diseases

- Obtaining a skin biopsy specimen is indicated in subsets of patients
- Treatment for prurigo nodularis is centered on topical, intralesional, and systemic neuroimmune modulatory therapies to break a short-circuited itch-scratch cycle
- There are currently no therapies for prurigo nodularis approved by the US Food and Drug Administration, which leads to highly variable practices in the prescription of off-label therapies and highlights the need for a multimodal approach to therapeutics

History and physical examination

PN is a clinical diagnosis, and therefore a thorough history and physical examination are essential for diagnosis. Patients with PN will endorse intense pruritus present for ≥ 6 weeks that can be constant, intermittent, or paroxysmal in nature, and is sometimes also accompanied by burning or stinging sensations.¹⁶ A complete history should be obtained, including a careful review of medications and supplements. In addition, a thorough history of all medical problems, including psychiatric history, can also be helpful in diagnosing conditions associated with PN.

On physical examination, patients with PN typically display clustered nodules located on ≥ 2 different extensor surfaces and may also involve the trunk. Though many patients with PN may also have associated dermatoses, such as atopic dermatitis, these hyperkeratotic and sometimes excoriated nodules are specific to PN. A more detailed discussion of the clinical features of PN can be found in the first article in this continuing medical education series.

Laboratory workup

As described in the first article in this series, there are several comorbid conditions associated with PN. It is important to identify underlying systemic diseases that may be contributing to PN. Focused laboratory work-up for a systemic etiology is especially important for patients without a history of underlying dermatoses, such as atopic dermatitis.^{16,17} The recommended laboratory work-up for patients with PN includes a complete blood cell count with a differential as well as liver and renal function tests. Additional testing for thyroid function testing, hemoglobin A1c/diabetes screening, HIV serology, and hepatitis B and C serologies is suggested based on the presence of risk factors, review of systems, and clinical examination.^{16,18} Other

laboratory tests to consider based on clinical history and review of systems are serum immunofixation, serum and urine protein electrophoresis, urinalysis, chest radiograph, stool examination for ova and parasites, and iron studies.^{16,17} Patients should also be up to date with age-appropriate malignancy screening. There should be greater concern for underlying associated malignancy in patients with PN with acute rather than chronic onset of pruritus (<1 year).

Additional testing may be warranted for subsets of patients. Although PN is a clinical diagnosis, obtaining a skin biopsy specimen may be indicated for atypical clinical presentations. Skin biopsy procedures, though not routine, can provide useful information in the work-up of PN, particularly when considering primary dermatoses as the cause of PN.^{16,19} On review of the biopsy specimen, the lesions of PN typically display orthohyperkeratosis, irregular epidermal hyperplasia, hypergranulosis, and an increased number of fibroblasts and capillaries.^{16,20} These changes correlate with scratch-induced injury and hyperkeratosis. As discussed earlier, cutaneous nerve studies have shown a decrease in epidermal nerve fiber density and an increase in dermal nerve fiber density within lesional PN skin. When accompanied by urticaria and in the elderly population, direct immunofluorescence studies can identify an underlying autoimmune blistering disorder, such as bullous pemphigoid.^{16,20}

Treatment approaches

PN remains a difficult condition to treat because there are currently no targeted treatments approved by the US Food and Drug Administration (FDA). Therefore, providers often prescribe off-label therapies with a high degree of variability among treatment regimens used.²¹ The overall goal in treating PN is to break the itch-scratch cycle and reduce pruritus to heal nodules.¹ To adequately treat PN, treatment regimens need to address both the neural and immunologic components of the disease. An individualized treatment plan, based on the patient's age, comorbidities, disease severity, and side effect profile of treatments is needed to personalize treatment. This is often best achieved by using a multimodal regimen including systemic and topical therapies.²² Current and emerging therapies for PN are shown in Table I, and a therapeutic ladder is shown in Figure 1.

Topical treatment. Topical therapies for PN that have been examined in randomized clinical trials include corticosteroids, pimecrolimus, and calcipotriol. The limited efficacy of these treatments

Table I. Current and emerging therapies for the treatment of prurigo nodularis

Locally acting agents	Phototherapy	Systemic neuromodulating agents	Systemic immunomodulating agents	Emerging therapies and therapeutic targets
Topical steroids/ flurandrenolide tape	NBUVB (2-3 times/week)	Gabapentin (100- 3600 mg/day)	Methotrexate (15-25 mg/ week)	Anti-IL-31: nemolizumab
Topical anesthetics	PUVA (2-3 times/week)	Pregabalin (75-600 mg/ day)	Cyclosporine (2.5-5 mg/ kg/day)	Anti-OSM beta receptor: KPL-716
Topical calcineurin inhibitors		Aprepitant (80 mg/day)	Mycophenolate mofetil (500-3000 mg/day)	Mu and kappa opioid receptors modulation: nalbuphine
Topical calcipotriene		Naltrexone (25-50 mg/ day)	Azathioprine (50- 150 mg/day)	NK1R inhibitor serlopitant
Topical capsaicin (0.025- 0.3% cream 4-6 times/ day)		Butorphanol (1 mg intranasally every 4 hours as needed)	Dupilumab* (600 mg induction followed by 300 mg every 2 weeks)	
Intralesional corticosteroids (10 mg/mL)		Duloxetine (20-60 mg/ day)		
		Paroxetine (10 mg/day for 3 days followed by maintenance 30- 60 mg/day)		
		Fluvoxamine (25 mg/day for 3 days followed by maintenance 50- 150 mg/day)		
		Thalidomide (50-150 mg/ day)		

NBUVB, Narrowband ultraviolet B light; NK1R, neurokinin-1 receptor; OSM, oncostatin M; PUVA, psoralen plus ultraviolet A light phototherapy.

highlights the need for continued research to develop more targeted topical therapies for PN.

The first-line topical therapy for PN remains high-potency topical corticosteroids. Betamethasone valerate 0.1% tape reduced pruritus and flattened nodules in patients with PN compared with moisturizing itch relief cream alone.²³ Flurandrenolide tape, a medicated occlusive skin barrier that can be occluded to specific nodules while sparing surrounding skin, can also be an effective treatment for patients with PN. Because flurandrenolide tape can be expensive, patients may also be offered alternatives such as high-potency topical steroids under occlusion with an Unna boot. In addition to enhancing the effect of the medication, treatments involving occlusion also act as a physical aversion to scratching the skin. In addition to topical agents, intralesional injections of corticosteroid can be effective in alleviating pruritus and flattening PN lesions. Intralesional injections of triamcinolone acetonide, usually started at 10 mg/mL, can demonstrate clinical improvement in PN.

Topical anesthetics are another alternative anti-pruritic treatment option for patients with chronic pruritus and that can provide modest itch relief in

patients with mild PN. Over the counter 1% pramoxine lotion, lidocaine spray, and compounded topical anesthetic creams may be used.

Other nonsteroid topical agents have also been studied for the treatment of PN, including topical calcineurin inhibitors (ie, pimecrolimus), vitamin D derivatives, and capsaicin. A previous study found that 1% pimecrolimus cream is helpful in treating itch in patients with PN with reductions in visual analog scale from 7.1 to 4.4.²⁴

Finally, capsaicin has been tried in PN to disrupt pain and pruritus via the depletion of neuropeptides in small sensory cutaneous nerve fibers.²⁵ One study of patients with PN showed remission of itching and healing of nodules with topical capsaicin 0.025% to 0.3% 4 to 6 times a day.²⁵ The study also showed depletion of neuropeptides in PN skin after treatment with capsaicin.²⁵ In the authors' experience, capsaicin has limited practical efficacy in PN because of the high frequency of application required, significant associated irritation, and minimal efficacy.

Phototherapy. Ultraviolet light therapy reduces pruritus in many skin conditions, including PN, through its antiinflammatory effects.²⁶ This is a particularly useful option in medically complex

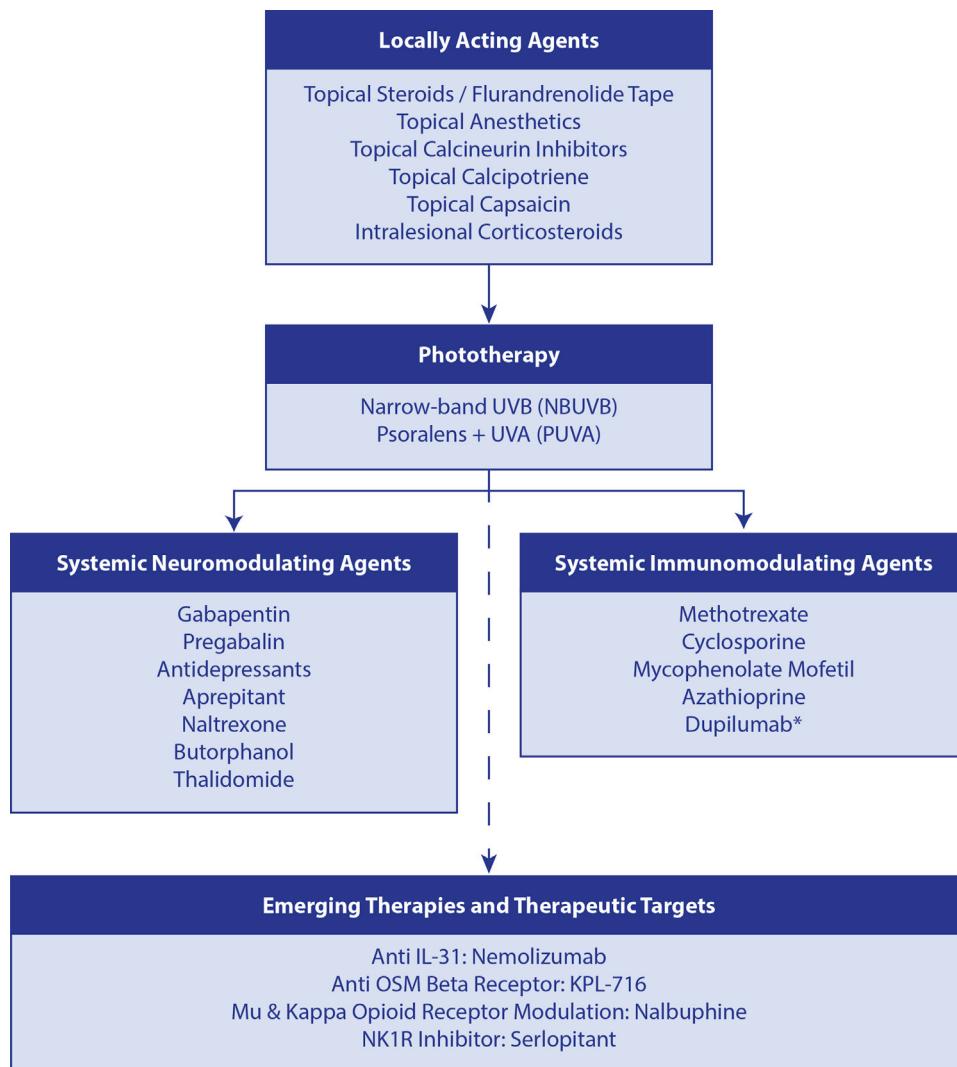


Fig 1. Prurigo nodularis (PN) therapeutic ladder. We recommend a multimodal approach to therapeutics for patients with PN involving topical, intralesional, phototherapy, and systemic agents tailored to patient comorbidities and severity of clinical presentation. Several emerging targeted antipruritic therapeutics are under development for use in PN. *Dupilumab has been approved by the US Food and Drug Administration for the treatment of atopic dermatitis and is undergoing trials for PN with published case reports indicating efficacy in PN. *IL-31*, Interleukin-31; *NK1R*, neurokinin-1 receptor; *OSM*, oncostatin M.

patients whose treatment options may be limited by comorbidities and drug interactions with other medications.²²

Of the available ultraviolet light therapies, narrow-band ultraviolet B light therapy 2 to 3 times weekly is considered to be first-line therapy for patients with PN. Ultraviolet A light, psoralen plus ultraviolet A light phototherapy, and ultraviolet B light have all shown some efficacy in treating PN.²² In addition, the efficacy of a modified Goeckerman regimen for pruritus has also been shown. However, because the Goeckerman regimen consists of daily broadband ultraviolet B light therapy followed by the

application of crude coal tar and topical corticosteroids under occlusion for 4 hours each day, it should be used with caution to minimize carcinogenic side effects.²⁷ Phototherapy along with topical therapy will only be sufficient treatment for a minority of patients with PN. Most patients with PN will require adjunctive systemic therapy as outlined below.

Systemic therapy. Patients with PN usually require treatment with systemic therapies because many patients are refractory to the treatments described above. Systemic options for the treatment of PN include immunosuppressants, gabapentinoids, antidepressants, and mu-opioid receptor

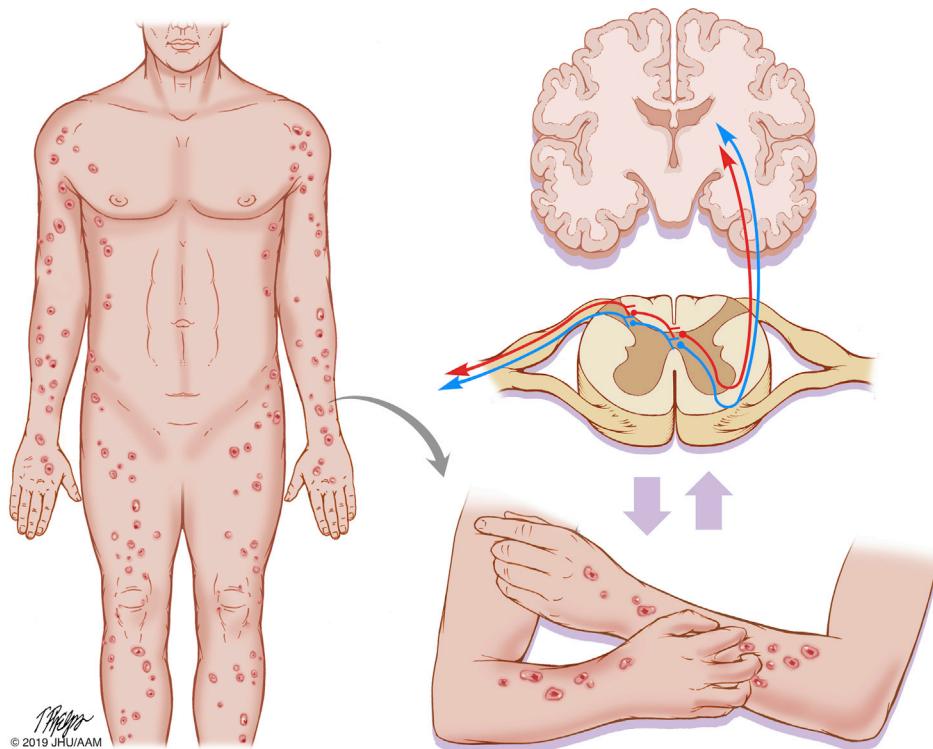


Fig 2. Prurigo nodularis itch neural transmission pathway. The itch transmission pathway is a bidirectional signaling process spanning from cutaneous nerve fibers in the skin to the dorsal root ganglion, spinal cord, and brain. A multimodal approach to therapy targets the itch signaling cascade at multiple points in the itch pathway.

antagonists.^{21,22} PN is a nonhistaminergic itch condition, and therapy with antihistaminergic agents is generally ineffective aside from its sedative properties and not recommended unless a comorbid histamine-mediated condition is suspected.^{22,28}

Given the important role of immune dysregulation in the pathogenesis of PN, systemic immunosuppressants are a commonly used medication class. Immunosuppressants that have been used to treat PN with evidence in retrospective studies include methotrexate and cyclosporine.²⁹ Two retrospective studies of methotrexate as treatment for PN showed significant relief from pruritus and healing of lesions in these patients.^{30,31} Given its favorable side effect profile, methotrexate is commonly used in the Johns Hopkins Itch Clinic as frontline immunosuppressive therapy starting at around 15 to 20 mg weekly along with topical therapy. For more severe cases on presentation, cyclosporine may also be used. Several reports show that cyclosporine 2 to 5 mg/kg/day provided improvement of PN symptoms and resolution of nodules.^{32,33} A drawback to treatment with cyclosporine is its significant side effect profile, requiring patients to have regular monitoring of blood pressure, renal function, hepatic function, and complete blood cell counts.^{32,33}

PN treatment also includes several agents specifically targeting the neural pathogenesis of itch transmission, which spans from neural innervation in the skin to the dorsal root ganglion, traversing through the spinal cord to the brain (Fig 2). Gabapentinoids are commonly prescribed, including gabapentin and pregabalin. These agents are thought to reduce itch via inhibition of calcium signaling.³⁴ Elderly patients are usually started at low doses (100 mg nightly) and gradually titrated up to higher doses given the risk of significant sedation. Younger patients may be started at 300 mg nightly and titrated upwards to ≤ 3600 mg daily (divided into thrice daily dosing). Pregabalin has a similar mechanism of action and is gradually titrated upwards with doses ranging from 75 to 600 mg daily. While these agents may be effective in subsets of patients because higher doses are often needed to reduce itch intensity, sedation often becomes an important side effect and is a top reason for treatment discontinuation.

Another drug class that has shown some efficacy in targeting the neural pathogenesis of itch are neurokinin-1 receptor antagonists, which are believed to reduce itch by blocking SP.^{35,36} One agent in this class, aprepitant, is approved by the FDA for chemotherapy-associated nausea and vomiting.

When used off-label for treatment of chronic pruritus, the dose can vary depending on the underlying disease but has been prescribed at 80 mg daily.^{35,37} An open-label study suggested that aprepitant may be effective in reducing itch associated with PN, but a randomized phase II trial failed to show efficacy of aprepitant in reducing itch severity in PN.³⁷ Similarly, serlopitant is another neurokinin-1 receptor antagonist that had promising phase II data only to fall short of its primary endpoint in 2 phase III trials.³⁸

Thalidomide is another neuroactive medication that can be used for patients with PN who are recalcitrant to treatment, often dosed between 50 and 150 mg daily.³⁹⁻⁴¹ However, it requires use with extreme caution because of its known neurotoxic and teratogenic effects, including an increased risk of peripheral neuropathy and birth defects in pregnant women.³⁹ For these reasons, thalidomide should be reserved for patients who have failed to improve on traditional therapeutic agents.

Imbalances between the mu- and kappa-opioid systems may also play a role in the development of pruritus.⁴² Several studies have examined the efficacy of opioid receptor-modulating drugs as therapies for chronic pruritus, with mixed kappa-opioid agonist/mu-opioid antagonists nalbuphine and butorphanol both showing promise.⁴²⁻⁴⁵ In particular, intranasal butorphanol 1 mg as needed has been used in PN and is also used in the Johns Hopkins Itch Clinic for recalcitrant cases to attempt to break the itch-scratch cycle.⁴² Lastly, the opioid antagonist naltrexone (50 mg) has also shown antipruritic effects in subsets of patients with PN.⁴³

Finally, antidepressants such as paroxetine, fluvoxamine, duloxetine, and amitriptyline can provide mild to moderate relief of pruritus.⁴⁶⁻⁵⁰ Paroxetine (10 mg daily for 3 days followed by maintenance dosing at 20-60 mg daily) or fluvoxamine (25 mg daily for 3 days followed by maintenance dosing at 50-150 mg daily) can reduce itch in patients with PN. Duloxetine 20 to 60 mg daily is an antidepressant approved for neuropathic pain that also may help with treating itch associated with PN.⁴⁷ Finally, several patients with PN responded to amitriptyline in a pilot study with an initial dosage of 60 mg daily for 3 weeks, followed by 30 mg daily for 2 weeks and 10 mg daily for 1 week.

Emerging therapies

New potential targets that are currently under investigation for itch pathogenesis in PN include IL-31, oncostatin m (OSM) beta receptor, and the IL-4 receptor.

With the recent discovery of elevated levels of IL-31 in patients with PN, IL-31 may be a new target for

therapy. A phase II clinical trial by Ruzicka et al⁵¹ on subcutaneous nemolizumab, a humanized antibody against IL-31 receptor A, reported significant improvement of pruritus in patients with atopic dermatitis.⁵² In addition, the FDA recently gave nemolizumab breakthrough therapy status for PN based on its phase II trial efficacy in reducing pruritus in these patients.⁵³ In this trial, a subcutaneous nemolizumab dose of 0.5 mg/kg of body weight showed dramatic improvement in peak pruritus of patients with PN in the treatment group compared with placebo.⁵⁴

OSM beta receptor is another novel target for combating itch in PN. As a proinflammatory signaling molecule similar to IL-6 cytokine family, OSM is activated by monocytes and T-lymphocytes to stimulate collagen production in dermal fibroblasts. KPL-716 is an OSM beta receptor monoclonal antibody that has been tried for itch in atopic dermatitis and is undergoing further study in the treatment of chronic pruritus in PN.

Finally, several case series have reported effective reduction in pruritus of PN with IL-4 receptor antagonists and both topical and oral cannabinoids.⁵⁵⁻⁶⁰ Dupilumab, a monoclonal antibody antagonist of the IL-4 receptor, has already been approved by the FDA for the treatment for atopic dermatitis.⁵⁶ Given its specificity for the IL-4 pathway and inhibition of itch-specific neural pathways, dupilumab has also been explored for PN treatment, with preliminary case reports showing promising results.⁵⁶⁻⁶⁰

With regard to cannabinoids, cannabinoid receptors 1 and 2 expressed on cutaneous nerve fibers are also thought to contribute to itch.⁵⁵ A systematic review study has shown significant symptom relief in patients with chronic pruritus who were treated with cannabinoids and who were refractory to first-line treatment.⁵⁵ However, larger studies with appropriate control groups are needed to better study the efficacy and safety of cannabinoids in the treatment of PN.

With novel therapeutics on the horizon for PN, it is important for clinicians to better understand the pathogenesis and current management of PN. We continue to learn about the etiology of this disease and identify new targets for effective therapies for this chronic, recalcitrant condition.

REFERENCES

1. Kwatra SG. Breaking the itch-scratch cycle in prurigo nodularis. *N Engl J Med*. 2020;382:757-758.
2. Schuhknecht B, Marziniak M, Wissel A, et al. Reduced intraepidermal nerve fibre density in lesional and nonlesional prurigo nodularis skin as a potential sign of subclinical cutaneous neuropathy. *Br J Dermatol*. 2011;165:85-91.

3. Almeida TA, Rojo J, Nieto PM, et al. Tachykinins and tachykinin receptors: structure and activity relationships. *Curr Med Chem.* 2012;11:2045-2081.
4. Zeidler C, Yosipovitch G, Ständer S. Prurigo nodularis and its management. *Dermatol Clin.* 2018;36:189-197.
5. Raap U, Günther C. Pathogenese der prurigo nodularis. *Hautarzt.* 2014;65:691-696.
6. Johansson O, Liang Y, Marcusson JA, Reimert CM. Eosinophil cationic protein- and eosinophil-derived neurotoxin/eosinophil protein X-immunoreactive eosinophils in prurigo nodularis. *Arch Dermatol Res.* 2000;292:371-378.
7. Lee MR, Shumack S. Prurigo nodularis: a review. *Australas J Dermatol.* 2005;46:211-220.
8. Liang Y, Marcusson JA, Jacobi HH, Haak-Frendscho M, Johansson O. Histamine-containing mast cells and their relationship to NGFr-immunoreactive nerves in prurigo nodularis: a reappraisal. *J Cutan Pathol.* 1998;25:189-198.
9. Sonkoly E, Müller A, Lauferma AI, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol.* 2006;117:411-417.
10. Dillon SR, Sprecher C, Hammond A, et al. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol.* 2004;5:752-760.
11. Grinstad Ø, Sawanobori Y, Vestergaard C, et al. Anti-interleukin-31-antibodies ameliorate scratching behaviour in NC/Nga mice: a model of atopic dermatitis. *Exp Dermatol.* 2009;18:35-43.
12. Pautrier LM. Le névrome de la lichenification circonscrite nodulaire chronique (lichen ruber obtusus corné, prurigo nodularis). *Ann Dermatol Syphil.* 1934;41:897-919.
13. Pereira MP, Pogatzki-Zahn E, Snels C, et al. There is no functional small-fibre neuropathy in prurigo nodularis despite neuroanatomical alterations. *Exp Dermatol.* 2017;26:969-971.
14. Hughes J-DM, Woo TE, Belzberg M, et al. Association between prurigo nodularis and etiologies of peripheral neuropathy: suggesting a role for neural dysregulation in pathogenesis. *Medicines (Basel).* 2020;7:4.
15. Haas S, Capellino S, Phan NQ, et al. Low density of sympathetic nerve fibers relative to substance P-positive nerve fibers in lesional skin of chronic pruritus and prurigo nodularis. *J Dermatol Sci.* 2010;58:193-197.
16. Kwon CD, Khanna R, Williams KA, Kwatra MM, Kwatra SG. Diagnostic workup and evaluation of patients with prurigo nodularis. *Medicines (Basel).* 2019;6:97.
17. Saco M, Cohen G. Prurigo nodularis: picking the right treatment. *J Fam Pract.* 2015;64:221-225.
18. Ständer HF, Elmariah S, Zeidler C, Spellman M, Ständer S. Diagnostic and treatment algorithm for chronic nodular prurigo. *J Am Acad Dermatol.* 2020;82:460-468.
19. Elmariah SB. Diagnostic work-up of the itchy patient. *Dermatol Clin.* 2018;36:179-188.
20. Weigelt N, Metze D, Ständer S. Prurigo nodularis: systematic analysis of 58 histological criteria in 136 patients. *J Cutan Pathol.* 2010;37:578-586.
21. Huang AH, Canner JK, Kang S, Kwatra SG. Analysis of real-world treatment patterns in patients with prurigo nodularis. *J Am Acad Dermatol.* 2020;82:34-36.
22. Zeidler C, Tsianakas A, Pereira M, Ständer H, Yosipovitch G, Ständer S. Chronic prurigo of nodular type: a review. *Acta Derm Venereol.* 2018;98:173-179.
23. Saraceno R, Chiricozzi A, Nistic SP, Tiberti S, Chimenti S. An occlusive dressing containing betamethasone valerate 0.1% for the treatment of prurigo nodularis. *J Dermatolog Treat.* 2010;21:363-366.
24. Siepmann D, Lotts T, Blome C, et al. Evaluation of the antipruritic effects of topical pimecrolimus in non-atopic prurigo nodularis: results of a randomized, hydrocortisone-controlled, double-blind phase II trial. *Dermatology.* 2014;227:353-360.
25. Ständer S, Luger T, Metze D. Treatment of prurigo nodularis with topical capsaicin. *J Am Acad Dermatol.* 2001;44:471-478.
26. Hammes S, Hermann J, Roos S, Ockenfels HM. UVB 308-nm excimer light and bath PUVA: combination therapy is very effective in the treatment of prurigo nodularis. *J Eur Acad Dermatol Venereol.* 2011;25:799-803.
27. Sorenson E, Levin E, Koo J, Berger TG. Successful use of a modified Goedeckerman regimen in the treatment of generalized prurigo nodularis. *J Am Acad Dermatol.* 2015;72: e40-e42.
28. Fostini AC, Girolomoni G, Tessari G. Prurigo nodularis: an update on etiopathogenesis and therapy. *J Dermatolog Treat.* 2013;24:458-462.
29. Pereira MP, Ständer S. Novel drugs for the treatment of chronic pruritus. *Expert Opin Investig Drugs.* 2018;27:981-988.
30. Spring P, Gschwind I, Gilliet M. Prurigo nodularis: retrospective study of 13 cases managed with methotrexate. *Clin Exp Dermatol.* 2014;39:468-473.
31. Klejzman T, Beylot-Barry M, Joly P, et al. Treatment of prurigo with methotrexate: a multicentre retrospective study of 39 cases. *J Eur Acad Dermatol Venereol.* 2018;32:437-440.
32. Siepmann D, Luger TA, Ständer S. Antipruritic effect of cyclosporine microemulsion in prurigo nodularis: results of a case series [in German]. *JDDG.* 2008;6:941-946.
33. Wiznia LE, Callahan SW, Cohen DE, Orlow SJ. Rapid improvement of prurigo nodularis with cyclosporine treatment. *J Am Acad Dermatol.* 2018;78:1209-1211.
34. Matsuda KM, Sharma D, Schonfeld AR, Kwatra SG, Gabapentin and pregabalin for the treatment of chronic pruritus. *J Am Acad Dermatol.* 2016;75:619-625.e6.
35. He A, Alhariri JM, Sweren RJ, Kwatra MM, Kwatra SG. Aprepitant for the treatment of chronic refractory pruritus. *Biomed Res Int.* 2017;2017:4790810.
36. Ständer S, Kwon P, Hirman J, et al. Serlopitant reduced pruritus in patients with prurigo nodularis in a phase 2, randomized, placebo-controlled trial. *J Am Acad Dermatol.* 2019;80:1395-1402.
37. Ständer S, Siepmann D, Herrgott I, Sunderkötter C, Luger TA. Targeting the neurokinin receptor 1 with aprepitant: a novel antipruritic strategy. *PLoS One.* 2010;5:e10968.
38. Terry M. Menlo's serlopitant for prurigo nodularis itching flunks two phase III trials. Available at: <https://www.biospace.com/article/menlo-s-serlopitant-for-prurigo-nodularis-itching-flunked-2-phase-iii-trials/>. Accessed April 16, 2020.
39. Sharma D, Kwatra SG. Thalidomide for the treatment of chronic refractory pruritus. *J Am Acad Dermatol.* 2016;74:363-369.
40. Taefehnorooz H, Truchetet F, Barbaud A, Schmutz JL, Bursztein AC. Efficacy of thalidomide in the treatment of prurigo nodularis. *Acta Derm Venereol.* 2011;91:344-345.
41. Andersen TP, Fogh K. Thalidomide in 42 patients with prurigo nodularis hyde. *Dermatology.* 2011;223:107-112.
42. Dawn AG, Yosipovitch G. Butorphanol for treatment of intractable pruritus. *J Am Acad Dermatol.* 2006;54:527-531.
43. Metze D, Reimann S, Beissert S, Luger T. Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases. *J Am Acad Dermatol.* 1999;41:533-539.
44. Lee J, Shin JU, Noh S, Park CO, Lee KH. Clinical efficacy and safety of naltrexone combination therapy in older patients with severe pruritus. *Ann Dermatol.* 2016;28:159-162.

45. Hawi A, Alcorn H, Berg J, Hines C, Hait H, Sciascia T. Pharmacokinetics of nalbuphine hydrochloride extended release tablets in hemodialysis patients with exploratory effect on pruritus. *BMC Nephrol.* 2015;16:47.
46. Ständer S, Böckenholz B, Schürmeyer-Horst F, et al. Treatment of chronic pruritus with the selective serotonin re-uptake inhibitors paroxetine and fluvoxamine: results of an open-labelled, two-arm proof-of-concept study. *Acta Derm Venereol.* 2009;89:45-51.
47. Hashimoto T, Satoh T, Yokozeki H. Prurigo successfully treated with duloxetine hydrochloride. *Australas J Dermatol.* 2019;60: 237-239.
48. Griffin JR, Davis MDP. Amitriptyline/ketamine as therapy for neuropathic pruritus and pain secondary to herpes zoster. *J Drugs Dermatol.* 2015;14:115-118.
49. Zalaudek I, Petrillo G, Baldassarre MA, et al. Amitriptyline as therapeutic and not symptomatic approach in the treatment of prurigo nodularis: a pilot study. *G Ital Dermatol Venereol.* 2006;141:433-437.
50. Boozalis E, Khanna R, Zampella JG, Kwatra SG. Tricyclic antidepressants for the treatment of chronic pruritus [e-pub ahead of print]. *J Dermatolog Treat.* 2019. <https://doi.org/10.1080/09546634.2019.1623369>. Accessed August 14, 2020.
51. Ruzicka T, Hanifin JM, Furue M, et al. Anti-interleukin-31 receptor a antibody for atopic dermatitis. *N Engl J Med.* 2017;376:826-835.
52. Schneider LC. Ditching the itch with anti-type 2 cytokine therapies for atopic dermatitis. *N Engl J Med.* 2017;376:878-879.
53. Park B. Nemolizumab gets breakthrough therapy status for prurigo nodularis. Available at: <https://www.empr.com/home/news/nemolizumab-gets-breakthrough-therapy-status-for-prurigo-nodularis/>. Accessed February 23, 2020.
54. Ständer S, Yosipovitch G, Legat FJ, et al. Trial of nemolizumab in moderate-to-severe prurigo nodularis. *N Engl J Med.* 2020; 382:706-716.
55. Khanna R, Khanna R, Denny G, Kwatra SG. Cannabinoids for the treatment of chronic refractory pruritus [e-pub ahead of print]. *J Dermatolog Treat.* 2019. <https://doi.org/10.1080/09546634.2019.1639603>. Accessed August 14, 2020.
56. Zhai LL, Savage KT, Qiu CC, Jin A, Valdes-Rodriguez R, Mollanazar NK. Chronic pruritus responding to dupilumab—a case series. *Medicines (Basel).* 2019;6:72.
57. Mollanazar NK, Elgash M, Weaver L, Valdes-Rodriguez R, Hsu S. Reduced itch associated with dupilumab treatment in 4 patients with prurigo nodularis. *JAMA Dermatol.* 2019;155: 121-122.
58. Beck KM, Yang EJ, Sekhon S, Bhutani T, Liao W. Dupilumab treatment for generalized prurigo nodularis. *JAMA Dermatol.* 2019;155:118-120.
59. Napolitano M, Fabbrocini G, Scalvenzi M, Nisticò SP, Dastoli S, Patruno C. Effectiveness of dupilumab for the treatment of generalized prurigo nodularis phenotype of adult atopic dermatitis. *Dermatitis.* 2020;31:81-84.
60. Rambhia PH, Levitt JO. Recalcitrant prurigo nodularis treated successfully with dupilumab. *JAAD Case Rep.* 2019; 5:471-473.

Answers to CME examination

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1. b
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