Acne and Rosacea
Method of
Daniel J. Van Durme, MD

Current Diagnosis: Acne

- Acne vulgaris is primarily found in teenagers and young adults and is characterized by microcomedones that develop into open and closed comedones (blackheads and whiteheads) as well as inflammatory papules and pustules, or nodules and cysts.
- Acne vulgaris lesions are primarily on the face, neck, upper arms, back, and chest.
- Acneiform lesions are typically found in various stages, with many patients having a predominant type.

Current Therapy: Acne

- Acne therapy involves prevention of new lesions and control over a long period of time. Response to therapy generally takes 6 to 8 weeks.
- Numerous topical and oral medications have demonstrated efficacy for patients with acne, and there is little evidence which is best.
- Benzoyl peroxide is an excellent starting agent owing to extensive safety and efficacy studies, its demonstrated benefit in controlling P. acnes, and some benefits in controlling abnormal keratinization and inflammation.
- Topical retinoids should also be considered as starting agents owing to their demonstrated benefits in controlling abnormal keratinization leading to microcomedones, a primary lesion in acne.
- Topical antibiotics such as clindamycin (Cleocin-T) and erythromycin (Akne-Mycin) should be used in combination with benzoyl peroxide for increased benefit and decreased likelihood of bacterial resistance.
- Oral antibiotics such as doxycycline (Vibramycin) should be used if acne is widespread or unresponsive to topical agents.
- Oral contraceptives have proven benefits for most types of acne.
- Oral isotretinoin (Accutane, Claravis) can be very effective and even cure many patients, but the teratogenic and other side effects are profound and mandate use with extreme caution.

Acne (or acne vulgaris) and rosacea (previously called acne rosacea and sometimes adult acne) are often thought of together. However, they actually represent different pathophysiologic processes and require different therapeutic approaches.
Diseases of the Skin

Differential Diagnosis
Differential diagnosis should include drug-induced acne (especially from steroids), which can be identified by seeing all lesions at nearly the same stage of development. Rosacea should also be considered in the differential diagnosis of acne vulgaris, though the age of onset and symptomatology are usually distinguishing.

Treatment
Treatment of acne begins with careful patient education and often involves a negotiation of management with teenagers who are taking responsibility for their health for the first time. It is increasingly important to address myths and misperceptions that they might hear from others or find on the Internet (such as the use of toothpaste for acne on YouTube). Additionally, it is key to set realistic expectations about how acne can be controlled with regular use of a variety of agents and how it can take 6 to 8 weeks to see improvement. If these issues are not addressed, the likelihood of adherence and long-term improvement are low.

Medical treatment should begin with a benzoyl peroxide agent because these are available over the counter and have an extensive history of safety and efficacy. They are available in a wide range of vehicles (soaps, lotions, gels), and strengths vary from 2.5% to 10%. Many patients go straight to the maximum strength and report significant irritation, so it is important to educate that higher strengths dry the skin but otherwise are no more effective against P. acnes than the lower strengths. Patients should be advised that this reflects the base of treatment upon which other agents are added. Benzoyl peroxide plays a key role as a combination with both topical and oral antibiotics in preventing the development of bacterial resistance. If necessary, the patient can use it every other day to develop a tolerance to any irritation and gradually work up to once- or twice-a-day dosing.

Topical retinoids (tretinoin [Retin-A, Renova, Avita], adapalene [Differin] or tazarotene [Tazorac]) are all extremely effective for abnormal keratinization and comedone development. These also can be irritating and come in a variety of strengths. All are contraindicated in pregnancy. Patients might need to start at the lowest strength with every-other-day dosing and work up to the highest strength needed and tolerated.

Salicylic acid preparations are comedolytic and can be used for the patients who can tolerate either benzoyl peroxide or topical retinoids, although salicylic acid preparations have not been shown to be as effective.

For patients with moderate inflammatory and comedonal lesions, it can be appropriate to start both benzoyl peroxide and topical retinoids at the initial visit; however, the application should be separated in time because the benzoyl peroxide will inactivate the retinoid. An effective regimen (if tolerated) is a benzoyl peroxide wash in the morning and topical retinoid at bedtime.

Antibiotics should be added if response to topical benzoyl peroxide and retinoids is inadequate at the 6- to 8-week follow-up visit. Topical clindamycin and erythromycin have demonstrated efficacy and can be used twice a day at the same time as the benzoyl peroxide. There are also combination agents that conveniently combine the two agents into a single preparation: clindamycin 1% plus benzoyl peroxide 5% gel (BenzaClin, Duc) and erythromycin 3% plus benzoyl peroxide 5% gel (BenzaClin, Duc). They are more expensive, however.

Oral antibiotics should be started if the acne is moderate to severe, if it is too widespread to reasonably cover with topical antibiotics, or if there is an inadequate response after 6 to 8 weeks of topical antibiotics. Effective oral agents include the tetracyclines, macrolides, and trimethoprim–sulfamethoxazole (TMP-SMX), but side effects of each must be considered, and bacterial resistance is an increasing issue.

Doxycycline (Doryx) at 100 mg/day is generally considered the optimal antibiotic despite some issues with photosensitivity. Minocycline (Minocin) at 100 mg twice daily has side effects that include pigment deposition in skin, mucous membranes, and teeth (as well as rare autoimmune hepatitis and other problems). TMP-SMX (Bactrim, Septra DS) taken twice daily also has side effects to consider but can be useful when other agents are not tolerated. Macrolides, particularly erythromycin (Ery-Tab), have had the most problems with bacterial resistance. For this reason they should be reserved for pregnant patients or when other agents cannot be used and should always be used with benzoyl peroxide to minimize that resistance. All oral agents should be used in combination with benzoyl peroxide and/or a topical retinoid but not in combination with topical antibiotics. If significant improvement is noted, oral agents should be decreased after 3 to 4 months and stopped in order to attempt maintenance control with topical agents.

Oral contraceptives can be very helpful in female patients with moderate acne owing to their antiandrogenic effects, which decrease sebum production. Several oral contraceptives have been FDA-approved for acne, including Ortho Tri-cyclen, Estrostep Fe, and Beyaz, although many others have also shown significant improvement in acne.

Several other topical agents have shown benefit for acne including azelaic acid (Azelex) used twice a day, although this seems less effective than other agents and can cause hypopigmentation. Topical sulfacetamide 10% (Klaran) applied twice daily has also shown benefit.

Oral isotretinoin has demonstrated marked benefit for patients with severe recalcitrant acne, even inducing a full remission. It is a potent teratogen and has a host of other significant side effects including cheilitis, epistaxis, photosensitivity, and many others. Prescribed at 0.5 to 2 mg/kg per day over 20 weeks, it is like chemotherapy for acne. It is extremely tightly regulated, and both prescribers and patients must register with the iPledge program in order to write for the medicine and to receive the prescriptions. See www.ipledgeprogram.com. When all the precautions are managed, it can be an extremely effective option for the patients with the worst cases of acne.

Rosacea

CURRENT DIAGNOSIS: ROSACEA

- Rosacea is most common in adults aged 30 to 50 years and can have any of four overlapping presentations: facial flushing and erythema with telangiectasias, inflammatory papules and pustules, ocular dryness and irritation, and nasal sebaceous gland hypertrophy leading to fibrotic changes and rhinophyma.

- Common exacerbating factors include alcohol, heat, spicy foods, and sunlight.

CURRENT THERAPY: ROSACEA

- Therapy is best chosen on the basis of severity and predominant manifestation(s).

- Avoidance of known triggers is key for all, especially the erythematotelangiectatic type.

- Topical antibiotics (metronidazole [Metrogel], azelaic acid [Finacea], sodium sulfacetamide, and sulfur [Sulfacet-R]) are appropriate for milder forms of papulopustular rosacea. Oral antibiotics (doxycycline [Oracea], minocycline,1 erythromycin,1 or metronidazole [Flagyl]) are used for more-severe cases.

- Ocular rosacea can be treated with increased eyelid hygiene, adding topical or oral antibiotics if needed.

- Rhinophyma (sebaceous gland hypertrophy and fibrosis) needs surgical management.

1Not FDA approved for this indication.
Rosacea is a common facial dermatosis found primarily in adults aged 30 to 50 years, particularly those of northern European or Celtic descent.

Diagnosis
Rosacea can have any of four primary manifestations, and although these overlap, most patients tend toward one predominant type. Facial erythema and flushing that also has telangiectasia is called erythematotelangiectatic type. The papulopustular type has inflammatory papules, small pustules, and occasionally small nodules. The presentation of papulopustular rosacea differs from acne vulgaris because the onset is in the 30- to 50-year-old age group instead of adolescence, and comedones are not present in papulopustular rosacea. When the sebaceous glands get markedly hypertrophic and fibrotic, this is called phymatous type and can lead to profound disfigurement of the nose called rhinophyma. Ocular type involves dryness of the eyes with decreased tear production, blepharitis, and conjunctivitis.

Treatment
One key aspect of management is to have the patient maintain a careful diary to determine their own triggers and avoid these. Common triggers include alcohol, heat (weather or related to food and drink), certain foods, sunlight, stress, menstruation, and others. Broad-spectrum sunblock (UV-A and UV-B) should be used daily. Cosmetics with a red-neutralizing green pigment can help appearance.

The erythematotelangiectatic type is the most difficult to treat, although some benefit can be found with topical antibiotics such as metronidazole 0.75% to 1% cream, lotion, or gel (Metrogel, Noritrate) or azelaic acid cream1 (Azelex) or gel (Finacea) applied once or twice daily. Sodium sulfacetamide with sulfur is made by several manufacturers, and some brands (Sulfacet-R) include a pigmenting agent to help hide the erythema. The sulfur component can also help in cases of coexisting seborrheic dermatitis. Persistent telangiectasias can be effectively treated with laser ablation.

Papulopustular rosacea can respond to topical antibiotics, but when it is moderate to severe, oral antibiotics are indicated. Doxycycline5 50 to 100 mg taken once or twice a day for 2 to 3 months can markedly decrease symptoms, and then the patient can switch to topical agents for long-term maintenance as needed. Minocycline (50 to 100 mg), erythromycin1 (250 to 300 mg), and lower-dose metronidazole (200 mg) can each be taken once or twice a day as alternatives. Side effects can limit longer-term use of these agents, especially metronidazole.

Ocular rosacea can often be controlled with increased eyelid hygiene, washing with warm water and baby (no-tears) shampoo twice a day along with artificial tears. If severe, it can be treated with topical erythromycin ointment or oral antibiotics. If it still persists, ophthalmology referral is necessary.

The disfigurement of rhinophyma is often of concern to patients with rosacea. They can be reassured that this is uncommon, and women can be further reassured that it is much more common in men. Unfortunately the only effective treatments involve surgery, often laser surgery.

References

Atopic dermatitis (AD) is a chronic inflammatory skin disease that is characterized by itch and a predilection of eczema on extensor areas in young infants or flexural areas in older children and adults. In the United States, AD affects about 15% of children and 2% of adults. For more than 85% of patients, AD begins during the first 5 years, but 50% of the children with AD improve significantly or outgrow the disease by age 7. The persistence of AD depends on various factors: early onset, severity, family history of AD, personal history of asthma, and food or inhalant allergies.

The itch associated with AD causes significant discomfort in these patients and often leads to sleep loss and to poor school or work performance. The quality of life of children with generalized AD is worse than that for children with diabetes, epilepsy, asthma, cystic fibrosis, or renal disease. The maternal stress in taking care of children with moderate to severe AD is equivalent to that associated with care of children with diabetes, Rett syndrome, profound deafness, or the need for enteral feeding.

Pathophysiology
AD is caused by a combination of genetic and environmental factors. Patients with AD have a defective skin barrier. This leads to a loss of skin hydration and susceptibility to environmental triggers. There is evidence that the skin barrier defects of AD are caused by genetic mutations. Studies have shown that many AD patients
Diseases of the Skin

Potential external triggers of AD include microbial pathogens and environmental allergens. Almost 100% of AD skin lesions are colonized by Staphylococcus aureus, which may produce toxins that trigger immune response in the skin. As a result, AD patients produce an increased amount of pro-allergic cytokines, such as interleukin-4 (IL-4), IL-5, and IL-13, in their skin. These cytokines lead to an increased infiltration of inflammatory T cells and eosinophils. IL-4 and IL-13 also are important for the production of serum IgE, the level of which is elevated in AD patients.

Diagnosis and Clinical Assessment

Most AD patients can be diagnosed by clinical history and physical examination. Typical presentation includes itch, dryness, flexural dermatitis, early age of onset, and atopy such as multiple food allergies. Patients with generalized eczema or adult-onset eczema can present as a diagnostic challenge. The differential diagnosis includes immunodeficiency (e.g., hyper-IgE syndrome, Omenn syndrome), malignancy (e.g., cutaneous T-cell lymphoma), zinc deficiency (i.e., acrodermatitis enteropathica), and celiac-associated dermatitis (i.e., dermatitis herpetiformis) (Table 1). AD children seldom present with failure to thrive, unless they are under severe dietary restriction. Failure to thrive should therefore prompt further investigation. Punch skin biopsies may be needed when the diagnosis is still unclear.

The prevalence of mild, moderate, and severe AD is 80%, 18%, and 2%, respectively. Most patients with mild to moderate disease have flexural, extensor, or facial involvement, whereas patients with severe disease often present with total-body involvement with or without erythroderma (Figure 1). Validated scales for assessing the severity of AD include Scoring of Atopic Dermatitis (SCORAD) and Eczema Area and Severity Index (EASI). These scoring systems or a simplified diagram documenting the extent of dermatitis are useful for more objective follow-up of the patient’s progress.

Management of Atopic Dermatitis and Associated Conditions

Daily Maintenance Care

Changes in humidity can adversely affect AD symptoms. Dry conditions lead to increased transepidermal water loss and dry AD skin. Extreme heat, humidity, and sweating may lead to irritation of AD skin. AD patients are at increased risk for contact or irritant dermatitis, which may occur with over-the-counter topical skin medications that contain multiple ingredients. Wool or synthetic acrylic fabrics may also be irritating to AD skin.

Table 1: Differential Diagnoses of Atopic Dermatitis

<table>
<thead>
<tr>
<th>DISEASE CATEGORY</th>
<th>DIFFERENTIAL DIAGNOSES</th>
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<tbody>
<tr>
<td>Dermatologic diseases</td>
<td>Contact dermatitis, seborrheic dermatitis, psoriasis, dyshidrotic eczema, eosinophilic pustular folliculitis, ichthyosis vulgaris</td>
</tr>
<tr>
<td>Neoplastic diseases</td>
<td>Cutaneous T-cell lymphoma, Langerhans cell histiocytosis</td>
</tr>
<tr>
<td>Immunodeficiencies</td>
<td>Hyper-IgE syndrome, severe combined immunodeficiency, Omenn syndrome, IPEX (immune dysregulation, polyendocrinopathy, enteropathy X-linked) syndrome</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>Scabies, cutaneous candidiasis, tinea versicolor</td>
</tr>
<tr>
<td>Nutritional deficiencies</td>
<td>Acrodermatitis enteropathica (zinc deficiency), essential fatty acid deficiency, biotin deficiency</td>
</tr>
<tr>
<td>Multisystemic disorders</td>
<td>Netherton syndrome, dermatitis herpetiformis</td>
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To improve barrier function, AD patients should bathe or shower for 10 to 20 minutes once or twice daily, followed immediately by gently drying the skin and applying an emollient on the unaffected areas and a topical antiinflammatory medication on the affected areas. A petrolatum-based emollient is recommended in infants and young children because of its occlusive property. In older children and adults, the ointment may not be tolerated well because of its greasy feel, and another emollient or moisturizer may be chosen based on the patient’s preference or experience.

Itch may continue to be a problem even if the rash has improved. The mechanisms of itch in AD are not fully understood but do not appear to be mediated solely by histamine. The use of first-generation antihistamines (diphenhydramine [Benadryl] and hydroxyzine [Vistaril]) in AD largely depend on their sedative effects and are best used at bedtime. The second-generation, nonsedating antihistamines such as loratadine (Claritin)1 and cetirizine (Zyrtec)1 have not proved helpful in treating AD. Low-dose Doxepin has been used anecdotally to treat itching in AD.

Table 2: Topical and Systemic Medications

The first-line medication for AD is a topical corticosteroid (TCS). For mild AD, a TCS with group VI and VII potency (Table 2) may suffice. However, for moderate to severe AD, a TCS with at least group III to V potency is chosen to increase efficacy and to shorten the duration of need for these medications.

The use of TCS is confronted with various obstacles, including rare side effects such as skin atrophy, but mostly patients’ misunderstanding of TCS. Studies have shown that twice-daily use of fluticasone propionate (Cutivate) 0.05% cream (group V) and desonide (DesOwen, Tridesilon) 0.05% ointment or aqueous gel (group V and VI, respectively) continuously up to 1 month in young children with AD results in no significant adverse effect. It is therefore important to clarify for patients or parents the safety and side effects based on the potency of the TCS.

1Not FDA approved for this indication.
Topical calcineurin inhibitors (TCI) (pimecrolimus [Elidel] 1% cream and Protopic/tacrolimus ointment) are alternative nonsteroidal antiinflammatory medications for AD. Elidel is indicated for mild to moderate AD in patients older than 2 years, whereas 0.03% and 0.1% Protopic are indicated for moderate to severe AD in patients 2 to 15 years old and in patients 16 years old or older, respectively. Both Elidel and Protopic have an FDA black box warning saying that their long-term use may be associated with cancer risk. It is recommended that these medications be used on a short-term and as-needed basis in minimal amounts. They continue to be useful alternatives for skin areas that are prone to atrophy, including the face, axillae, and groins.

A third class of topical medications (so-called barrier creams) emphasize skin barrier repair. These medications include Atopiclair, MymiX, Eletone, and EpiCeram. Only EpiCeram has been compared directly with TCS. It was shown to be as effective as fluticasone propionate 0.05% cream in children with moderate to severe AD in a preliminary study. Atopiclair and MymiX may be effective for patients with mild to moderate AD. There is no published study on Eletone. These barrier creams have no age limitations, but they require a prescription because they have been approved as a medical device by the FDA.

Bet-wrap treatment, phototherapy, and systemic immunosuppressive therapies (e.g., cyclosporine [Sandimmune, Neoral], azathioprine [Imuran], methotrexate [Trexall], and mycophenolate mofetil [CellCept]) are reserved for severe AD patients. Because of the potential serious adverse effects associated with these treatments, referral to an allergist or dermatologist is recommended before their initiation.

Systemic corticosteroids usually are not recommended for AD because of their known adverse effects, including stunted growth in children, adrenal suppression, osteoporosis, and cataracts. A rebound of AD symptoms is common after the medication is stopped. If a systemic corticosteroid is used, it should be tapered over a short period (e.g., a week) while topical antiinflammatory treatment is intensified.

Accurate diagnosis of food allergies in AD patients is crucial, because it can prevent life-threatening anaphylaxis or unnecessary food restriction.

The diagnosis of food allergy involves one or more of the following: history taking, skin tests, serum-specific IgE tests, and food challenge. History taking is helpful in the diagnosis of food allergy in most patients. It is often useful to begin by asking the patients whether they have any problems or reactions with any of the seven food allergens: milk, egg, peanut, wheat, soybean, seafood, and tree nuts. These foods account for more than 90% of food allergies. Almost all food allergic reactions occur in the first hour. AD patients may complain of immediate worsening of itching after ingestion. Symptoms of anaphylactic reactions include throat-clearing, cough, shortness of breath, vomiting, dizziness, fainting, and headache, which may be attributed to hypotension. Most food allergic reactions also manifest with skin symptoms, including hives, swelling, or generalized itching.

Skin tests are useful in the context of negative test results because they have a negative predictive value of more than 95%. A positive test result has only a 50% positive predictive value. Quantitative serum-specific IgE antibodies (ImmunoCAP, Pharmacia) have become useful in the diagnosis of food allergies because of their high positive predictive values (Table 3). These tests are more specific than skin tests and allow the detection of low levels of specific IgE antibodies in the serum. However, these tests are not as sensitive as skin tests, and false-negative results can occur.

### TABLE 2 Classification of Topical Steroids Based on Potency

<table>
<thead>
<tr>
<th>GROUP</th>
<th>TOPICAL CORTICOSTEROIDS</th>
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<tr>
<td>I (most potent)</td>
<td>Clobetasol propionate 0.05% (Temovate) (cream, ointment, gel), betamethasone dipropionate, augmented 0.05% (Diprolene) (cream, ointment), dexamethasone propionate 0.05% (Pсорcon) (ointment)</td>
</tr>
<tr>
<td>II</td>
<td>Aminocorticosterone 0.1% (Cyclocort) (ointment), betamethasone propionate 0.05% (Diprosone) (ointment), mometasone furoate 0.1% (Elocon) (ointment), halcinonide 0.1% (Halog) (cream), fluticasone 0.05% (Lidex) (gel, cream, ointment), dexamethasone propionate (Topicort) (0.05% gel, 0.25% cream, 0.25% ointment)</td>
</tr>
<tr>
<td>III</td>
<td>Fluticasone propionate 0.005% (Cutivate) (ointment), aminocorticosterone 0.1% (Cyclocort) (lotion, cream), dexamethasone propionate 0.05% (Florone) (cream), betamethasone valerate 0.1% (Valisone) (ointment)</td>
</tr>
<tr>
<td>IV</td>
<td>Flurandrenolide 0.05% (Cordran) (ointment), mometasone furoate 0.1% (Elocon) (cream), triamcinolone acetonide 0.1% (Kenalog) (cream), fluocinolone acetonide 0.025% (Synalar) (ointment), hydrocortisone valerate 0.2% (Westcor) (ointment)</td>
</tr>
<tr>
<td>V</td>
<td>Flurandrenolide 0.05% (Cordran) (cream), fluticasone propionate 0.05% (Cutivate) (cream), hydrocortisone butyrates 0.1% (Locoid) (cream), fluticasone propionate acetonide 0.025% (Synalar) (cream), desonide 0.05% (Tridesilion) (ointment), betamethasone valerate 0.1% (Valisone) (cream), hydrocortisone valerate 0.2% (Westcor) (cream), prednicarbate 0.1% (Dermatop) (cream)</td>
</tr>
<tr>
<td>VI</td>
<td>Alclometasone propionate 0.05% (Aclovate) (cream, ointment), fluocinolone acetonide 0.01% (Synalar) (solution, cream) (Derma-Soothe/FS Oil), Desonide 0.05% (Tridesilton) (cream and aqueous gel)</td>
</tr>
<tr>
<td>VII (least potent)</td>
<td>Hydrocortisone 1%/2.5% (lotion, cream, ointment).</td>
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### TABLE 3 Predictability of ImmunoCAP-Specific IgE

<table>
<thead>
<tr>
<th>REACTION</th>
<th>MILK</th>
<th>SOY</th>
<th>EGG</th>
<th>WHEAT</th>
<th>PEANUT</th>
<th>FISH</th>
<th>TREE NUTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction highly probable</td>
<td>&gt;15 kU/L</td>
<td>&gt;60 kU/L</td>
<td>&gt;7 kU/L</td>
<td>&gt;80 kU/L</td>
<td>&gt;14 kU/L</td>
<td>&gt;20 kU/L</td>
<td>&gt;15 kU/L</td>
</tr>
<tr>
<td>Reaction highly probable (young children)</td>
<td>&gt;5 kU/L (&lt;1 y)</td>
<td>&gt;2 kU/L (&lt;2 y)</td>
<td></td>
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*Because of their high positive predictive values, quantitative serum-specific IgE antibodies are used in the diagnosis of food allergies.

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1 Not FDA approved for this indication.

7 Available as a dietary supplement.
also useful for deciding whether a food challenge is necessary to confirm the diagnosis.

Although history, skin tests, and serum-specific IgE values are useful in the diagnosis of food allergy, a double-blind, placebo-controlled food challenge remains the gold standard in diagnosing food allergy. Food challenge should be done in consultation with an allergist because of the risk of anaphylaxis.

Patients with confirmed food allergy should avoid any amount of the food allergen. Parents or patients should be instructed to read food allergen labels carefully. All packaged foods in the United States are required to label the contents of milk, eggs, peanuts, wheat, soybeans, fish, shellfish, or tree nuts. Organizations, such as the Food Allergy and Anaphylaxis Network, can provide patients and parents with useful information on potential hidden food allergens and alternative food sources.

AD children often have multiple food allergies, including cow’s milk and soy, and the use of a hydrolyzed or amino acid–based formula can provide an alternative source of nutrition. For these patients, consultation with a dietitian can be helpful in managing food avoidance and nutrition needs.

Patients or parents of children with anaphylactic reactions should be prescribed and instructed on the use of an epinephrine autoinjector (EpiPen or Twinject; 0.15 mg for patients who weigh more than 1.5 kg but less than 30 kg; 0.3 mg for patients who weigh 30 kg or more).

Withholding highly allergenic foods in early childhood remains controversial. However, for infants who are at high risk for food allergy (e.g., children with AD and multiple food allergies), it is recommended that they avoid eggs, peanuts, tree nuts, fish, and shellfish in the first 3 years, unless there are major issues such as nutrition or social hindrance. Further studies are needed to confirm the role of this practice in preventing food allergies.

Infections

Most AD patients are colonized by *S. aureus* on their skin lesions or in their nostrils. The frequency of colonization increases with AD severity. Exacerbation of AD is frequently associated with secondary *S. aureus* skin infections. Other common skin pathogens in AD include group A beta-hemolytic Streptococcus and herpes simplex virus (HSV), which causes eczema herpeticum (Figure 2). Many reports have documented invasive *S. aureus* infections such as bacteremia, septic arthritis, osteomyelitis, and endocarditis in AD patients. Persistent fever or focal limb pain should alert the physician to the possibility of these infections.

The reasons for the high rate of bacterial colonization and skin infections in AD are not completely understood. A defective skin barrier and decreased cutaneous innate immunity (i.e., deficiency in natural skin antibiotics) likely contribute to the frequency of skin infections in patients with AD.

Because of the concern about increasing bacterial resistance, antibiotics are not recommended for treating *S. aureus* colonization in patients with AD. An area of active research involves the use of silver-coated fabrics or antimicrobial-coated silk fabrics to reduce *S. aureus* colonization and improve symptoms in AD patients.

Inhalant Allergies and Asthma

Eighty-five percent of AD infants have concurrent respiratory allergies or are at risk for allergic rhinitis or asthma. However, whether inhalant allergens lead to a worsening of AD remains controversial. Randomized, double-blind, placebo-controlled studies have shown positive and negative effects of house dust mites (HDM) as a trigger for AD symptoms. Because there is no serious side effect associated with the use of HDM-proof bed and pillow encasings, unless cost is an issue, these encasings are recommended for AD patients with HDM sensitization. Further research is needed to confirm the role of inhalant allergens, including furry pets and pollens, as triggers for AD.

**Investigational Treatments for Atopic Dermatitis**

Because of the concern about potential side effects associated with existing therapies of AD, several agents are being investigated for the treatment of AD. They include a topical nuclear factor-κB decoy, phosphodiesterase 4 inhibitors, uric acid oxidation products, vitamin B₁₂, rose bengal disodium, *Vitreoscilla filiformis*, alfacet (Amieve)⁴, and piratikrin (Aerovant). Subcutaneous and sublingual allergen immunotherapy may also be helpful in a subgroup of patients with HDM sensitization. Topical opioid receptor antagonists, systemic chymase inhibitors, and cannabinoid receptor agonists are potential anti-itch medications for AD. Topical capsaicin may be effective in controlling local itching in select AD patients.

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**Figure 2.** Eczema herpeticum.

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**References**


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¹Not FDA approved for this indication.
²Investigational drug in the United States.
The spectrum of bacterial diseases of the skin ranges from superficial, localized, easily recognized, and treated skin eruptions to deep, aggressive, gangrenous, or necrotizing infections that may appear innocuous at first but quickly become life threatening. The prompt recognition and treatment of these infections are paramount in limiting morbidity and mortality. A healthy respect for the aggressiveness of gangrenous and necrotizing infections of the skin and soft tissues is developed by first harboring a high index of suspicion to provide early recognition and appropriate treatment before overwhelming clinical infection occurs.

**Common Infections**

**Impetigo**

Impetigo is the most common bacterial infection of the skin. It is highly contagious and can occur at any age from infancy to adulthood, but it is most common in preschool-age children. There are two classic forms of impetigo: nonbullous and bullous. Both forms have a predominantly staphylococcal cause, but they manifest with different morphologic characteristics.

Nonbullous (crusted) impetigo can be recognized by the development of a serous, yellow-brown exudate, which dries into a golden crust. Lesions rarely elicit pain but can be associated with erythema and pruritus. They are most common on exposed areas such as the hands, feet, face, and legs and are often associated with a minor traumatic event such as an insect bite, abrasion, or laceration. Crusted impetigo is usually caused by a heavy mixed flora of staphylococci and streptococci. Streptococcal impetigo has been associated with the postinfectious sequelae of post-streptococcal glomerulonephritis.

The bullous variety usually manifests as a rapidly spreading papule, which may progress to a thin-walled vesicle if the lesion is infected with *Staphylococcus aureus*, an organism that produces an exfoliative toxin. These lesions occur most often in warm, moist areas of the body. Predisposing factors include warm ambient temperatures, humidity, poor hygiene, and crowded living conditions.

Treatment of impetigo begins with eradication or with the environmental factors thought to be influential in its development. Aggressive lesion débridement with mesh gauze sponges or brushes and antimicrobial soap is encouraged. Special attention to hygiene and disinfection of towels and bedding are also necessary. Topical antibiotic treatment with mupirocin (Bactroban) or bacitracin has been effective in mild to moderate cases. In more extensive cases, oral antibiotic therapy with a penicillinase-resistant synthetic penicillin (oxacillin) is the treatment of choice (Table 1). However, a high percentage of methicillin-resistant strains of *S. aureus* (MRSA) are isolated in institutional and community settings. Patients should be treated for at least 5 to 7 days. If no improvement is seen, lesions should be cultured and antibiotics adjusted appropriately.

Systemic complications from impetigo are very uncommon. Cellulitis has occurred but is usually susceptible to systemic antibiotic therapy. Septicemia and staphylococcal scaled skin syndrome are rare complications of impetigo. When they occur, systemic therapy is indicated.

**Folliculitis**

Folliculitis is a pyoderma that arises within a hair follicle. The process is known as a furuncle (boil) when the infection extends beyond the hair follicle. These lesions occur most frequently in the moist areas of the body and in areas subject to friction and perspiration. Host factors known to predispose one to folliculitis include obesity, blood dyscrasias, defects in neutrophil function, immune deficiency states (e.g., diabetes, transplantation-related immunosuppression, acquired immunodeficiency syndrome [AIDS]), and treatment with corticosteroids or cytotoxic agents. The offending organism in most immunocompetent patients is *S. aureus*; however, specific etiologic agents are more common in immunocompromised patients.

**TABLE 1**

Suggested Antibiotic Therapy for Gram-Positive Bacterial Isolates

<table>
<thead>
<tr>
<th>ISOLATE</th>
<th>ORAL</th>
<th>PARENTERAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABHS</td>
<td>Penicillin G or V</td>
<td>Penicillin G</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>Ampicillin/sulbactam</td>
</tr>
<tr>
<td></td>
<td>First-generation</td>
<td>(Unasyn)</td>
</tr>
<tr>
<td></td>
<td>cephalosporin</td>
<td>First-generation</td>
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<td></td>
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<td>cephalosporin</td>
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<td></td>
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</tr>
<tr>
<td><em>Staphylococcus aureus</em> (methicillin sensitive)</td>
<td>Penicillinase-resistant synthetic penicillin (Oxacillin)</td>
<td>First-generation cephalosporin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clindamycin (Cleocin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxacillin</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (methicillin resistant)</td>
<td>Linezolid (Zyvox)</td>
<td>Vancomycin (Vancocin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daptomycin (Cubicin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linezolid (Zyvox)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ceftaroline (Tellaro)</td>
</tr>
<tr>
<td>Clostridial species</td>
<td>Penicillin G or V</td>
<td>Penicillin G</td>
</tr>
<tr>
<td></td>
<td>Clindamycin (Cleocin)</td>
<td>Clindamycin (Cleocin)</td>
</tr>
<tr>
<td></td>
<td>Metronidazole (Flagyl)</td>
<td>Metronidazole</td>
</tr>
</tbody>
</table>

Abbreviation: GABHS = group A β-hemolytic *Streptococcus.*
when immunosuppression impairs host defenses, gram-negative organisms (Klebsiella, Enterobacter, and Proteus species) can be involved. *Pseudomonas* species such as aeruginosa or cepacia are associated with hot-tub folliculitis, which involves numerous hair follicles. It is usually self-limited, resolving in 7 to 10 days.

Successful treatment of folliculitis depends on correcting the predisposing factors that promote the development of this condition. For patients with localized disease, topical wound care including antibiotics such as mupirocin (Bactroban) is effective. Patients with furunculosis or multiple lesions with surrounding erythema of more than 2.5 cm should be treated with orally administered systemic antibiotics that are effective against *S. aureus*. Any fluctuant nodules or abscesses should be incised and drained. Patients with recurrent furunculosis should have their nares cultured for methicillin-susceptible *Staphylococcus aureus* (MSSA) or MRSA because nose rubbing and self-inoculation are the usual means of developing infection. This not only determines which type of *Staphylococcus* is causing the infection, but illustrates to the patient the importance of self-inoculation. Intranasal bacitracin or mupirocin (Bactroban) and daily baths with chlorhexidine (Hibiclens) or hexachlorophene (PHisoHex) (adults only) may break the cycle of nasal colonization and reinfection.

**Cellulitis**

Cellulitis is an acute infection of the skin and underlying soft tissues. It commonly begins as a hot, red, edematous, sharply defined eruption and may progress to lymphangitis, lymphadenitis, or in severe cases, necrotizing fasciitis and gangrene. Cellulitis usually occurs in local skin trauma caused by insect bites, abrasions, surgical wounds, contusions, or other cutaneous lacerations. Immunosuppressed patients are particularly susceptible to the progression of cellulitis to regional or systemic infections, and these patients should be treated aggressively with systemic antibiotics, drainage, and debridement when indicated. Cellulitis is 20-fold more common in patients with chronic venous stasis or lymphedema. Recurrent cellulitis may occur in patients at the exact site of saphenous donor site surgery.

Initial presentation is that of a rapidly expanding, tender, erythematous, indurated area of skin. An ascending lymphangitis may be present, especially in cellulitis involving an extremity often associated with regional lymphadenopathy. Systemic signs and symptoms can eventually evolve and when present, mandate hospitalization and treatment with systemic antibiotics. Offending organisms are most commonly group A β-hemolytic *Streptococcus* (GABHS) species and *S. aureus*. Cellulitis caused by *S. aureus* usually is associated with localized abscess, furuncles, or carbuncles. In diabetic patients, cellulitis can be caused by group B *Streptococcus*.

Localized processes are treated with oral antibiotics (see Table 1). If fever, sepsis, or other signs of advancement to deeper tissues are present, the patient should be admitted to the hospital for blood and wound cultures, parenteral antibiotics (see Table 1), and observation. If a prompt response is not observed after parenteral antibiotic treatment, surgical exploration of the involved area may be indicated to establish an etiologic diagnosis and rule out the presence of necrotic or gangrenous tissue. Immunosuppressed patients or patients with recurrent cellulitis should be extensively examined to exclude chronic sources of infection, and these patients should be treated with parenteral antibiotics until the cellulitis resolves, followed by 5 to 7 days of oral antibiotics.

**Abscess**

Local skin signs and symptoms such as pain (dolor), redness (rubor), warmth (calor), and swelling (tumor) often denote an abscess. Loss of function associated with fluctuation may also indicate abscess formation. Localization of purulent fluid necessitates surgical drainage and local wound care. The administration of oral or parenteral antibiotic therapy should not be used routinely after incision and drainage of localized abscesses. They should be administered only when clinically indicated, and antibiotic therapy should be based on culture and sensitivity testing.

**Life-Threatening Infections**

**Group A β-Hemolytic Streptococcal Gangrene**

Group A β-hemolytic streptococcal gangrene is an extremely rapidly progressing skin and soft tissue infection commonly caused by *Streptococcus pyogenes*. These organisms secrete hemolysins and streptolysins O and S, which are cardiototoxic, leukocytic, and responsible for the characteristic hemolysis. Gangrene results when the cutaneous blood vessels thrombose, a finding that is often associated with intense local pain. The involved skin is initially erythematous and indurated and quickly evolves to hemorrhagic blebs with focal necrotic zones. The potential for extensive tissue loss and mortality exists, especially if treatment is delayed. Prompt, aggressive tissue debridement and antibiotic therapy are necessary for a favorable outcome (see Table 1).

**Synergistic Necrotizing Cellulitis**

Synergistic necrotizing cellulitis (SNC) is an extremely aggressive, often lethal, polymicrobial infection of the skin and soft tissues that exhibits progressive invasion superficial to fascial planes. This condition may initially begin as a benign process with scant indication of its impending severity. The initial lesion is typically an erythematous, tender pustule or abscess with a small area of necrosis. The benign appearance of this lesion belies the widespread and aggressive tissue destruction that has occurred beneath it.

Direct inspection through skin incisions reveals extensive gangrene of the superficial tissues and fat that rarely involves the underlying fascia and muscles. These lesions characteristically exude a thin, brown, malodorous discharge, which manifests mixed flora with abundant polymorphonuclear leukocytes with a Gram stain. Crepitus, which is caused by the accumulation of gas in the tissue produced by facultative or obligate anaerobes, can be palpated in 25% of patients, and it mandates immediate surgical attention.

The most common site of involvement is the perineum, which is involved in 50% of patients with SNC. Predisposing factors include perirectal abscess and ischiorectal abscess, both of which may track to the deeper structures of the pelvis, leading to abscess formation and subsequent septicemia. The thigh and leg are involved in approximately 40% of patients. This infection can occur after amputation and is usually associated with diabetes mellitus (75% of cases) or peripheral vascular disease (50% of cases). The relative immunosuppression and poor circulation that accompany these significant causes of morbidity are also responsible for upper extremity and neck SNC, which account for the remaining 10% of cases.

Synergistic necrotizing cellulitis is commonly caused by mixed flora originating in the gastrointestinal tract. Coiiforms are the most prevalent aerobes (*Escherichia coli*, Klebsiella, Proteus), and anaerobic flora include Bacteroides, Peptostreptococcus, Clostridium, and Fusobacterium. The primary treatment modality is aggressive debridement of nonviable skin and subcutaneous tissues. This may involve several operations and dressing changes under general anesthesia, which should be performed until all necrotic tissue is removed. Rotation or free myocutaneous flaps and split-thickness skin grafting may cover areas of tissue loss when necessary. If the perineum is involved, fecal diversion by colostomy may be necessary to facilitate healing. Empiric parenteral antibiotics effective against polymicrobial gram-positive and gram-negative aerobic and anaerobic flora are also a mainstay of therapy. However, antibiotic coverage must be modified as soon as culture and susceptibility testing reveal specific offending organisms (Table 2) to reduce the emergence of resistant organisms.

**Clostridial Myonecrosis**

Clostridial myonecrosis (i.e., gas gangrene) is a destructive infectious process of muscle associated with infections of the skin and soft tissues. It is often associated with local crepitus and systemic signs of toxemia, which are caused by the anaerobic, gas-forming
bacilli of the *Clostridium* species. This infection most often occurs after abdominal operations on the gastrointestinal tract; penetrating trauma, such as gunshot wounds, and frostbite can also expose muscle, fascia, and subcutaneous tissues to these organisms. Common to all these conditions is an environment containing tissue necrosis, low oxygen tension, and sufficient amounts of amino acids and calcium to allow germination of clostridial spores and production of the lethal z toxin.

Clostridia are gram-positive, spore-forming, obligate anaerobes that are widely found in soil contaminated with animal excreta. They have also been isolated in the human gastrointestinal tract and skin, most importantly in the perineum and oropharynx. *Clostridium perfringens* is the most common isolate (in 80% of cases) and is among the fastest growing clostridial species, having a generation time under ideal conditions of approximately 16 minutes. This organism produces collagenases and proteases that cause widespread tissue destruction and produces z toxin, which is associated with the high mortality rate of clostridial myonecrosis. The z toxin, a phospholipase C, causes platelet-neutrophil complexes, vascular obstruction, and extensive compromised vascular perfusion, leading to necrosis of the muscle and overlying fascia, skin, and subcutaneous tissues.

Historically, clostridial myonecrosis was a disease associated with battle injuries, but 60% of current cases occur after trauma: 50% after automobile accidents and the remainder after crush injuries, industrial accidents, and gunshot wounds. Mortality can be the result of a failure to recognize that clostridial infection is underway, which leads to a delay in the debridement of devitalized tissues. Patients often complain of a sudden onset of pain at the site of trauma or surgical wound, which increases rapidly in severity and extends beyond the original borders of the wound. The skin initially exhibits tense edema, but its pale appearance progresses to a magenta hue. Hemorrhagic bullae and a thin, watery, foul-smelling discharge are common. A Gram stain examination of wound discharge reveals abundant gram-positive rods with a paucity of leukocytes.

The diagnosis of gas gangrene is based on the appearance of the muscle on direct visualization by surgical exposure, because many changes are not apparent when inspected through a small traumatic wound. Initially, the muscle is pale, edematous, and unresponsive to stimulation. As the disease process continues, the muscle becomes frankly gangrenous, black, and extremely friable. This occurs as a late event and is often accompanied by septicemia and shock. Despite profound hypotension and impeding organ failure, these patients may be remarkably alert and extremely sensitive to their surroundings. They feel their impending doom and activity failure, these patients may be remarkably alert and extremely sensitive to their surroundings. They feel their impending doom and soon panic just before slipping into toxic delirium and eventually into coma.

The clinical features should arouse suspicion early in the course, so the disease can be recognized and treated with aggressive surgical débridement. Gas in the wound is a relatively late finding, and by the time crepitation is observed, the patient may be near death. Approximately 15% of blood cultures are positive, but this is also a late finding. Serum creatinine kinase levels, although relatively nonspecific, are always elevated in cases with muscle involvement.

The mortality rate for gas gangrene is as high as 60%. It is highest in cases involving the abdominal wall and lowest in those affecting the extremities. Among the signs that prognosticate a poor outcome are leukopenia, thrombocytopenia, hemolysis, and severe renal failure. Myoglobinuria is common and can contribute significantly to worsening renal function. Frank hemorrhage may also be present and indicates disseminated intravascular coagulation.

Successful treatment of this life-threatening infection depends on early recognition and débridement of devitalized and infected tissues. Hyperbaric oxygen and systemic antibiotics are important adjuncts. Surgical intervention should include wide débridement of all necrotic tissue and amputation if extremities are involved. Hyperbaric oxygen (100% O₂ at 3 atm) has been reported to reduce associated tissue loss and mortality; however, core treatment is surgical débridement, and it should never be delayed to arrange for hyperbaric oxygen treatments. In animal studies of gas gangrene, hyperbaric oxygen was not efficacious, whereas clindamycin (Cleocin) treatment had dramatic effects in reducing mortality.

A parenteral antibiotic is directed toward the offending organism (see Table 1). Clindamycin is the treatment of choice because of its ability to suppress toxin production. Cardiovascular collapse mandates careful monitoring of intravenous fluid resuscitation, which may require large volumes. Failure to adequately resuscitate these patients compromises therapy by limiting oxygen delivery and antibiotic distribution to the affected tissues and may promote progression to multisystem organ failure.

A less life-threatening form of this disease is known as clostridial cellulitis. In this process, the bacterial tissue invasion is primarily superficial, extending to the fascial layer without muscle involvement. Prompt recognition and treatment can reduce morbidity and mortality. Spontaneous gas gangrene caused by *Clostridium septicum* can occur in the absence of trauma in patients with gastrointestinal lesions such as carcinoma of the colon.

### Necrotizing Fasciitis

Necrotizing fasciitis is an aggressive soft tissue infection involving the fascia with extensive undermining and tracking along anatomic planes. This process usually occurs in patients with significant comorbidity, such as diabetes mellitus or peripheral vascular disease, but it is also seen in obese or malnourished patients and intravenous drug abusers. Cellulitis is a frequent occurrence, and progressive necrosis to subcutaneous tissue results from thrombosis of the perforating vessels. Necrotizing fasciitis can be caused by single organisms such as GAS and staphylococci (MRSA), *Vibrio vulnificus* or *Aeromonas hydrophila*, or a combination of a variety of organisms, including aerobic streptococci, staphylococci, and coliforms, as well as anaerobic *Peptostreptococcus* and *Bacteroides*. Ninety percent of these infections have a polymicrobial cause, and it is common to culture up to five organisms from the fascial planes involved with this infection.

Polymicrobial necrotizing fasciitis most commonly evolves from a benign-appearing skin lesion (80% of cases). Minor abrasions, insect bites, injection sites, and perirectal abscesses have been implicated. Rare cases have been reported in women with Bartholin’s gland abscess, from which the infection has spread to fascial planes of the perineum and thigh. The remaining 20% of patients have no visible skin lesion. Surgical procedures, especially bowel resections, and penetrating trauma can be complicated by superficial wound infections that evolve into necrotizing fasciitis. The infection commonly involves the buttocks and perineum, which results from untreated perirectal abscesses or decubitus ulcers; intravenous drug abusers commonly participate in *skin popping*, which leads to infections of the upper extremities.
Fifty percent of group A streptococcal necrotizing fasciitis patients have a portal of entry such as an insect bite, slivers, surgical procedures, or burns, whereas the other 50% have no portal of entry, and the infection begins at the exact site of nonpenetrating trauma, such as a muscle strain or bruise. This idiopathic form, commonly known as spontaneous necrotizing fasciitis, is particularly dangerous because of the frequent delay in diagnosis.

For those with a portal of entry, the initial presentation is a slowly advancing cellulitis that progresses to a firm, tense, woody feel of the subcutaneous tissues. This entity may be distinguished from other aggressive anaerobic soft tissue infections (e.g., SNC) by the brawny, pale, erythematous appearance of the skin overlying subcutaneous tissues that are unyielding, making fascial planes and muscle groups indistinguishable during palpation. Often, a broad, erythematous tract along the route of the underlying fascial plane can be discerned through the skin. If an open wound exists, probing the edges with a blunt instrument permits ready dissection of the superficial fascia well beyond the wound margins, and this is the most important diagnostic feature of necrotizing fasciitis. On direct inspection, the fascia is swollen and dully gray in appearance, with stringy areas of fat necrosis. A thin, brown exudate can be expressed from the wound, but frank purulent drainage is rare. These wounds are remarkably insensate when found and mandate immediate débridement.

As with other gangrenous soft tissue infections, the most important component of the treatment plan is aggressive, total débridement of all devitalized and necrotic tissue. This often necessitates frequent operations and dressing changes. Wide débridement and parenteral antibiotics have a profound effect on survival, and limited or staged débridement has no place in the treatment of this very aggressive, life-threatening infection. Parenteral antibiotics (see Table 2) should be directed against the polymicrobial aerobic and anaerobic microorganisms isolated from these infections. Every effort should be made to quickly identify the offending organisms, and antibiotic therapy should be changed accordingly.

In patients with no defined portal of entry, severe pain at the site of previous nonpenetrating trauma is common. Early in the course, there may be no cutaneous evidence of infection. Severe pain and fever may be the only presenting symptoms. These patients usually have a slightly elevated white blood cell count with a left shift and an elevated pulse. Later, erythema, induration, and warmth occur and may rapidly progress to violaceous skin, ecchymosis, and blister formation. A markedly elevated creatine phosphokinase level in a patients with any erythematous rash may suggest a necrotizing process. By the time these late cutaneous findings are present, most patients have evidence of shock and organ failure. Misdiagnosis and delay in diagnosis are common and associated with significant morbidity and mortality. Surgical exploration with débridement of infected and necrotic tissue in addition to systemic antibiotic therapy directed toward the aerobic Streptococcus organism can result in decreased morbidity and mortality (see Table 1).

Special Circumstances

**Fournier’s Gangrene**

Fournier’s gangrene is a necrotizing fasciitis that originates as a necrotic black area on the scrotum of male patients or the labia of female patients, and it most often has a cryptogenic origin. In my experience, Fournier’s gangrene occurs more commonly without a predisposing event or after routine, uncomplicated hemorhoidectomy. Less commonly, this condition has occurred after urologic manipulation or as a late complication of deep anorectal suppuration.

Fournier’s gangrene is characterized by necrosis of the skin and soft tissues of the scrotum or perineum and is associated with a fulminant, painful, and severely toxic infection. Definitive diagnosis is made by identification of a necrotic black area on the scrotum associated with local and systemic signs of infection. Left untreated, death ensues from uncontrollable, severe systemic sepsis and multiple-organ failure. Prompt recognition and treatment can minimize tissue loss, especially the skin and soft tissues of the scrotum, labia, and perineum, and may prevent complete loss of genitalia.

The infection is often polymicrobial, as with necrotizing fasciitis, with several species of aerobic and anaerobic bacteria predominating. Successful treatment is based on early recognition and vigorous surgical débridement, occasionally including diversion of the fecal stream. Empiric treatment is appropriate until results of culture and susceptibility testing are available (see Table 2). The therapeutic benefit of hyperbaric oxygen treatments has not been proved, and it should be used only as an adjunct to surgical débridement.

**Ecthyma Gangrenosum**

Occasionally, hospitalized patients with overwhelming pseudomonal septicemia develop a patchy dermal and subcutaneous necrosis. Although sepsis caused by *Pseudomonas aeruginosa* is often indistinguishable from other types of gram-negative sepsis, a characteristic skin lesion may develop with erythematous macular eruptions that quickly become bullous with central ulceration and necrosis. This lesion may resemble a decubitus ulcer with the characteristic black eschar. There are usually multiple lesions occurring in different stages of development. They may concentrate on the extremities or the gluteal region. These lesions may be distinguished from the lesions of pyoderma gangrenosum (a noninfectious dermatosis) by their association with clinical signs of infection (i.e., fever and leukocytosis) in addition to the isolation of *P. aeruginosa* from culture of the lesion.

Treatment is primarily administration of antimicrobial therapy effective against the *Pseudomonas* organism and by débridement of the multiple lesions. This may lessen the bacterial burden, perhaps allowing greater antibiotic efficacy.

**Sea and Freshwater Infections**

Infections caused by *V. vulnificus* and *A. hydrophila* can be extremely aggressive, with necrosis often occurring within hours and necessitating rapid, wide débridement. Although infections caused by these organisms cannot be differentiated from those caused by mixed infections, a history of exposure to sea water (*V. vulnificus*) or fresh water (*A. hydrophila*) and the rapidity with which the infection spreads often suggest the cause of the infection. The antibiotics of choice for *V. vulnificus* infection are doxycycline (Vibramycin) or tetracycline and an aminoglycoside. In patients with impaired renal function, chloramphenicol (Chloromycetin) may be used. *A. hydrophila* is susceptible to cephalosporins such as ceftazidine (Fortaz), cefuroxime (Ceftin), and fluoroquinolones such as levofloxacin (Levaquin) and ciprofloxacin (Cipro).

**Conclusions**

The many types of soft tissue infections caused by bacteria may be distinguished by their presenting signs, symptoms, and body location and by the time course of the pathologic processes unique to each. Early recognition is of paramount importance to an effective treatment plan, which most often includes aggressive surgical débridement and specific antimicrobial therapy. This approach can often minimize tissue damage and promote recovery.

**References**


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and neutrophils, to the basement membrane, as well as activation chemotaxis of inflammatory cells, particularly eosinophils. The latter results in antibodies against one or more components of the basement membrane. The pemphigus group of diseases is associated with antibodies to different desmosomal proteins. There is strong direct experimental evidence that these antibodies cause acantholysis and blister formation directly without significant participation of cellular components of the immune system. The subepidermal autoimmune bullous diseases, however, result from genetically controlled immune dysregulation. Because autoimmune bullous disorders result from immune dysregulation, the principle of treatment is immune modulation. Immune modulation can be accomplished by several methods: blocking antibody production by B cells and plasma cells, eliminating antibodies from the circulation, suppressing inflammation, or inducing resistance of target epithelial cells to separation and blister formation. Antibody production by B cells and plasma cells may be blocked by destroying the B cell lineage or suppressing activation of T or B cells. The former is accomplished by the drug rituximab (Rituxan) and, to a lesser degree, cyclophosphamide (Cytoxan), and the latter may be accomplished by many immunosuppressive agents including corticosteroids, azathioprine (Imuran), cyclosporine (Neoral), cyclophosphamide, methotrexate (Trexall), and mycophenolate mofetil (Cellcept). Antibodies may be eliminated from circulation by plasma exchange, or plasmapheresis, immunoapheresis. Plasmapheresis, immunoapheresis is rarely required for blister formation. Experimental animals that lack complement or leukocytes fail to develop lesions when injected with patients’ serum antibodies.

Prevention
There are no methods for preventing autoimmune bullous diseases. These disorders result from genetically controlled immune dysregulation.

Clinical Manifestations
Clinical manifestations are described for each disease separately under the section on therapy.

Complications
Severe blistering can lead to extensive erosions that heal slowly, especially in the elderly and in those with nutritional deficiencies or systemic disease. Slow healing of extensive erosions predisposes patients to considerable loss of fluids and electrolytes as well as secondary bacterial infection and sepsis. Superficial erosions can become ulcers owing to increased local pressure in immobile and bedridden patients. Temperature regulation can also be compromised following loss of large areas of epidermis. Over the past several decades, mortality from bullous disease has decreased significantly. At present, the common causes of death are complications of the pharmacologic agents used in the treatment.

Diagnosis
The diagnosis of autoimmune bullous diseases requires clinical evaluation, histopathology, direct immunofluorescence, and indirect immunofluorescence. The ideal specimen for direct immunofluorescence should be from normal-appearing skin immediately adjacent to a lesion (peri-lesional skin). Immunofluorescence tests are usually performed in specialized immunopathology laboratories and are best interpreted by a dermatopathologist with special expertise in the area of immunofluorescence and autoimmune bullous diseases.

Differential Diagnosis
An accurate diagnosis is essential for predicting the course and prognosis of a disease as well as for choosing therapy. Autoimmune bullous diseases overlap clinically and histologically, hence the need for immunofluorescence studies. For example, epidermolysis bullosa acquisita can have clinical and histologic overlap with both bullous pemphigoid and linear IgA disease. The three diseases, however, have different courses and therapeutic responses and may be easily differentiated on the basis of immunofluorescence tests.

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Because autoimmune bullous disorders result from immune dysregulation, the principle of treatment is immune modulation. Immune modulation can be accomplished by several methods: blocking antibody production by B cells and plasma cells, eliminating antibodies from the circulation, suppressing inflammation, or inducing resistance of target epithelial cells to separation and blister formation. Antibody production by B cells and plasma cells may be blocked by destroying the B cell lineage or suppressing activation of T or B cells. The former is accomplished by the drug rituximab (Rituxan) and, to a lesser degree, cyclophosphamide (Cytoxan), and the latter may be accomplished by many immunosuppressive agents including corticosteroids, azathioprine (Imuran), cyclosporine (Neoral), cyclophosphamide, methotrexate (Trexall), and mycophenolate mofetil (Cellcept). Antibodies may be eliminated from circulation by plasma exchange, or plasmapheresis, immunoapheresis. Plasmapheresis, immunoapheresis is rarely required for blister formation. Experimental animals that lack complement or leukocytes fail to develop lesions when injected with patients’ serum antibodies.

Prevention
There are no methods for preventing autoimmune bullous diseases. These disorders result from genetically controlled immune dysregulation.

Clinical Manifestations
Clinical manifestations are described for each disease separately under the section on therapy.

Complications
Severe blistering can lead to extensive erosions that heal slowly, especially in the elderly and in those with nutritional deficiencies or systemic disease. Slow healing of extensive erosions predisposes patients to considerable loss of fluids and electrolytes as well as secondary bacterial infection and sepsis. Superficial erosions can become ulcers owing to increased local pressure in immobile and bedridden patients. Temperature regulation can also be compromised following loss of large areas of epidermis. Over the past several decades, mortality from bullous disease has decreased significantly. At present, the common causes of death are complications of the pharmacologic agents used in the treatment.

Diagnosis
The diagnosis of autoimmune bullous diseases requires clinical evaluation, histopathology, direct immunofluorescence, and indirect immunofluorescence. The ideal specimen for direct immunofluorescence should be from normal-appearing skin immediately adjacent to a lesion (peri-lesional skin). Immunofluorescence tests are usually performed in specialized immunopathology laboratories and are best interpreted by a dermatopathologist with special expertise in the area of immunofluorescence and autoimmune bullous diseases.

Differential Diagnosis
An accurate diagnosis is essential for predicting the course and prognosis of a disease as well as for choosing therapy. Autoimmune bullous diseases overlap clinically and histologically, hence the need for immunofluorescence studies. For example, epidermolysis bullosa acquisita can have clinical and histologic overlap with both bullous pemphigoid and linear IgA disease. The three diseases, however, have different courses and therapeutic responses and may be easily differentiated on the basis of immunofluorescence tests.

Treatment
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plasmapheresis, high-dose intravenous immunoglobulin (IVlg, Gammagard), and immunoadsorption.

Inflammation that is required for blister formation, especially in subepidermal bullous diseases, may be suppressed by several agents. These include systemic and topical corticosteroids, dapsone, tetracyclines, erythromycin, nicotinamide, and etanercept (Enbrel). Although not yet available, agents that experimentally inhibit signal transduction and agents that inhibit apoptosis can induce resistance of the target epidermal or epithelial cell to separation (acantholysis) and blister formation.

The choice of agents in therapy of bullous diseases requires evaluation of both disease-specific parameters and patient-specific parameters. Disease-specific parameters include the pathophysiology of the disease and its severity; patient-specific parameters include age and concomitant illness such as diabetes, hypertension, active infection, or cancer. There are very few controlled studies that provide high-quality evidence for bullous disease therapy. This is primarily a result of the rarity of many of these disorders. Because of the relative frequency of bullous pemphigoid, some controlled studies have been performed on the disease in Europe. Most of the evidence for bullous disease therapy is available from case reports, case series, and personal experience.

Pharmacologic Treatment

Glucocorticoids
Glucocorticoids (prednisone, prednisolone) have both antiinflammatory and immunosuppressive effects. Long-term use of glucocorticoids is associated with well-known adverse effects.

Azathioprine
Azathioprine (Imuran) interferes with de novo purine synthesis and hence DNA synthesis. This results in suppression of T-cell function and a decrease in B-cell antibody production. In low doses (1–2 mg/kg/day), azathioprine is usually well tolerated. In higher doses (2–4 mg/kg/day), bone marrow may be suppressed, resulting in leukopenia (most commonly) and, less commonly, thrombocytopenia and anemia. Severe bone marrow suppression can occur in patients who are homozygous deficient for the enzyme thiopurine methyltransferase. Other adverse effects include hepatoxicity and gastrointestinal toxicity as well as pancreatitis and severe in patients who are genetically predisposed, and agranulocytosis (not dose-related and usually occurs in the first 3 months of therapy).

Mycophenolate Mofetil
Mycophenolate mofetil is a purine analogue antimetabolite that inhibits inosine monophosphate dehydrogenase, resulting in suppression of purine and DNA synthesis and hence suppression of both T and B cell function. Mycophenolate mofetil is usually well tolerated.

Methotrexate
Methotrexate is an antimetabolite and a folic acid analogue. Its metabolites inhibit folate-dependent enzymes of de novo purine and thymidylate synthesis. This results in the suppression of DNA and RNA synthesis, which causes decreased lymphocyte function and hence immune modulation.

Cyclophosphamide
Cyclophosphamide is an alkylating agent that binds DNA, resulting in cell cycle arrest, DNA repair, and cell death. The most susceptible cells reside in rapidly proliferating tissues. The toxicity of cyclophosphamide is significantly higher than that of azathioprine, mycophenolate mofetil, and methotrexate. Acute myelosuppression is common, with a nadir at 6 to 10 days and recovery in 2 to 3 weeks. Both cellular and humoral immunity are suppressed.

Cyclosporine
Cyclosporine significantly suppresses cellular immunity and preferentially inhibits antigen-triggered signal transduction in T lymphocytes, which results in decreased expression of several lymphokines. Cyclosporine forms complexes with the receptor protein cyclophilin in the cytoplasm. The complex binds and inhibits calcineurin, resulting in failure of T cells to respond to antigenic stimulation.

Several drugs can interact with cyclosporine and influence its blood level. Agents that can increase cyclosporine blood level include calcium channel antagonists (diltiazem [Cardizem], nicardipine [Cardene], and verapamil [Calan]), systemic antifungal agents (fluconazole [Diflucan], itraconazole [Sporanox], and ketoconazole [Nizoral]), antibacterials (clarithromycin [Biaxin], erythromycin), methylprednisolone (Medrol), other drugs (allopurinol [Zyloprim], bromocriptine [Parlodel], danazol [Danocrine], metoclopramide [Reglan], colchicine [Colcrys], and amiodarone [Cordarone]), and grapefruit juice.

Dapsone
Dapsone is highly effective in neutrophil-mediated conditions. The mechanism of action of dapsone is not well understood. Its clinical benefit in inflammatory conditions probably results from inhibition of neutrophil chemotaxis. Dapsone is associated with multiple potential adverse effects that include dose-related hemolysis, methemoglobinemia (which is common and may be severe in patients who are genetically predisposed), and agranulocytosis (not dose-related and usually occurs in the first 3 months of therapy).

Niacinamide
Niacinamide (Nicotinamide) is a vitamin whose mechanism of action in cutaneous disorders including autoimmune bullous diseases is not known.

High-Dose Intravenous Immunoglobulin
IVlg is a purified human source of immunoglobulin that is given as a slow infusion over 6 to 8 hours. Treatment is repeated every 3 to 4 weeks. IVlg is highly expensive.

Rituximab
Rituximab is a chimeric monoclonal antibody against CD20 on the surface of pre-B, mature B, and malignant B cells and is not expressed on stem, pre-B, or plasma cells. B cells are depleted primarily by antibody-dependent cellular cytotoxicity and, to a lesser degree, by complement-dependent cytotoxicity or apoptosis. Rituximab is given in different regimens, including 375 mg/m²/week (approximately 500 mg for an average-size adult) for 4 consecutive weeks, or 1000 mg once or on two occasions 2 weeks apart.

Plasmapheresis and Immunoapheresis
Plasmapheresis and immunoapheresis are procedures that aim to physically remove pathogenic antibodies. Plasmapheresis consists of withdrawing the patient’s blood, filtering cellular elements from the plasma, and returning the cellular components to the patient. Immunoapheresis consists of exposing the patient’s plasma to an immunoglobulin-binding matrix that contains the disease-specific antigen. Plasmapheresis and immunoapheresis are usually used in

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1Not FDA approved for this indication.
Dermatitis Herpetiformis

Dermatitis herpetiformis results from an immune response to gluten and manifests as pruritic papulovesicles over the elbows, knees, buttocks, and scalp. A gluten-free diet is extremely helpful and is often the addition of this combination to prednisone can have a corticosteroid-sparing effect.

Mucous Membrane Pemphigoid

Therapy for mucous membrane pemphigoid varies with the disease location, extent, and severity. In limited oral disease, local therapy with topical anesthetic agents and topical glucocorticoids in addition to oral hygiene can suffice. The steroid may be applied under occlusion with a prosthesis device or may be injected intraorally. Patients with extensive oral involvement can require systemic therapy.

Dapsone is effective in some patients with oral mucous membrane pemphigoid. The drug may be started at 50 mg daily and increased gradually. Tetracyclines, with or without niacinamide, may be effective. In patients with severe oral disease and in patients with ocular, pharyngeal, or laryngeal involvement, systemic glucocorticoids, in combination with cyclophosphamide are indicated. In my experience, most patients have an excellent response, with a prolonged remission after treatment with the combination of prednisone (1 mg/kg/day for 6 months) and cyclophosphamide (1–2 mg/kg/day for 18–24 months).

Azathioprine and mycophenolate mofetil are generally less effective but may be used if there are contraindications to steroid or cyclophosphamide use. High-dose IVIg may be used for patients who are refractory to other therapy.

Patients with severe ocular scarring might benefit from cryotherapy ablation of eyelashes. Ocular surgery is contraindicated when the disease is active. Surgical intervention may cause severe flares of the disease.

Epidermolysis Bullosa Acquisita

Unlike bullous pemphigoid and other subepidermal autoimmune bullous diseases, epidermolysis bullosa acquisita is generally resistant to therapy. The disease waxes and wanes, with periods of exacerbation and remission. Trauma contributes to blister formation, especially in the classic form of epidermolysis bullosa acquisita. The inflammatory form of epidermolysis bullosa acquisita responds more easily to therapy than the classic form.

Because of the neutrophil predominance in the inflammatory form, patients might respond to dapsone. The drug may be started at a dose of 50 mg daily and increased by 50 mg every week until clinical remission (usually 100–250 mg). The dose is maintained for several months. If the patient remains in remission, the dose may be decreased slowly and ultimately discontinued. Colchicine 0.6 mg two or three times daily is variably effective. Patients who do not tolerate or do not respond to colchicine and dapsone may be treated with oral glucocorticoids such as prednisone in a dose of 0.5–1 mg/kg/day in divided doses. The response is variable. If there is no response to glucocorticoids or the patient develops adverse effects, cyclosporine 4–6 mg/kg/day may be initiated and is usually associated with a rapid response. Once disease activity is controlled, the dose may be slowly decreased. Cyclosporine should be discontinued if there is no response in a few weeks.

The duration of treatment varies with the course of the disease. The same agents used for the inflammatory form may be used for the classic form. The latter is generally more resistant to treatment. Patients who fail to respond may be treated with immunosuppressive agents such as azathioprine, cyclophosphamide, mycophenolate, or methotrexate in a manner similar to pemphigus vulgaris, bullous pemphigoid, or mucous membrane pemphigoid. Patients who are resistant to these agents may be treated with extracorporeal photochemotherapy or with IVIg alone or in conjunction with plasmapheresis.

Dermatitis Herpetiformis

Dermatitis herpetiformis results from an immune response to gluten and manifests as pruritic papulovesicles over the elbows, knees, buttocks, and scalp. A gluten-free diet is extremely helpful and is often
associated with a marked decrease in the requirement for pharmacologic therapy. A strict gluten-free diet can result in complete remission of the disease without requiring dapsone. Reintroduction of gluten-containing diet results in rapid recurrence of the disease.

Many patients find a strict gluten-free diet too restrictive and instead choose pharmacologic therapy. The drug of choice is dapsone. Treatment is initiated with dapsone 50 mg daily and is increased by 25 to 50 mg every week as needed and as tolerated. The average daily maintenance dose is 100 mg. Some patients require slowly increasing doses several years later, likely secondary to increased deposition of IgA in the skin that results in increased disease activity.

In patients who are intolerant or allergic to dapsone, therapy with sulfapyridine may be considered. The initial dose is 500 mg three times daily and may be increased slowly to 2 g three times daily. The response to sulfapyridine is not as predictable as that to dapsone. Patients who are allergic to dapsone often tolerate sulfapyridine.

Patients who are intolerant or allergic to dapsone and sulfapyridine may be treated with colchicine, cholestyramine (Questran), heparin, tetracycline, or nicotinamide. These agents are much less effective than dapsone and sulfapyridine. Topical steroids are only minimally effective.

**Linear Immunoglobulin A Disease**

Linear IgA disease is mediated by neutrophils and clinically mimics bullous pemphigoid and dermatitis herpetiformis. Dapsone is the first-line agent. The drug may be started at 25 to 50 mg daily and increased by 25 to 50 mg every 1 to 2 weeks until an effective dose is reached. Patients with early disease tend to respond to lower doses of dapsone.

Sulfapyridine is an alternative agent for patients who cannot tolerate dapsone. The starting dose is 500 mg twice daily and may be increased by 1000 mg every 1 to 2 weeks until the disease is adequately controlled. Colchicine 0.6 mg 2–3 times daily may also be used if a patient is allergic to dapsone. Glucocorticoids may be added if patients do not respond completely to these agents.

Tetracyclines in combination with niacinamide have been reported to be effective. The dose of tetracycline is 500 mg 4 times daily. Alternatively, doxycycline or minocycline 100 mg twice daily may be used. The dose of niacinamide is 500 mg three times daily. Cyclosporine or high-dose IVIg may be used in resistant cases.

**Pemphigus**

**Pemphigus Vulgaris.** Pemphigus vulgaris often manifests with erosions in the oral cavity that may be followed by skin blisters. Successful therapy suppresses the production of pathogenic auto-antibodies. Therefore immunosuppressive drugs are used. A positive clinical response is associated with a decrease in or absence of pathogenic circulating autoantibodies in the serum and then absence of bound autoantibodies in the skin. There has been a dramatic decrease in the mortality of pemphigus vulgaris owing to the increasing availability of immunosuppressive drugs and glucocorticoids, as well as earlier diagnosis and treatment.

Unless there is an absolute contraindication, the initial therapy of pemphigus vulgaris is systemic glucocorticoids. Prednisone is the most commonly used agent. The initial dose is 1 mg/kg/day divided into two or three doses. Most patients obtain remission within 4 to 12 weeks. The dosage is maintained for 6 to 10 weeks, then decreased by 10 to 20 mg every 2 to 4 weeks. If there is no recurrence, the patient is maintained on 5 mg daily or every other day for several years. Pulsed-steroid therapy with intravenous methylprednisolone, 1 g daily for 3 consecutive days, is reserved for severe cases. The goal of this approach is to quickly achieve the immunosuppressive effects of glucocorticoids while avoiding the long-term side effects.

If prednisone fails to induce a remission, or if the patient develops serious adverse effects, adjuvant immunosuppressive drugs should be instituted. My practice is to initiate adjuvant therapy concomitant with steroid therapy to decrease the total dose of glucocorticoid used. The glucocorticoid is tapered rapidly and the patient is maintained on the steroid-sparing agent for 24 to 36 months. The most commonly used steroid-sparing immunosuppressive drugs are azathioprine and mycophenolate mofetil. Cyclophosphamide is used for resistant cases at a dose of 2 to 3 mg/kg/day, azathioprine at a dose of 3 to 5 mg/kg/day, and mycophenolate at a dose of 2 to 3 g daily (or 40 mg/kg/day in two divided doses). Methotrexate may also be used, but it is generally less effective than other treatments.

The response of pemphigus vulgaris to cyclosporine is controversial. High-dose IVIg has a rapid onset of action and appears most effective when used as an adjuvant to conventional therapy, especially as a steroid-sparing agent. Plasmapheresis is used in refractory cases. To avoid the rebound phenomenon (increased production of autoantibodies), immune suppression (usually with cyclophosphamide) is used concomitantly with plasmapheresis. Rituximab has been used successfully in several cases of pemphigus vulgaris and other autoimmune bullous diseases. For resistant cases, extracorporeal photochemotherapy may be considered.

**Pemphigus Foliaceus.** The principles and practice of managing pemphigus foliaceus are similar to those for pemphigus vulgaris.

**Paraneoplastic Pemphigus.** Paraneoplastic pemphigus is a unique intraepidermal blistering disease associated with antibodies against a unique set of skin and internal organ antigens. The most common associated neoplasms are lymphoproliferative. The management of paraneoplastic pemphigus consists of the treatment of the underlying neoplasm as well as immune suppression. Surgical excision of benign neoplasms such as thymoma and Castleman’s disease can result in clinical and serologic improvement. In patients with malignant neoplasms, treatment of the associated neoplasm might not result in remission. Generally, skin lesions respond more rapidly than mucosal lesions.

Systemic glucocorticoids are often used as the first-line agent in a dose of 1 to 2 mg/kg/day. Patients usually have a partial response and rarely have complete resolution of lesions. Other immunosuppressive drugs have been used with variable success. These include mycophenolate mofetil, azathioprine, and cyclosporine.

Rituximab has been reported to be effective in a case of paraneoplastic pemphigus associated with CD20-positive follicular lymphoma and in a case of paraneoplastic pemphigus associated with follicular non-Hodgkin’s lymphoma. Immunoapheresis has been used successfully occasionally.

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*Not FDA approved for this indication.*

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*Not FDA approved for this indication.*
Nonmelanoma skin cancer (NMSC) is a heterogeneous group of skin malignancies that includes basal cell cancer (BCC) and squamous cell cancer (SCC). These are the most common skin cancers and NMSC in the stricter sense of the definition (Figure 1). The more-inclusive use of the term NMSC also includes malignant neoplasms of adnexal, fibrohistiocytic, and vascular origin, as well as Merkel cell carcinoma and metastatic tumors. The vast majority of NMSCs are slowly growing and locally invasive neoplasms that are often diagnosed and treated by dermatologists. Management of the more aggressive tumors often requires a team approach to diagnosis, treatment, and clinical follow-up (Table 1).

**Basal Cell Carcinoma**

BCC accounts for the majority of NMSC seen in the United States and is increasingly diagnosed in younger patients. Light skin complexion and history of ultraviolet (UV) light exposure are the predominant risk factors for BCC in the majority of the population. Intermittent intense UV light exposures early in life, but not cumulative UV light exposure, pose the highest risk factor for developing BCC later in life. Other risk factors for BCC include exposure to ionizing radiation, psoralen photochemotherapy, arsenic, and smoking. A history of BCC also increases one’s risk for developing a subsequent BCC. Immunosuppression, especially in recipients of solid-organ transplants, presents a significant risk factor for BCC. Inherited genodermatoses such as Gorlin’s, Bazex’s, and Rombo’s syndromes, xeroderma pigmentosum, and some forms of albinism are predisposing factors for BCC as well. Mutations in PTCH1 that are found in Gorlin’s syndrome have been shown to be an early event underlying BCC pathogenesis.

Clinically, BCC is most commonly found on the head and neck region, though any part of the body can develop this tumor. The presentation varies depending on the histologic subtype of the tumor. Although many histologic variants of BCC exist, the most common subtypes are superficial, nodular and micronodular, morpheaform, and metatypic. The histologic heterogeneity results in variable clinical findings. Superficial BCC typically forms an erythematous scaly patch or plaque. Nodular BCC is the more classic appearing lesion, a pink pearly nodule with or without central crust or ulcer. Unlike these subtypes, morpheaform BCC clinically resembles an ill-defined scar; it is the most histologically aggressive variant with a tendency for deep local invasion. Metatypic BCC is also known as basosquamous carcinoma, because it has histologic features of both BCC and SCC; though it is distinguished from the latter by molecular markers. This subtype also has a tendency for more-aggressive growth.

Although it is potentially locally destructive, BCC rarely metastasizes. Successful treatment of this tumor involves its local eradication. A number of treatment options exist and depend on the histologic subtype of the tumor. For small, superficial tumors, a nonsurgical approach can suffice, though nonsurgical treatment often carries a higher risk of recurrence than surgical treatment. Nonsurgical options include topical 5-fluorouracil (Efudex 5%), topical imiquimod (Aldara), liquid nitrogen cryotherapy, photodynamic therapy, and local radiation therapy. Electrodesiccation and curettage (ED&C) is an option that has a high cure rate for small and superficial tumors (95% to 98%). Standard excision with adequate margins is an appropriate surgical treatment providing good cure rates, especially for tumors with nonaggressive histologic pattern. Mohs micrographic surgery (MMS) offers the advantage of precise margin examination during excision and therefore carries the lowest overall rate of recurrence. This tissue-sparing procedure is also advantageous in terms of reconstruction on cosmetically sensitive regions. MMS is indicated to treat recurrent tumors, those in immunosuppressed patients, aggressive histologic variants, and BCCs located on certain areas of the face known to carry a higher risk of recurrence.

**Squamous Cell Carcinoma**

Cutaneous squamous cell carcinoma (SCC) is the second most common skin malignancy. Its incidence is rising among both men and women in the United States. Development of SCC is intimately linked to the cumulative ultraviolet radiation exposure of the patient via a mechanism that combines DNA damage with immunosuppression. History of ionizing radiation exposure is a risk factor as well. Similar to BCC, occupational exposures such as arsenic can also predispose one to SCC. Patients with xeroderma pigmentosum or oculocutaneous albinism also are at higher risk for SCC.

Chronic inflammation or injury can predispose to epidermal malignant transformation. Examples of this phenomenon are SCC developing within scars from burns, in chronic ulcers and skin overlying osteomyelitis, and in persistent lichen sclerosus or lichen planus. These tumors have a more-aggressive behavior and higher rates of metastasis. Human papilloma virus (HPV) predisposes to SCC. Verrucous carcinoma, a well-differentiated subtype of SCC, has a well-documented association with HPV types 6 and 11.

Transplant patients are at high risk for SCC that correlates with the degree of immunosuppression. In fact, SCC development is up to 250 times greater in the immunosuppressed compared to the general population, whereas BCC increases to a lesser extent with immunocompromise. A more common association between HPV and SCC has been noted in the immunocompromised population and might account for the disproportional increase of SCC over BCC in this population.

As with BCC, history of previous SCC has been found to be a risk factor for developing a subsequent SCC. This risk appears especially pronounced in smokers.

Unlike BCC, SCC often has a precursor lesion: actinic keratosis. Histologically, actinic keratosis demonstrates partial thickness...
atypia of the epidermis, and patients often describe it as waxing and waning. Full-thickness histologic atypia is seen in SCC in situ (Bowen’s disease), whereas invasive SCC penetrates the basement membrane to invade underlying dermis. Histologically, the degree of differentiation of SCC tends to correlate with its clinical behavior. Well-differentiated lesions tend toward local invasion, as opposed to poorly differentiated SCC, which more commonly is infiltrative.

The typical clinical presentation of SCC is that of a hyperkeratotic pink plaque. More-advanced lesions may be nodular and can ulcerate. In most cases, SCC shows only local invasion; however, perineural invasion and rarely metastasis are more likely with SCC than BCC. The central face, temples, and scalp present high-risk zones for recurrence and metastasis.

Treatment of SCC involves modalities similar to those used for BCC. Cryotherapy is the mainstay of treatment for actinic keratoses. Topical treatment with 5-fluorouracil (Carac 0.5%, Fluoroplex 1%, Fluorouracil 2%, Efudex 5%), imiquimod (Aldara) or photodynamic therapy is often used as field therapy to depopulate large regions of the skin of actinic keratosis lesions. Continued sun protection has been shown to be of benefit to prevent progression from actinic keratosis to SCC, especially in the immunocompromised population. SCC in situ may be treated with ED&C. Excision with a clear surgical margin is often used in treatment of SCC on the trunk or extremities, but MMS yields the highest cure rates, especially in high-risk areas such as the face and scalp. Adjuvant radiotherapy may be used along with surgical excision for more-aggressive tumors. Overall, the prognosis for a patient with cutaneous SCC depends heavily on location, degree of histologic differentiation, invasion, and metastasis.

### Neoplasms of Adnexal Origin

The adnexal structures of the skin include the pilosebaceous unit as well as apocrine and eccrine glands and ducts. A great number of benign and malignant tumors of adnexal origin occur in the skin. Most of the adnexal malignancies are rare. Sebaceous carcinoma and microcystic adnexal carcinoma (MAC) are two of the more common adnexal carcinomas that have an aggressive nature and may be subtle at presentation.

#### Sebaceous Carcinoma

Sebaceous carcinoma is an aggressive malignancy that is most commonly found on the head and neck region. More specifically, it is one of the more common tumors of the eyelid and periorcular area. Due to its nonspecific clinical presentation it is often treated as chalazion before biopsy and diagnosis. Population-based risk factors associated with development of sebaceous carcinoma...
include older age and European ethnicity. History of irradiation and immunosuppression predisposes to sebaceous carcinoma development, similar to BCC and SCC. Sebaceous carcinoma is one of the cutaneous neoplasms characteristic of Muir-Torre syndrome, which results from mutations in DNA mismatch repair genes and is associated with multiple sebaceous neoplasms and internal malignancy.

Clinical diagnosis of sebaceous carcinoma is difficult, and therefore progressive or nonresolving eyelid lesions require biopsy. Treatment of sebaceous carcinoma is primarily surgical. Wide local excision with 5- to 6-mm margins or MMS is indicated. A lower rate of recurrence with MMS (11.1%) has been shown as compared to local excision (32%). Close follow-up is indicated to monitor for recurrence and metastasis.

Microcystic Adnexal Carcinoma
Microcystic adnexal carcinoma (MAC) is another adnexal malignancy with predilection for the head and neck. In the United States it is most prevalent in the white population and on the left side of the body, suggesting UV irradiation as a risk factor. Although it can be seen in a wide age range of patients, older patients have a higher risk of developing MAC. The low incidence of this tumor makes it difficult to evaluate other risk factors, though cases have been reported in immunosuppressed patients and those with a history of radiation therapy.

Clinically, MAC occurs as a slowly growing, pink to flesh-colored ill-defined plaque. Paresthesia and/or numbness are common complaints and have been attributed to the high degree of perineural invasion by this tumor. MAC is a locally aggressive tumor with an unpredictable pattern of infiltrative growth. Histologically, MAC exhibits both pilar and sweat duct differentiation, deep invasion with a desmoplastic stromal response, and perineural invasion.

Surgical excision is the standard of care treatment for MAC, and radiation as an adjunct therapy is reported in a few cases. Because this tumor can extend for centimeters subclinically, MMS is favored as the first-line surgical treatment because it allows complete examination of the surgical margins intraoperatively and has been reported to have a lower recurrence rate than standard excision.

Fibrohistiocytic Malignancies
Fibrohistiocytic tumors of the skin are derived from the mesenchymal tissue and range from those of intermediate malignant potential to aggressive pleomorphic sarcomas. Of these overall rare malignancies, dermatofibrosarcoma protubersans (DFSP) and atypical fibroxanthoma are more frequently encountered.

Dermatofibrosarcoma Protubersans
DFSP is the most common fibrohistiocytic malignancy of the skin. It occurs at various ages ranging from infancy to older adulthood. The pathogenesis of DFSP involves a translocation between chromosomes 17 and 22 that fuses the collagen type 1 alpha 1 gene (COL1A1) with the platelet-derived growth factor B-chain gene (PDGFB). This fusion gene results in overexpression of PDGFB, which acts as a potent growth stimulant for mesenchymal cells. In general slowly growing, DFSPs are locally invasive and infiltrative rather than metastatic. Therefore, treatment of this tumor is primarily surgical.

A high recurrence rate has been noted in a number of studies and is attributed to the infiltrative growth of the tumor. MMS reduces recurrence rates, and is often recommended. DFSP is thought to be a radiosensitive tumor, and adjunctive radiation therapy has been successful used both pre- and postoperatively. The discovery of COL1A1-PDGFB fusion has led to trials of imatinib (Gleevec) therapy as an adjunct to surgery for DFSP. So far, a limited number of clinical reports have demonstrated regression of DFSPs during treatment with imatinib. Larger studies and long-term follow-up are needed to determine whether this warrants a change to the current treatment recommendations.

Atypical Fibroxanthoma
Atypical fibroxanthoma is a low-grade sarcoma of the skin. This locally invasive tumor favors sun-damaged skin of the head and neck region in older adults. Patients with xeroderma pigmentosum have a higher risk for developing atypical fibroxanthoma. It has a nonspecific clinical presentation, and a biopsy with histopathology is needed for diagnosis. Histologically, this tumor often exhibits marked pleomorphism and frequent mitoses. Often immunohistochemical staining is necessary for definitive diagnosis. Surgery is the treatment of choice for atypical fibroxanthoma. Either wide local excision or MMS may be used, though lower recurrence rates have been reported with MMS. Despite the pleomorphic microscopic appearance, this tumor rarely metastasizes, and the prognosis with appropriate treatment is favorable.

Vascular Malignancies
Vascular neoplasms of the skin are rare. Kaposi's sarcoma (KS) and angiosarcoma, both increasingly encountered in healthy older adults as well as immunosuppressed patients, are discussed here.

Kaposi's Sarcoma
Controversy exists regarding the nature of cell proliferation seen in KS. Some regard it as a true malignancy, and others view it as a reactive proliferation. Four types of KS exist: KS of elderly men of Jewish and Mediterranean origin, African endemic KS, immunosuppression-associated KS, and AIDS-associated KS. Infection with human herpesvirus 8 (HHV 8) is involved in the pathogenesis of all types of KS. Clinical findings include nonblanching purpuric patches and plaques that can progress to nodules with ulceration. KS can be isolated to the skin or can become disseminated to the lymph nodes and viscera. Diagnosis is established with histopathology and immunostaining. Management of KS is complex owing to the varied clinical course of the four subtypes. In cases of localized lesions, surgery, cryotherapy, or laser treatment may be useful. Radiotherapy can also be used for localized disease. Patients with disseminated KS are generally treated with chemotherapy. In AIDS-associated KS, institution of HIV medications has been shown to effect resolution of KS.

Angiosarcoma
Angiosarcoma is a more rare but aggressive vascular cutaneous malignancy that tends to metastasize and carries a poor prognosis. Clinically, angiosarcoma favors the head and neck area of elderly men; it can also arise within sites of previous radiation therapy or chronic lymphedema. No association between angiosarcoma and HHV 8 has been found. Patients present with an asymptomatic enlarging purpuric plaque that can eventually develop a nodular component. Angiosarcoma may have multifocal involvement that is often not appreciated clinically. The treatment for angiosarcoma involves wide local excision and postoperative radiation. The overall prognosis is poor, and distant metastasis-free 5-year survival rates range between 20% and 37%.

Other Nonmelanoma Skin Cancers
Merkel Cell Carcinoma
Merkel cell carcinoma (MCC) is a rare but often fatal NMSC that derives from cutaneous neuroendocrine cells. Fair skin and a history of exposure to UV light are risk factors for developing MCC. Like many other NMSCs, MCC favors the head and neck and is much more common in the elderly. Immunosuppression appears to be a risk factor for MCC development because its incidence is significantly increased in patients with AIDS and recipients of organ transplants. Polyomavirus has been implicated in the pathogenesis of MCC.
This malignancy is often metastatic upon presentation. Clinically, it occurs as a nonspecific, red asymptomatic papule or nodule. A biopsy with immunohistochemical analysis is diagnostic. The therapy for MCC involves surgery with wide local excision or MMS. Sentinel lymph node biopsy can be performed for staging purposes but should be considered on a case-by-case basis. MCC is sensitive to radiation therapy, which is a recommended adjuvant treatment for patients with lymph node involvement. Palliative chemotherapy often produces a response; however, recurrence is common. Prognosis is poor for metastatic disease or lymph node involvement.

Paget's Disease

Paget's disease refers to intraepidermal spread of adenocarcinoma. Two types are seen in the skin: mammary Paget's disease and extramammary Paget's disease. Mammary Paget's disease is most commonly seen in women and has a strict association with adenocarcinoma of the breast. The lesions are usually unilateral, scaly red plaques that favor the nipple. Often the underlying tumor is not clinically present but is detected through imaging. Other dermatoses of the nipple can resemble mammary Paget's disease, and therefore definitive diagnosis requires biopsy and immunohistochemistry. Surgical excision along with appropriate treatment of the breast cancer is the recommended treatment. Prognosis depends on the extent of breast cancer diagnosis, though it appears to be worse for breast cancer patients with mammary Paget's disease than those without.

Extramammary Paget's disease consists of two types of disease: type I disease, which is associated with distant adenocarcinoma, and type II, primary cutaneous EMPD. Both are very rare but, like mammary Paget's disease, have a female predominance. Most commonly extramammary Paget's disease is found in the genital or perianal region; however, other areas of the skin can be affected less frequently. Clinically, extramammary Paget's disease manifests as a well-demarcated red plaque that can become erosive. Long-standing disease can spread from the groin to the trunk, mimicking an inflammatory dermatosis. Definitive diagnosis is based on biopsy findings, and further work-up includes extensive screening for associated internal malignancy. Treatment relies on surgical excision with wide margins. MMS can be used to examine margins intraoperatively. Prognosis for type I extramammary Paget's disease depends on the extent of underlying tumor, but that for type II is favorable.

Cutaneous Metastases

Metastasis to the skin often heralds the systemic spread of an internal malignancy. Primary malignancy underlying the skin metastasis tends to differ by sex and age. In men, lung cancer is the most common source of skin metastasis, whereas breast cancer is the more common primary tumor in women. The head and neck are favored as sites of skin metastasis in men but the trunk is favored in women.

The clinical presentation of skin metastasis is varied and often nonspecific. A new, asymptomatic cutaneous or subcutaneous nodule may be the reason for a biopsy that reveals metastasis of an unknown primary tumor. Diagnosis is made by histopathology and appropriate molecular staining. Specific clinical patterns of metastasis may be encountered. Inflammatory carcinoma can be seen with cutaneous breast cancer metastases. Occasionally, neoplastic infiltration leads to localized areas of alopecia. Zosteriform distribution of skin metastasis has been reported with breast, colon, or squamous cell cancer. Leukemia cutis refers to skin involvement with acute myelogenous leukemia, chronic myelogenous leukemia, myelodysplastic syndromes, chronic lymphocytic leukemia, or adult T-cell lymphoproliferative disorders. In rare cases, skin involvement precedes bone marrow disease and is termed aleukemic leukemia cutis. In chronic leukemias, skin involvement tends to predict disease progression into the acute phase. Children appear to have a higher incidence of leukemia cutis as compared to adults but have a better overall prognosis.

Metastatic skin tumors are distinguished from primary cutaneous malignancies histologically. Treatment is always geared toward the primary malignancy. Regardless of type of neoplasm or site of metastasis, spread of an internal malignancy to the skin carries a poor prognosis.

References

Dermatitis typically manifests as papules and vesicles with weeping and oozing that can become lichenified and scaly when chronic. When this clinical picture is secondary to an exogenous substance coming into contact with the skin, it is termed contact dermatitis. Further delineation leads to irritant versus allergic contact dermatitis, although in practice these often overlap.

Irritant contact dermatitis is not an allergic process. It represents damage to the skin from repeated and cumulative exposure to an agent. Irritants do not require prior sensitization. Decreased barrier function of the skin, for example with frequent hand washing, can predispose or exacerbate the condition. Examples include alkalis (in soaps, detergents, and cleansers), acids (in germicides, dyes, and pigments), hydrocarbons (in petroleum and oils), and solvents.

Allergic contact dermatitis is an immunologic process classified as a type IV cell-mediated delayed hypersensitivity reaction. Poison ivy is a classic example. It requires an initial exposure to the contactant in which sensitization occurs but without outward physical effect. Subsequent exposure can elicit a striking response that is independent of the amount of the contactant.

The most common contact allergens from 1994 to 2005 have changed very little. Based on studies performed by the North American Contact Dermatitis Group (NACDG) and the Mayo Clinic Contact Dermatitis Group (MCCDG), the allergens most consistently in the top ten were nickel sulfate, balsam of Peru, fragrance mix, quaternium-15, neomycin, bacitracin, formaldehyde, and cobalt chloride (Box 1). Common sources of exposure to nickel include costume jewelry, snaps, zippers, and other metal objects. Balsam of Peru and fragrance mix 1 are markers for fragrance sensitivity. Sources of exposure to formaldehyde include skin-care products, household products, and the resins in plastics and clothing. Quaternium-15 is a formaldehyde releasing preservative and may be found in products such as skin care products, paper, inks, and photocopier toner. Neomycin and bacitracin are topical antibiotics available alone and in combination with

### CURRENT THERAPY

- Avoidance of irritants and allergens using prepared patient handout
- CARD shopping list free of most common allergens (if patch testing is not performed)
- Customized CARD shopping list based on patch test results
- Topical corticosteroids
  - Hydrocortisone 2.5% bid for face, neck, axillae, groin, intertriginous areas
  - Triamcinolone 0.1% bid for body
- Short-term, higher-potency steroids for severe reaction (e.g., clobetasol 0.05% bid)
- Sedating antihistamines: doxepin 10–20 mg nightly 2 hours before bed
- Steroid-sparing topical agents: tacrolimus 0.1%, pimecrolimus 1%
- Systemic corticosteroids: several-week tapering course for severe acute episodes (e.g., prednisone 60 mg for 5 days, 40 mg for 5 days, and 20 mg for 5 days)
- Longer-term systemic therapy for severe or recalcitrant disease
  - Phototherapy with narrowband ultraviolet B
  - Azathioprine 1–3 mg/kg daily
  - Mycophenolate mofetil 0–3 g daily
  - Methotrexate 10–25 mg weekly
  - Cyclosporine 2.5–5 mg/kg daily

### CURRENT DIAGNOSIS

- Gather Detailed History on Skin Exposures
  - Irritants
    - Alkalis: soaps, detergents, cleansers
    - Acids
    - Hydrocarbons: petroleum, oils
    - Solvents
  - Allergens
    - Nickel sulfate
    - Balsam of Peru (fragrance)
    - Fragrance mix
    - Quaternum-15 (formaldehyde-releasing preservative)
    - Neomycin
    - Bacitracin
    - Formaldehyde
    - Cobalt chloride (metals, personal products)

- Examine Skin for Location and Pattern of Eruption
  - Eyelid: nail polish
  - Postauricular scalp: perfume
  - Perioral area: chewing gum, toothpaste
  - Trunk: dyes, clothing finish
  - Wrist: nickel, chrome
  - Waistline: rubber
  - Feet: shoes
  - Wounds: topical antibiotic ointment

- Perform Patch Testing
  - TRUE Test with 35 allergens (note: one common allergen is not included in this panel)
  - Customized series with 65 or more allergens
Introduction

Eczema, also known as dermatitis, is an inflammation of the skin due to dryness, irritation, or possible external allergy. Eczema/dermatitis is not contagious. Some skin care products contain fragrance even though the package says “fragrance free” or “unscented.” Therefore, please choose the skin care products as listed below by their exact brand name.

Suggestions

Soaps/Cleansing
- Vanicream® Cleansing Bar
- Free and Clear® Liquid Cleanser
- Aveeno® Moisturizing Bar for Dry Skin Fragrance Free or Aveeno® Advanced Care Body Wash
- Oilatum® Unscented Soap
- Neutrogena® Original Formula Fragrance-Free (bar or liquid)

Any of the shampoos listed in this brochure may be used as your hand or body soap.
- Vanicream® Shave Cream for Sensitive Skin

Moisturizers
- Vanicream®, Vanicream® Lite
- Aveeno® Daily Moisturizing Lotion Fragrance Free
- Plain Vaseline®, Vaniply®
- DML® Unscented
- Use moisturizers twice daily.
- All of the above are OK to use on the face.
- After showering, blot excess water with hands and apply cream. Do not use a towel to dry.
- Robathol® bath oil

Deodorants
- Almay® unscented antiperspirants
- Plain cornstarch from the grocer can be used.

Shampoo
- Free and Clear® Shampoo and Conditioner
- DHS® Clear Shampoo and DHS® Conditioner
- If you have dandruff, use DHS® Sal Shampoo or Neutrogena® T-SAL Shampoo (not T-Gel).
- Conditioners can be used as “leave on” hair gel.

Hairspray
- Fragrance-Free hairspray such as Free and Clear® Hairspray
- Caution: Hairsprays labeled as “unscented” may not be fragrance free.

Laundry and Home Care
- Unscented laundry detergents (Tide® Free, Cheer® Free and Gentle, All® Free Clear, Arm & Hammer® Unscented, Wisk® Free, Purex® Unscented)
- Wash all new clothes and linens five times before using.
- Old clothes and fabrics are preferred.
- Use white vinegar in rinse cycle to help remove soap.

Hand, Nail, and General Skin Care Tips
- Wear cotton gloves under rubber/vinyl gloves for any activities where hand-wetting is expected.
- Trim nails short. Long nails are dangerous to skin especially when sleeping.

Avoid
Soaps/Cleansing
- No hot water (use lukewarm).
- Avoid hot tubs.
- No rubbing alcohol.

Moisturizers
- No creams, lotions, oils or powders other than those recommended in this brochure.
- No Neosporin®, Triple antibiotic, or bacitracin antibiotic ointments.

Fragrances
- No perfumes, colognes, after-shave, or pre-shave on any part of body/clothing.

Laundry and Home Care
- No fabric softener in washer.
- Bounce® Unscented fabric softener sheets in dryer if desired.
- No washing machine water softener such as Calgon® (In-house water softeners are acceptable).
- White vinegar may be used as a general household cleaner.

Hand, Nail, and General Skin Care Tips
- No wetting of hands more than 5 times a day.
- Avoid tight-fitting clothes unless your doctor has advised you to wear a pressure garment such as support hose.
- No scrubbing! No loofah! No pumice stone!
- Do not pull off dead skin. Snip with scissors instead.

Make-ups/Cosmetics
- If you would like a list of make-ups and cosmetics that are free of the most common allergy-causing ingredients, ask your provider about a “virtual patch testing” printout from our Mayo CARD program.

Figure 1. Sample of prepared handout (used at Mayo Clinic Arizona) with recommendations for the patient on hypoallergenic skin care products.
polymyxin (Neosporin), antifungals, and corticosteroids. Cobalt is found with other metals, including zinc, and in items such as jewelry, crayons, hair dye, and antiperspirants.

Others in the top ten less consistently during that period were methylidibromo glutaronitrile, gold sodium thiosulfate, potassium dichromate, benzalkonium chloride, $p$-phenylenediamine, and thiuram mix. Methylidibromo glutaronitrile is a preservative and can be found in health care and personal products. Clinically relevant sources of gold may be found in jewelry and dental appliances. Potassium dichromate is used in cement, leather, and steel surfaces. Benzalkonium chloride is used commonly in the health care field as a cleanser, antiseptic, and preservative, but it is also found in personal care products and medications. Permanent hair dyes are the usual source of $p$-phenylenediamine. Thiuram mix is in rubber and some personal products.

**Diagnosis**

The evaluation of a patient with suspected contact dermatitis begins with the history. Specific questions directed at the patient’s occupation, hobbies, and home routine will be helpful. Examination should note the location and pattern of the eruption. Although eyelid dermatitis may be seen in the atopic patient, nail polish may be the source of the offending allergen. Dyshidrotic eczema occurs as vesicles along the lateral aspects of the fingers, whereas eczematous changes along the dorsal hands is more commonly due to an allergen. Other distributions as clues include postauricular scalp (perufe), perioral area (chewing gum, toothpaste), trunk (dyes or clothing finish), wrist (nickel or chrome), waistline (rubber), feet (shoes), and history or presence of wounds (topical antibiotic ointment).

Patch testing can confirm or reveal a contact allergy. It involves placement of allergens against the skin of the patient’s back for 48 hours. Then an initial reading is done with follow-up readings typically at 96 hours. Prepared series include the thin-layer rapid-use epicutaneous test (TRUE Test), which consists of 35 allergens and one negative control (www.truetest.com); customized series such as the NACDG Standard Series with 65 allergens and the Mayo Clinic’s Standard series with 74 allergens must be manually assembled. The majority of dermatologists performing patch testing use the TRUE Test. Note that benzalkonium chloride is not included in that panel.

In addition to ascertaining degree of positivity, relevance must be determined. This involves collaborating with patients to assess the likelihood that they are currently exposed to the positive antigen.

**Treatment**

Ideally, the allergen(s) will be identified and avoided. Realistically, compliance is a challenge. To assist patients in avoiding antigens in skin care products, the Contact Allergen Replacement Database (CARD) was created in 1999. It includes approximately 9000 ingredients and 4800 individual over-the-counter and prescription skin-care products. Once the patient’s allergens have been identified with patch testing, they can be entered into the database, and a list of products free of those substances is generated. The patient should be reminded that even small and infrequent exposures can perpetuate the eczema.

Topical corticosteroids twice daily are helpful in hastening resolution and may also be used for disease control when the allergen is unknown. Low-potency corticosteroids such as 2.5% hydrocortisone (Hytone) are recommended for the thinner skin of the face, neck, axillae, groin, and intertriginous areas. Mid-potency steroids such as triamcinolone 0.1% (Kenalog, Kenonel) are appropriate for the thicker skin of the body. Short-term use of higher-potency steroids may be necessary if the reaction is severe. If there is significant pruritus, sedating antihistamines such as doxepin (Sinequan)$^1$ 10 to 20 mg taken nightly 2 hours before bedtime can provide relief.

Steroid-sparing topical immunosuppressants such as tacrolimus (Protopic)$^1$ and pimecrolimus (Elidel)$^1$ may be helpful adjuncts. Treatment for severe acute episodes can entail a several-week tapering course of systemic corticosteroids, especially if the eruption is widespread. Other longer-term systemic therapies for severe or resistant disease include phototherapy or systemic immunosuppressants such as azathioprine (Imuran)$^1$, mycophenolate melfetil (Cellcept)$^1$, methotrexate$^1$, or cyclosporine (Neoral).$^3$

It may take many weeks before the skin reverts to a normal appearance despite successful avoidance of antigens. A prepared handout with concrete recommendations for the patient on truly hypoallergenic skin care is beneficial. A sample of that used at Mayo Clinic Arizona is shown in Figure 1.

If patch testing is not performed, an initial approach may be to instruct the patient on avoiding the most common contact allergens via such a handout and prescribing symptomatic treatment including topical and oral therapies. CARD can generate a shopping list of products free of the top 10 allergens as identified by the NACDG and the MCCDG. Patients may access CARD independently (at www.AllergyFreeSkin.com or at Apple’s App Store under “contact dermatitis”) to generate this list. Some physicians follow these measures for several months, especially if the eruption is mild, before pursuing formal patch testing.

An excellent primer for the physician interested in learning more about contact allergy diagnosis and management is *Contact and Occupational Dermatology*.  

$^1$Not FDA approved for this indication.

**References**


Thin-layer rapid-use epicutaneous test (TRUE-test). Available at: http://www.truetest.com/PatientPDF/File18.pdf [accessed 12.08.10].

Cutaneous T-Cell Lymphomas

Classification

Virtually every subtype of T-cell lymphoma involves the skin primarily or secondarily. The principal types of primary cutaneous T-cell lymphomas (CTCLs) recognized in the World Health Organization classification include mycosis fungoides (MF) and its leukemic variant, the Sézary syndrome (SS); CD30+ large cell lymphoma; CD30+ small- or medium-cell lymphoma; and pleomorphic CD4+ small or medium-cell variants (Table 1). All other primary CTCLs comprise only a few percent of the total. This discussion focuses on MF and SS because they account for up to 75% of primary cutaneous cases.

Standard Diagnosis and Staging Methods

The evaluation of CTCL patients begins with a thorough clinical history and physical examination. Key elements of the history include the pace and nature of disease development, the presence or absence of spontaneous regression of lesions, prior therapy, and ingestion of drugs (e.g., anticonvulsants, antihistamines, other agents with antithymic properties) that have been associated with pseudolymphomatous skin eruptions that can mimic CTCLs. The review of systems should establish the presence of lymphoma-associated constitutional symptoms (e.g., fever of unknown origin, night sweats, weight loss, fatigue). In addition to general aspects, the physical examination should document the type and distribution of skin lesions and whether there is lymphadenopathy, hepatosplenomegaly, or edema of extremities (i.e., potential sign of lymphatic obstruction).

Histopathologic analysis of representative lesional skin biopsy specimens is the primary means of confirming the clinical diagnosis. Biopsy specimens should be deep enough to include the deepest portions of the cutaneous lymphoid infiltrates because these areas often exhibit the most diagnostic features. Putative extracutaneous involvement should be confirmed by biopsy if it is relevant to clinical management.

Routine blood tests include a complete blood cell count, differential, and general chemistry panel. A “Sézary prep” is used to assess peripheral blood involvement.

Internal nodal and visceral involvement by lymphoma usually is assessed with chest radiography, computed tomography (CT), or combined positron emission tomography and CT (PET/CT) scans of the chest, abdomen, and pelvis. These radiologic studies usually are not needed for patients with early forms of MF (i.e., nontumorous skin lesions without evidence of extracutaneous involvement assessed by physical examination); however, they are usually obtained during the work-up of other types of CTCLs. The role of immunopathologic and molecular biologic assays in the diagnosis and staging of CTCLs is discussed later.

An algorithm for the diagnosis of early MF has been proposed by the International Society for Cutaneous Lymphomas (ISCL) (see Pimpinelli et al. in References). It relies on a combination of clinical, histopathologic, immunopathologic, and clonality criteria. This differs from former approaches that have been based primarily on histopathologic criteria.

Mycosis Fungoides, Sézary Syndrome, and Variants

Clinical Features

MF classically manifests as erythematous, scaly, variably pruritic, flat patches or indurated plaques, often favoring the most sun-protected areas. The patches or plaques may progress to cutaneous tumors and involvement of lymph nodes or viscera, although this usually does not occur as long as the skin lesions are reasonably well controlled by therapy. SS manifests as total-body erythema and scaling (i.e., erythroderma), generalized lymphadenopathy, hepatosplenomegaly, and leukemia. Large-plaque parapsoriasis is essentially the prediagnostic patch phase of MF. Lesions may exhibit poikiloderma (i.e., atrophy, telangiectasia, and mottled hyperpigmentation and hypopigmentation) and have then been referred to as poikiloderma atrophicans vasculare.

Follicular mucinosis refers to a papulonodular eruption in which hair follicles are infiltrated by T cells and contain pools of mucin. In hairy areas, this may result in alopecia. Follicular mucinosis may exist as a leisional variant of MF (i.e., follicular MF) or as a clinically benign entity (i.e., alone or associated with other lymphomas).

Granulomatous slack skin is a variant of MF that manifests with pendulous skin folds in intertriginous areas. Lesional skin biopsy specimens contain atypical T cells in a granulomatous background.

Pagetoid reticulosis manifests as a solitary or localized, often hyperkeratotic plaque containing atypical T cells that are frequently confined to a hyperplastic epidermis. Some authorities regard it as a variant of unilesional MF, whereas others think it is a distinct entity.

Other variants of MF include hypopigmented, palmoplantar, bullous, and pigmented purpuric forms. The latter form shows clinicopathologic overlap with the pigmented purpuric dermatoses. Tumor d’emblée MF is an outmoded concept used in the past to refer to supposed cases of MF that manifested as cutaneous tumors in the absence of patches or plaques. Most experts now prefer to classify such cases as other forms of CTCL, depending on their histopathologic features.

Histopathologic and Cytologic Features

A well-developed plaque of MF contains a bandlike, cytologically atypical lymphoid infiltrate in the upper dermis that infiltrates the epidermis as single cells and cell clusters known as Pautrier’s
microabscesses. The atypical lymphoid cells exhibit dense, hyperchromatic nuclei with convoluted, cerebriform nuclear contours and scant cytoplasm. The term ‘cerebriform’ comes from the brain-like ultrastructural appearance of these nuclei. In more advanced cutaneous tumors, the infiltrate extends diffusely throughout the upper and lower dermis and may lose its epidermotropism. In the earlier patch phase of the disease, the infiltrate is sparser, and lymphoid atypia may be less pronounced. In some cases, it may be difficult to distinguish early patch-type MF from various types of chronic dermatitis. The presence of lymphoid atypia and absence of significant epidermal intercellular edema (i.e., spongiosis) help to establish the diagnosis of early MF.

Involvement of lymph nodes by MF begins in the paracortical T-cell domain and may progress to complete effacement of nodal architecture by the same types of atypical lymphoid cells that infiltrate the skin. These cells can be seen in low numbers in the peripheral blood of many MF patients; however, those with SS develop gross leukemic involvement, usually defined as at least 1000 tumor cells/mm³. These cells are known as Sézary cells, and they are traditionally detected by manual review of the peripheral blood smear (the so-called Sézary prep). They may also be defined by various immunophenotypic criteria.

**Immunophenotyping**

Cellular antigen expression is usually assessed by immunoperoxidase methods for tissue biopsy specimens and by flow cytometry for blood specimens. Almost all cases of MF or SS begin as phenotypically and functionally mature CD4⁺ T-cell neoplasms of skin-associated lymphoid tissue (SALT). They express the SALT-associated homing molecule cutaneous lymphocyte antigen (CLA) and most mature T-cell surface antigens, with the exceptions of CD7 and CD26, which are often absent. As disease progresses, the tumor cells often dedifferentiate and lose one or more mature T-cell markers, such as CD2, CD3, or CD5.

Cases typically express the α/β form of the T-cell receptor. At least in advanced cases, the cytokine profile is consistent with the Th1/2 subset of CD4⁺ T cells (i.e., production of interleukin [IL]-4, IL-5, and IL-10 rather than Th1 cytokines such as IL-2 and interferon-γ). Expression of the high-affinity IL-2 receptor (CD25, TAC) ranges widely, with most cases showing a variable minority of lesional CD25⁺ cells. Tumor cells can be induced to express a regulatory T-cell phenotype (Treg) in vitro. MF cases that express CD8⁺ or other aberrant phenotypes occur occasionally but behave like conventional cases. They should not be confused with rare aggressive CTCLs exhibiting cytotoxic T-cell differentiation.

In addition to tumor cells, MF and SS lesions contain a minor component of immune accessory cells (i.e., Langerhans cells and macrophages) and CD8⁺ T cells with a cytolytic phenotype. This presumed host response correlates positively with survival and tends to decrease as lesions progress. A favorable response to therapy such as photopheresis appears to correlate with normal levels of circulating CD8⁺ cells.

### Molecular Biology

Well-developed MF or SS is a monoclonal T-cell lymphoproliferative disorder. Southern blotting or polymerase chain reaction (PCR) assays demonstrate monoclonal T-cell receptor gene rearrangements. The greater sensitivity of PCR assays allows the demonstration of dominant clonality in many early patch-type lesions of MF. These assays sometimes detect dominant clonality in lesional skin showing only chronic dermatitis histopathologically. These cases are called *clonal dermatitis* and may represent the earliest manifestation of MF because several have progressed to histologically recognizable MF within a few years. However, some cases of clinicopathologically defined early-phase MF lack a detectable monoclonal T-cell population until later in their clinical course.

In addition to aiding initial diagnosis, gene rearrangement analysis has facilitated staging and prognosis. Because some patients without MF or SS can have low levels of circulating Sézary-like cells and because not all cases of peripheral blood involvement in MF or SS exhibit morphologically recognizable tumor cells, the demonstration of dominant clonality that matches the clone in lesional skin has proved to be a useful diagnostic adjunct. The same holds true for assessing lymph node involvement. T-cell receptor gene rearrangement analysis of MF and SS lymph nodes is more sensitive than histopathology and possesses at least some prognostic relevance.

### TNMB Staging

Although several proposed methods have used a weighted extent approach to more accurately determine the MF or SS tumor burden, the preferred approach is the TNMB system, which is detailed in Tables 2 and 3. The original tumor (skin), lymph nodes, and metastasis (visceral organs) version of this system has been modified by the ISCL to incorporate the extent of blood involvement (B classification) into the staging process. Table 2 shows the TNMB classification relevant to MF and SS, and Table 3 shows how this information is used to determine the stage of disease. The prognostic relevance of this staging system has been supported by numerous studies, and use of the TNMB helps to guide the selection of therapies. For example, early-stage MF is the most amenable to control with topically directed treatments, whereas advanced MF or SS with extracutaneous involvement usually requires systemic therapies or topical plus systemic combinations.

### Treatment

Treatment guidelines for CTCL published by the National Comprehensive Cancer Network can be found at www.nccn.org. Rather than cure, which is attained in less than 10% of cases, the goal of MF and SS therapy is to reduce the impact of the skin disease on quality of life. For most patients, this is achieved by reducing pain, itch, and infection and improving clinical appearance. Appearance is affected by the disfigurement of the eruption and by the profound degree of scale shedding in some patients. Because the natural history of early-stage MF predicts a virtually normal life span, the goal of treatment must be directed at quality of life. For more advanced stages, prolongation of life expectancy may be a reasonable treatment goal.

| TABLE 2 | TNMB Classification of Mycosis Fungoides and Sézary Syndrome |
| Skin (T) | Lymph Nodes (N) |
| T1 | N0 | Patches and/or plaques; <10% body surface area | Not clinically enlarged; histopathology not required |
| T2 | N1 | Patches and/or plaques; ≥10% body surface area | Clinically enlarged; histopathologically negative |
| T3 | N2 | Tumors with/without other skin lesions | Clinically enlarged; histopathologically equivocal |
| T4 | N3 | Generalized erythroderma | Clinically enlarged; histopathologically positive |
| Visceral Organs (M) | Peripheral Blood (B) |
| M0 | B0 | No involvement | Atypical cells ≤5% of leukocytes |
| M1 | B1 | Involvement | Atypical cells >5% of leukocytes |
| | B2 | Atypical cells ≥1000/mm³ |

³Exceeds dosage recommended by the manufacturer.
TABLE 3
TNMB Staging System for Mycosis Fungoides and Sézary Syndrome

<table>
<thead>
<tr>
<th>STAGE</th>
<th>SKIN</th>
<th>LYMPH NODES</th>
<th>VISCERA</th>
<th>BLOOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>B0–1</td>
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<tr>
<td>IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>B0–1</td>
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<td>M0</td>
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<td>N0–2</td>
<td>M0</td>
<td>B0</td>
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<td>M0</td>
<td>B1</td>
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<tr>
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<td>M0</td>
<td>B2</td>
</tr>
<tr>
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<td>M0</td>
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</tr>
<tr>
<td>IVB</td>
<td>T1–4</td>
<td>N0–3</td>
<td>M1</td>
<td>B0–2</td>
</tr>
</tbody>
</table>


Regardless of presentation, relief of symptoms should be addressed early. For dryness and scaling, the use of emollient ointments is indicated. These include petrolatum, Aquaphor, and commercially available shortening such as Crisco (an inexpensive alternative). For modest dryness, creams (e.g., Nivea, Cetaphil, Eucerin) can be adequate and more acceptable to patients. Mild superfatted soaps such as Dove and Oil of Olay are recommended. Soap substitutes such as Cetaphil are also acceptable. Pruritus can be addressed with oral agents such as hydroxyzine (Atarax) or diphenhydramine (Benadryl) 2 to 5 mg/kg/day and divided into four daily doses. Antipruritics work better when used on a regular basis rather than on an as-needed basis. Nonsedating antihistamines tend to be less effective. Measures to reduce dryness also help to reduce pruritus. Secondary infection needs to be treated with appropriate antibiotics. Their selection is guided by results of skin cultures but usually involves coverage of gram-positive organisms.

Phototherapy

Two main phototherapeutic regimens are used to treat CTCLs. Ultraviolet B radiation (290–320-nm broad band or 311-nm narrow band) can be used for patients with patches but not those with well-developed plaques or tumors. Seventy percent of patients achieve total clinical remission, usually within about 3 to 5 months. Another 15% achieve partial remission. Narrow-band UVB usually is more effective than broadband UVB and achieves maximal responses more rapidly.

Psoralen–ultraviolet A (PUVA) photochemotherapy uses oral 8-methoxypsoralen (8-MOP) 0.6 mg/kg as a photosensitizer before UVA (320–400 nm) exposure. Fifty-five percent of patients with patch or plaque disease achieve complete remissions, and 30% have partial responses to this modality. For most patients, maximal responses are achieved within 3 months, and after 5 months, it is unlikely that further improvement will be gained. Limitations of these modalities include actinic damage, photocarcinogenesis, retinal damage (if eyes are not protected), and the inconvenience of getting to phototherapy centers. PUVA also has the risk of nausea and a theoretical risk of cataract induction without proper eye protection.

During the clearing phase of treatment, phototherapy treatments usually are administered three times per week. After resolution of skin lesions, treatment frequency is usually tapered gradually to once weekly for UVB and once every 4 to 6 weeks for PUVA. These maintenance regimens are often continued for months to years because abrupt cessation of phototherapy is commonly associated with rapid relapse, which is probably related to the persistence of microscopic disease after clinical clearing.

Topical Therapy

Like phototherapeutic regimens, topical therapies are appropriate for disease confined to the skin (stage I). Topical corticosteroids are frequently used for CTCLs, often before diagnosis. Low-potency formulations are useful on the face and skin folds. Medium-potency preparations are appropriate for the trunk and extremities. High-potency formulations are useful for recalcitrant lesions; however, prolonged use of such potent agents can cause local atrophy and adrenal suppression. Roughly half of patients achieve complete remissions, and most others have partial remissions. Response duration varies widely with the individual pace of disease and patient compliance. Topical corticosteroids are particularly useful as a means to relatively quickly ameliorate severe signs and symptoms and as an adjuvant therapy in combination with other primary treatments.

Mechlorethamine (nitrogen mustard, H,N Mustargen) 1 is applied topically in an aqueous solution or in an ointment, such as Aquaphor. The aqueous form is prepared at home and involves a daily dose totaling 10 mg in 60 mL water. The ointment form is prepared by a pharmacist in 1-pound lots at a concentration of 10 mg of mechlorethamine per 100 g of ointment. Only the amount of ointment needed to apply a thin layer is used. Either formulation is usually applied at bedtime to lesional skin for limited disease or to the entire skin surface (excluding the head unless it is also involved) for more extensive disease. It is then showered off every morning using soap and water. Results are similar to those from PUVA. Advantages include therapy at home and availability in all regions of the country. Disadvantages are daily preparation (aqueous form only), daily application, and possible allergic contact dermatitis (more common with the aqueous preparation). Maximal efficacy is expected within 6 months. Mild flare-ups of disease may occur during the first few months of treatment and probably represent inflammation of subclinical skin lesions, analogous to the clinical accentuation of actinic damage during topical therapy with 5-fluorouracil (Efudex). As with phototherapy, topical mechlorethamine is tapered gradually after remission is achieved in an effort to delay clinical relapse.

Carmustine (BCNU, BiCNU) 1 is applied to the total skin surface as an alcohol/aqueous solution (10 to 20 mg in 60 mL). Complete responses are seen in 83% of patients with stage IA disease (<10% involvement) and 50% of patients with stage IB disease (>10% involvement). Another 10% of patients obtain partial responses. Advantages include those described for nitrogen mustard and reports of success with application only to lesional skin. Disadvantages include skin irritation followed by telangiecstasia formation and possible bone marrow suppression necessitating blood monitoring.

A topical gel formulation of the retinoid X receptor (RXR)–specific retinoid, bexarotene (Targretin), is useful for localized or limited skin lesions. The principal side effect is local irritation.

Radiotherapy

Conventional radiotherapy for mycosis fungoides therapy has been used for approximately 100 years. It is useful in the treatment of isolated, particularly problematic lesions such as recalcitrant tumors or ulcerated plaques. In addition to benefit from the photons delivered by radiotherapy, electron beam therapy (0.4 Gy per week for 8 to 9 weeks) is also useful for CTCL therapy. An approximately 85% complete response rate of skin disease with a median duration of 16 months is expected with electron beam therapy. An advantage is an excellent rate of complete response. Disadvantages include limited access to required equipment and expertise and cutaneous toxic effects, such as alopecia, sweat gland loss, radiation

1Not FDA approved for this indication.

6May be compounded by pharmacists.
Systemic Chemotherapy

Various regimens of single-agent and multiagent chemotherapy have been used in the treatment of MF and SS. Oral methotrexate, chlorambucil (Leukeran)\(^1\) with or without prednisone,\(^1\) and etoposide (VePesid)\(^1\) have shown therapeutic activity. The best response has been in erythrodermic patients treated with methotrexate (5 to 125 mg weekly),\(^1\) who have shown a 58% response rate. The combination of low-dose methotrexate and interferon alfa has been reported to yield a high response rate in advanced-stage MF and SS.

The use of multiagent regimens is controversial because of the small number of patients treated with any given regimen. There is even some evidence that for some populations of CTCL patients, survival may be reduced. For individual patients with advanced disease, however, cyclophosphamide (Cytoxan),\(^1\) doxorubicin (Adriamycin),\(^3\) vincristine (Oncovin),\(^4\) and prednisone\(^1\) (CHOP regimen) can provide some short-term palliation. In some cases, CHOP has successfully eradicated large cell transformation of MF and returned patients to their more clinically indolent patch or plaque baseline disease. Idarubicin (Idamycin)\(^1\) in association with etoposide, cyclophosphamide, vincristine, prednisone, and bleomycin (Blenoxane)\(^7\) (VICOP-B regimen) has demonstrated response rates of 80% (36% complete response rate) for patients with stage II through IV disease and 84% for MF patients, with a median duration of response longer than 8 months. Other regimens have been used with more modest success.

Several purine nucleoside analogues have been used for CTCL treatment, including erythrodermic variants. These include 2-chlorodeoxyadenosine (cladribine [Leustatin],\(^1\) with a response rate of 28%), 2-deoxycoformycin (pentostatin [Nipent],\(^1\) with a response rate of 39%), and fludarabine (Fludara).\(^1\) Toxicities include pulmonary edema, bone marrow and immune suppression, and neurotoxicity.

Retinoids

Retinoids have therapeutic activity against MF and SS alone and in combination with other therapies, such as interferon alfa or PUVA (the latter combination is called Re-PUVA). Arotinoid,\(^3\) acitretin (Soriatane),\(^5\) and 13-cis-retinoic acid (isotretinoin [Accutane])\(^1\) have various degrees of efficacy, and they typically are used in conjunction with other modalities. A newer RXR-specific retinoid, bexarotene, has an overall response rate of about 40% and can be used alone or in combination with phototherapy and other systemic agents such as interferon alfa-2. Disadvantages of bexarotene therapy include signs of hypothyroidism and vitamin A toxicity, particularly hyperlipidemia.

Enzyme Inhibitors

Vorinostat (Zolinza) is the first histone deacetylase inhibitor to be FDA approved for MF and SS. The overall response rate approaches 40% using a standard oral dose of 400 mg/day. Side effects include gastrointestinal symptoms, thrombocytopenia, and cardiac conduction abnormalities. Romidepsin (Isotodax) is an intravenously administered histone deacetylase inhibitor recently approved by the FDA for MF and SS. Forodesine\(^3\) is a purine nucleoside phosphorylase inhibitor that preferentially affects T cells because they contain relatively high concentrations of this enzyme. Forodesine is undergoing clinical trials for MF and SS in the United States and appears to have a response rate of about 40%.

Miscellaneous Therapies

Various other therapies have been tried for MF and SS with modest success. Nonmyeloablative allogeneic stem cell transplantation has led to favorable responses in some patients; however, the total number treated is small. Cyclosporine (Sandimmune)\(^1\) has been used for MF and SS. Transient improvement is followed by worsened survival due to immunosuppression, and it is not a recommended

\(^{1}\)Not FDA approved for this indication.

\(^{2}\)Exceeds dosage recommended by the manufacturer.

\(^{3}\)Investigational drug in the United States.

\(^{4}\)May be compounded by pharmacists.
therapy. Thymopentin\(^1\) has given excellent results in SS patients (i.e., 40% complete response rate and 35% partial response rate, with a median duration of response of 22 months). The lack of follow-up reports in recent decades leaves the status of this therapy in question.

**Selection of Therapy**

Initial choices among conventional treatments for MF and SS depend on the types of lesions and the stage of disease. Disease subsets are followed by recommended initial treatments in parentheses: unilesonal or localized MF (local radiation therapy), patch MF (broad- and narrow-band UVB, PUVA, methotrexamine), patch/plaque MF (PUVA, methotrexamine), thick plaque/tumor MF (electron beam radiation therapy, interferon alpha-2, bexarotene, histone deacetylase inhibitors), erythodermic MF/SS (photopheresis), and nodal or visceral MF or SS (interferon alpha-2, bexarotene, histone deacetylase inhibitors, denileukin diftitox, experimental systemic therapies, systemic chemotherapy).

Second-line therapeutic choices often involve interferons, retinoids, or histone deacetylase inhibitors, usually in combination with primary modalities. Multimodality combinations, often at reduced doses, are used commonly to treat patients with stage IIB or more advanced disease. Medium-potency topical corticosteroids, such as 0.1% triamcinolone cream or ointment (Kenalog), are useful adjuncts to many different therapies. The optimal use of newer therapeutic agents in various subtypes and stages of MF and SS is still being established. Evidence-based guidelines for MF and SS therapy have been developed by the National Comprehensive Cancer Network (NCCN) (www.nccn.org).

**Lymphoproliferative Disorders Associated with Mycosis Fungoides and Sézary Syndrome**

**Types and Clinical Features**

Patients with MF or SS are at increased risk for large T-cell lymphomas, lymphomatoid papulosis, and Hodgkin’s disease. Molecular biologic analysis has shown that these disorders and MF often share the same clonal T-cell receptor gene rearrangement that they arise in the same individual. As a consequence, they are considered to be subclones of the original MF tumor clone. The development of large T-cell lymphoma in a patient with MF or SS is referred to as *large cell transformation of MF*. This occurs in up to 20% of cases in some series and is associated with a median survival of only 1 to 2 years. One half of these large T-cell lymphomas are CD30\(^+\); however, the generally favorable prognosis of primary cutaneous CD30\(^+\) anaplastic large cell lymphoma does not extend to these secondary forms of CD30\(^+\) lymphoma. These patients are usually treated with systemic chemotherapy such as CHOP or with experimental systemic therapies (e.g., interferons, retinoids, histone deacetylase inhibitors, denileukin diftitox).

Lymphomatoid papulosis manifests as recurrent, usually generalized crops of spontaneously regressing, erythematous papules that can exhibit crusting or vesiculation before resolution. It is the clinically benign end of a disease continuum that has primary cutaneous CD30\(^+\) anaplastic large cell lymphoma as its other extreme. Intermediate forms of disease can occur. Histopathologically, lesions contain a mixed-cell infiltrate, including large, atypical T cells that resemble Reed-Sternberg cells and their monoclonal variants (so-called type A) or large MF-type cells (so-called type B). Type A cells are CD30\(^+\). A type C form is also recognized. It has sheets of type A cells histologically mimicking CD30\(^+\) large T-cell lymphoma but is different from it clinically. A type D variant containing CD8\(^+\) CD30\(^-\) large atypical cells has also been described recently. All types of lymphomatoid papulosis behave similarly. Patients with lymphomatoid papulosis sometimes respond to tetracycline or erythromycin (500 mg PO bid), presumably on the basis of antiinflammatory activity. Most cases improve within 1 month with low-dose methotrexate (10 to 20 mg PO every week). PUVA and narrow-band UVB given three times per week are other therapeutic options.

**References**


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\(^1\)Not FDA approved for this indication.

\(^2\)Investigational drug in the United States.
Names used to describe isolated cutaneous vasculitis have included hypersensitivity vasculitis and leukocytoclastic vasculitis (LCV). In 1990, the American College of Rheumatology proposed five criteria for the classification of hypersensitivity vasculitis: age older than 16 years, possible drug trigger, palpable purpura, maculopapular rash, and skin biopsy showing neutrophils around vessel. At least three out of five criteria yield a sensitivity of 71% and specificity of 84%. In 1994, a new nomenclature proposed at the Chapel Hill International Consensus Conference in North Carolina further classified vasculitis (Box 1). The term “hypersensitivity vasculitis” was not used, because most vasculitides that would have previously been in this category fall into either microscopic polyangiitis or cutaneous LCV. LCV is vasculitis restricted to the skin without involvement of vessels in other organs. Cutaneous vasculitis may be a clue to systemic vasculitis and guides the clinician to a comprehensive evaluation (Table 1).

**Box 1** Chapel Hill Consensus 1994 Classification of Vasculitis

<table>
<thead>
<tr>
<th>Large-Vessel Vasculitis</th>
<th>Medium-Vessel Vasculitis</th>
<th>Small-Vessel Vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giant cell arteritis</td>
<td>Classic polyarteritis nodosa</td>
<td>Churg-Strauss syndrome</td>
</tr>
<tr>
<td>Takayasu’s arteritis</td>
<td>Kawasaki’s disease</td>
<td>Cutaneous leukocytoclastic vasculitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Essential cryoglobulinemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Henoch-Schönlein purpura</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Microscopic polyangiitis (polyarteritis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wegener’s granulomatosis</td>
</tr>
</tbody>
</table>

**TABLE 1** Diseases with Cutaneous Vasculitis as a Component of Their Presentation

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>SKIN LESIONS</th>
<th>CLUES AND CONFIRMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticarial vasculitis</td>
<td>Individual lesions look like urticaria but last &gt;24 h; typical urticaria last a few hours, always &lt;24 h</td>
<td>Pruritus, burning of skin lesions; May be associated with connective tissue disease, medications, low complement, viral infections (e.g., hep B, hep C, EBV); Skin biopsy.</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td>Wheals progress to petechia, ecchymoses and palpable purpura; Lesions are in gravity-dependent or pressure-dependent areas such as legs or the buttocks in toddlers</td>
<td>Arthralgia or arthritis, hematuria, abdominal pain, melena; Skin biopsy and DIF for IgA</td>
</tr>
<tr>
<td>Essential mixed cryoglobulinemia</td>
<td>Palpable purpura</td>
<td>Peripheral neuropathy, GN Hep C positive Serum cryoglobulins.</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td>Palpable purpura, hemorrhagic lesions, petechiae, skin ulcers</td>
<td>c-ANCA &gt;80%; Pulmonary hemorrhage, GN Biopsy affected organ.</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
<td>Maculopapular rash, palpable purpura, hemorrhagic lesions, subcutaneous nodules, livedo reticularis or Raynaud's disease</td>
<td>ANCA (50%); Asthma, allergic rhinitis Eosinophilia &gt;1.5 x 10^9/L Pulmonary infiltrates, pulmonary neuropathy Biopsy affected organ</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>Palpable purpura, hemorrhagic lesions, petechiae, skin ulcers, splinter hemorrhages</td>
<td>p-ANCA &gt;60%; Pulmonary hemorrhage, GN Biopsy affected organ</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Livedo reticularis, tender nodules, skin ulcers, bullae or vesicles</td>
<td>Hypertension, elevated creatinine, abdominal pain, constitutional symptoms (fever) Abnormal angiogram Biopsy affected organ</td>
</tr>
</tbody>
</table>

**Abbreviations:** c-ANCA = classic antineutrophil cytoplasmic antibody; DIF = direct immunofluorescence; EBV = Epstein-Barr virus; GN = glomerulonephritis; hep = hepatitis; lg = immunoglobulin; p-ANCA = protoplasmic-staining antineutrophil cytoplasmic antibody.
Diseases of the Skin

Deposition, degenerate inflammatory cells, and extravasated erythrocytes. Histology shows destruction of postcapillary venules with fibrin identified.

Kidney involvement, with subsequent evaluation and management if should have a urinalysis to evaluate for hematuria as a sign of kidney in the postcapillary venules. The appearance may be necrotizing or non-necrotizing.

Diagnosis

To confirm a clinical impression of LCV, perform a punch biopsy in the center of a nonulcerated cutaneous lesion that is less than 24 to 48 hours old and submit the sample in 10% formalin (standard medium). It is important to biopsy an intact, nonulcerated active lesion (Figure 2) because ulcers can show histologic features simulating vasculitis regardless of whether the patient has true vasculitis or not.

Pathology reveals a mononuclear or polymorphonuclear inflammation of the small blood vessels (called LCV), most prominent in the postcapillary venules. The appearance may be necrotizing or non-necrotizing.

Differential Diagnosis

LCV manifests as erythematous papules or occasionally as papulopustules that can simulate a variety of entities (see Table 1). The review of systems and physical examination should be directed to evaluate for diseases that have cutaneous vasculitis as a component of their presentation (see Table 1). All patients with LCV should have a urinalysis to evaluate for hematuria as a sign of kidney involvement, with subsequent evaluation and management if identified.

Treatment

The primary goal in the management of LCV is to identify and treat instigating factors, including infection and medications. Supportive treatment includes resting, elevating legs, and wearing support hose. When review of systems, physical examination, and urinalysis do not reveal associated systemic diseases, treatment of LCV is generally not necessary. Lesions typically remit without treatment. In rare patients with symptomatic, extensively pustular, or progressive lesions, a short course of prednisone1 dosed at 1 mg/kg/day initially and tapered over 3 to 6 weeks may be used, although no controlled trials have been performed using oral corticosteroids for isolated LCV. Rapid steroid taper can lead to rebound. Systematic evaluation of the use of other medications, such as colchicine1 or dapsone,2 to treat isolated LCV has not been performed.

Monitoring

Patients with LCV are at risk for recurrent or chronic vasculitis. In addition, apparent LCV can occur as a systemic disease that is not recognizable at the first episode. Patients with persistent or recurrent LCV require follow-up to ensure disease clearance, to monitor for medication side effects, and to evaluate for evolving disorders known to be associated with cutaneous vasculitis (see Table 1).

Complications

Isolated LCV generally resolves without sequelae. However, pustular or ulcerative LCV may be complicated by local sequelae such as cutaneous ulcerations and scars.

Cutaneous Vasculitis Associated with Systemic Vasculitis

Cutaneous vasculitis may be a component of the presentation of multiple diseases (see Table 1). When a clinician reads a pathology report from a biopsy of a skin lesion that states "vasculitis," it is important to realize that this term is a descriptor of the histopathology. It is the clinician’s challenge to determine whether "vasculitis" is as potentially innocuous as LCV or part of a more severe systemic disease. Symptoms that are clues to a systemic process can include fever, arthralgias, myalgias, anorexia, abdominal pain, pulmonary abnormalities, or neurologic symptoms.

Skin biopsy may aid in the diagnosis of a systemic vasculitis (Henoch-Schönlein purpura), but biopsy of an affected end organ may be necessary to confirm a diagnosis. Pathology focuses on the confirmation of vasculitis in a small, medium, or large vessel.

Aside from Henoch-Schönlein purpura, treatment of systemic vasculitis is typically much more aggressive than treatment of LCV and should be pursued in conjunction with involvement of a rheumatologist, nephrologist, or pulmonologist. Systemic disease leads to severe complications including renal failure, pulmonary damage, permanent vascular disease, or neurologic insult depending on the viscera affected.

References


Not FDA approved for this indication.
CURRENT DIAGNOSIS

- A sudden increase in shedding most commonly represents telogen effluvium.
- Hair thinning is more likely to represent pattern alopecia.
- Scarring alopecia generally requires a biopsy for diagnosis.
- Most medically significant hirsutism results from polycystic ovarian syndrome.
- New-onset virilization suggests the possibility of a tumor.

CURRENT THERAPY

- Pattern alopecia in men is treated with oral finasteride (Propecia), topical minoxidil (Rogaine), or both.
- Pattern alopecia in women is treated with antiandrogens (such as spironolactone [Aldactone]), topical minoxidil, or both.
- Alopecia areata can require intralesional corticosteroid injections, topical immunotherapy, or systemic therapy with agents such as methotrexate (Trexall).
- A scalp biopsy is critical to guide therapy in scarring alopecia.
- Hirsutism may be treated with laser epilation or systemic antiandrogens. Topical eflornithine (Vaniqa) can slow regrowth of hair.

Epidemiology

Hair disorders are common, with more than half of the population affected by pattern alopecia and the prevalence of hirsutism varying significantly by ethnicity.

Risk Factors

Most causes of alopecia and hirsutism are genetically determined.

Pathophysiology

Pattern alopecia relates to increased sensitivity to dihydrotestosterone. Telogen effluvium relates to an alteration in the normal hair cycle, with many hairs shedding synchronously. Alopecia areata represents an inflammatory insult directed against melanocytes in the hair bulb. There is strong evidence that the disease is mediated by T$_{H}1$ lymphocytes. Polycystic ovarian syndrome is an insulin-resistance syndrome resulting in excess production of androgens.

Prevention

Little can be done to prevent hair disorders, so the focus is generally on diagnosis and treatment.

Clinical Manifestations

Pattern alopecia manifests with apical scalp thinning. In men, receding of the hairline at the temples is typical, whereas women demonstrate widening of the part but retain the anterior hairline. Telogen effluvium manifests with diffuse shedding of telogen hairs (hairs with a nonpigmented bulb). Alopecia areata typically occurs with patchy hair loss. Shed hairs demonstrate tapered fracture at the base. Syphilitic alopecia resembles alopecia areata but often affects smaller areas, with only partial hair loss, resulting in a moth-eaten appearance. Scarring alopecia shows permanent areas of smooth alopecia lacking follicular openings.

Polycystic ovarian syndrome manifests with evidence of anovulation and excess androgen production. Signs of virilization suggesting a possible tumor include new onset of hirsutism, deepening of the voice, change in body habitus, and clitoromegaly.

Diagnosis

Alopecia

The first step is to determine if a hair shaft abnormality exists (Box 1). This is particularly important in black patients, in whom trichorrhexis nodosa is a common cause of hair loss. Trichorrhexis nodosa results from overprocessing of the hair. Hair density is normal at the level of the scalp, but hairs break off, leaving patches of short hair.

The next step is to determine if telogen effluvium exists. Telogen effluvium manifests with increased shedding of hairs with a blunt nonpigmented bulb (Figure 1), and it commonly follows an illness, surgery, delivery, or crash diet by 3 to 5 months. Hairs can often be easily extracted with a gentle hair pull or 1 minute of combing.

Diseases of the Hair

Trichodystrophy

Types

Trichorrhexis nodosa

Inherited trichodystrophies

Fractures

Causes

- Alopecia areata
- Chemotherapy
- Heavy metal

Determine Type

Anagen Effluvium

Tapered fractures can be caused by

- Alopecia areata
- Chemotherapy
- Heavy metal

Loose anagen can be caused by

- Loose anagen syndrome
- Easily extractable anagen in scarring alopecia

Telogen Effluvium

Increased shedding of club hairs can be caused by

- Diet, illness
- Pregnancy
- Medication
- Papulosquamous disorders
- Pattern alopecia

Diagnosis

Laboratory Studies

Iron

Thyroid stimulating hormone

Endocrine studies in virilized women

Biopsy

Nonscarring types

- Telogen effluvium
- Pattern alopecia
- Alopecia areata

Scarring types

- Lupus erythematosus
- Lichen planopilaris
- Folliculitis decalvans

Other Permanent Alopecia

Idiopathic pseudopelade

Morphea

1Not FDA approved for this indication.
The presence of tapered fracture suggests alopecia areata, syphilis, or heavy metal poisoning. Alopecia areata can result in diffuse hair loss, but it more commonly manifests with well-defined round patches of hair loss. The skin is either normal or salmon pink. Syphilis more often shows a moth-eaten pattern of alopecia (Figure 2).

Most patients with hair loss need only limited laboratory testing or none at all. Thyroid disorders and iron deficiency are common, and testing for them is relatively inexpensive. I recommend them when telogen effluvium is present. Their presence can also accelerate the course of pattern alopecia, and it is reasonable to test for them in women with this disorder. Thyroid-stimulating hormone is the best screen for thyroid disorders. The role of iron deficiency in telogen hair loss is controversial, but iron deficiency is common, easily established, and inexpensive to correct. Iron status also serves as an indicator of overall nutritional status. Although a low ferritin level proves iron deficiency, ferritin behaves as an acute phase reactant and a normal level does not rule out iron deficiency. Therefore, I recommend measurement of ferritin, serum iron, iron binding capacity, and saturation.

A scalp biopsy is required in any patient with scarring alopecia. It may also be necessary in other patients if history and physical examination do not establish a diagnosis and the alopecia is progressive. The scalp biopsy should be performed with a 4-mm biopsy punch oriented parallel to the direction of hair growth. Gelfoam can be placed into the resulting hole to stop bleeding and eliminate the need for sutures. The biopsy should be done in a well-established but still active area of inflammation if one can be identified. A combination of vertical and transverse sections increases the diagnostic yield and is usually recommended. In patients with scarring alopecia, half of the vertically bisected specimen should be sent for direct immunofluorescence. An additional biopsy of an end-stage scarred area can demonstrate characteristic patterns of scarring with an elastic tissue stain. This can help distinguish among causes of scarring alopecia such as lupus erythematosus (Figure 3), lichen planopilaris, pseudopelade, and folliculitis decalvans.

Hirsutism
Patients with new-onset virilization should be evaluated to rule out an ovarian or adrenal tumor. Ovarian and adrenal imaging studies and a total testosterone level are the best screens. A total testosterone more than 200 ng/dL or dehydroepiandrosterone sulfate (DHEAS) more than 8000 ng/dL suggests tumor. In patients with physical signs of Cushing’s disease, a 24-hour urine cortisol should be obtained. Most patients with chronic medically significant hirsutism have polycystic ovarian syndrome (PCOS). The diagnosis is established by means of history and physical examination, and the most important laboratory tests are serum lipids and fasting glucose to establish associated cardiac risk factors. A clinical diagnosis of PCOS requires the presence of hirsutism, acne or pattern alopecia, and evidence of anovulation (fewer than 9 periods per year or cycles longer than 40 days). Ratios of luteinizing hormone (LH) to follicle-stimulating hormone (FSH) have poor sensitivity and specificity for diagnosing PCOS. Imaging for ovarian cysts seldom affects management.

Differential Diagnosis
Syphilis can mimic alopecia areata, and serologic testing should be performed in any sexually active patient with a new diagnosis of alopecia areata. Correct diagnosis of scarring alopecia depends on a thorough examination for other cutaneous signs of lupus erythematosus or lichen planus as well as the results of a skin biopsy.

Tinea capitis can occur as inflammatory boggy areas with hair loss (kerion) or with subtle seborrheic-type scale and black-dot areas of hair loss. A KOH examination can be performed by

Figure 1. Telogen hair on left, anagen hair on right for comparison.

Figure 2. Moth-eaten syphilitic alopecia.

Figure 3. Scarring alopecia secondary to chronic cutaneous lupus erythematosus.
rubbing the affected area with moist gauze and examining broken hairs that cling to the gauze.

Hirsutism should be distinguished from hypertrichosis. Hirsutism is a male pattern of hair growth occurring in a woman and is hormonal in nature. Hypertrichosis is excess hair growth that occurs outside of an androgen-dependent distribution. It can be found in metabolic disorders such as porphyria or may be a sign of internal malignancy (Figure 4).

Nonclassic 21-hydroxylase deficiency accounts for up to 10% of patients with medically significant hirsutism. Screening with a baseline morning 17-OH-progesterone is associated with many false positive results. A stimulated 17-OH-progesterone is more specific, but the results of testing seldom affect management because outcomes with dexamethasone (Decadron) are no better than with spironolactone (Aldactone).\(^1\)

### Treatment

**Alopecia**

Telogen effluvium commonly resolves spontaneously once the cause has been eliminated. Poor diet and papulosquamous diseases of the scalp such as seborrheic dermatitis and psoriasis can perpetuate a telogen effluvium and should be treated. Seborrheic dermatitis responds to topical corticosteroids. Medicated shampoos containing selenium sulfide (Selsun Blue) or zinc pyrithione (T-gel Daily Control) can be helpful. Scalp psoriasis can require more potent topical steroids such as fluocinonide solution (Lidex) and calcipotriene (Dovonex) applied on weekends or daily. Systemic agents such as methotrexate (Trexall) at doses of 7.5 to 20 mg once weekly may be required to control severe scalp psoriasis.

Pattern alopecia in men is mediated by dihydrotestosterone (DHT). Men with pattern alopecia may be treated with daily topical minoxidil 2% to 5% (Rogaine) or oral finasteride (Propecia) at a dose of 1 mg daily. In women, the pathogenesis is complex, and adrenal androgens may play a larger role. Finasteride\(^1\) is of no benefit to the majority of women with pattern alopecia. Spironolactone\(^1\) 100 mg twice daily can be helpful. In women of childbearing potential, spironolactone should always be used in conjunction with an oral contraceptive. Side effects are uncommon but can include urinary frequency, irregular periods, and nausea. Most patients demonstrate a minor increase in serum potassium. Those with kidney failure are at risk for life-threatening potassium retention. Topical 2% minoxidil can also be of benefit, but women derive little added benefit from higher concentrations. All patients with pattern alopecia should be evaluated for superimposed causes of telogen effluvium such as inadequate diet and seborrheic dermatitis.

Tinea capitis is often overlooked in adults and black children, in whom the manifestations of inflammation can be subtle. Black dot and seborrheic tinea are common in black children. Patchy hair loss is an important clue to the diagnosis. Treatment is summarized in Table 1.

Localized patches of alopecia areata respond to intralesional injections of triamcinolone hexacetonide (Aristospan) (2.5–5 mg/mL) given once per month. Approximately 0.1 mL/cm\(^2\) is injected to a maximum of 3 mL during any one session. Minoxidil\(^1\) solution produces slow regrowth in some patients who cannot tolerate other treatments. Anthralin (Dritro-Scalp 0.5%)\(^1\) is sometimes used in children. It is applied 30 minutes before showering. It can stain skin and anything else it touches.

Topical immunotherapy with dinitrochlorobenzene (DNCB),\(^1\) squaric acid dibutylerster (SADBE)\(^1\) or diphenylcycloprenopene (DPCP)\(^1\) is more effective than either minoxidil or anthralin. DNCB is mutagenic in the Ames assay and none of the topical immunotherapies are currently approved for human use. A 2% solution of the sensitizer is applied to the arm in acetone to induce initial sensitization. Subsequently, diluted solutions, starting at about 0.001%, are applied weekly to the scalp with a cotton-tipped applicator. Roughly 20% to 60% of patients have responded to this regimen in various studies.

Biologic agents have been disappointing, but methotrexate\(^1\) in psoriatic doses (7.5–20 mg weekly for an adult) can be effective. Sulfasalazine (Azulfidine)\(^1\) is sometimes effective in doses ranging from 300 to 1500 mg three times a day.\(^3\) Patients should be encouraged to read about new therapies on the National Alopecia Areata Foundation website (www.naaaf.org).

Early, aggressive therapy for discoid lupus erythematosus is recommended to prevent permanent scarring. Topical corticosteroids are rarely sufficient. Intraleional injections are performed in a manner similar to that described above. Initial control of severe disease can be achieved with a single 3-week tapered course of oral prednisone at a dose of 60 mg daily for the first week, 40 mg daily for the second week, and 20 mg daily for the third week. Intraleional steroid injections or a systemic steroid-sparing agent are required for maintenance therapy. Systemic agents that can be effective include antimalarials, dapsone,\(^1\) methotrexate,\(^1\) mycophenolate mofetil (CellCept),\(^1\) and thalidomide (Thalomid).\(^1\)

I generally begin treatment with hydroxychloroquine (Plaquenil) at a dose of 400 mg daily for an adult. Dapsone is used at a dose of 100 mg daily for an adult. Thalidomide has been used effectively at doses of 50 to 100 mg daily, but peripheral neuropathy and teratogenicity limit its use. Mycophenolate mofetil is used

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**Table 1** Treatment of Tinea Capitis

<table>
<thead>
<tr>
<th>ANTIFUNGAL AGENT</th>
<th>DOSAGE</th>
<th>USUAL DURATION OF THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griseofulvin (Fulvicin U/F)</td>
<td>Required dosages are often higher than reflected in the product label; 4–10 mg/kg/d is a good starting dosage</td>
<td>1 mo or more</td>
</tr>
<tr>
<td>Fluconazole (Diflucan)(^1)</td>
<td>5–6 mg/kg/d</td>
<td>1 mo or more</td>
</tr>
<tr>
<td>Itraconazole (Sporanox)(^1)</td>
<td>3–5 mg/kg/d</td>
<td>1 wk, repeated monthly until cured</td>
</tr>
<tr>
<td>Terbinafine (Lamisil)</td>
<td>Patient &lt;20 kg: 62.5 mg/d; Patient 20–40 kg: 125 mg/d; Patient &gt;40 kg: 250 mg/d</td>
<td>1 mo or more</td>
</tr>
</tbody>
</table>

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\(^1\)Not FDA approved for this indication.

\(^2\)Exceeds dosage recommended by the manufacturer.

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Figure 4. Malignant hypertrichosis secondary to ovarian cancer.
at a dose of 1 gram twice daily, and methotrexate is used at doses of 7.5 to 20 mg weekly.

End-stage cicatricial alopecia is best treated by scalp reduction and hair transplantation. The disease can flare up in response to surgery, and it is best to plan a 3-week tapered course of prednisone\(^1\) as described to help prevent the flare.

Lichen planopilaris is treated in a manner similar to lupus, except that hydroxychloroquine\(^1\) is of less benefit and oral retinoids (Soriatane\(^1\) at doses of 25 to 50 mg daily) are more likely to be successful. Mycophenylate mofetil 1 g twice daily is often effective when other treatments fail.

Folliculitis decalvans manifests with crops of pustules that result in permanent scarring. Patients respond to weekend applications of clobetasol (Clobex, Olux) together with prolonged use of anti-staphylococcal antibiotics such as doxycycline (Doryx)\(^1\) 100 mg twice daily.

**Hirsutism**

Treatment options include laser epilation, efomithine (Vaniqua) cream to reduce the rate of hair growth, or spironolactone\(^1\) at a starting dose of 100 mg twice daily as described for pattern alopecia. Cyproterone acetate is used in some countries but is not available in the United States. Other options that are less commonly used include insulin sensitizers, flutamide (Eulexin), metformin (Glucophage), and leuprolide (Lupron)\(^1\) plus estrogen.

**Monitoring**

Patients treated with topical or intralesional corticosteroids should be monitored for cutaneous atrophy. Those on hydroxychloroquine should be monitored for ocular toxicity, including corneal deposits and retinal damage, although these are very rare at usual doses. They should also be monitored periodically for thrombocytopenia, agranulocytosis, and hepatitis. Patients beginning dapsone therapy should be screened for G6PD deficiency. Potential side effects include hemolysis, methemoglobinemia, and neuropathy. Monitoring includes periodic blood count assessment and measurement of strength and sensation. Mycophenolate mofetil can produce pancytopenia, and blood counts should be monitored. Methotrexate is cleared by the kidneys, and kidney function should be assessed at baseline. Periodic assessment of liver-function tests and blood count is warranted, as is a yearly chest radiograph. I also monitor procollagen 3 terminal peptide levels quarterly to assess the risk of hepatic fibrosis.

**Complications**

Patients with pattern alopecia and polycystic ovarian syndrome have a greater risk of metabolic syndrome with cardiac complications. They should be evaluated for lipid abnormalities and glucose intolerance and treated appropriately.

\(^1\)Not FDA approved for this indication.

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**References**


Chang KH, Robjunsakool S, Goldberg LJ. Treatment of severe alopecia areata with low-dose oral dapsone therapy should be screened for G6PD deficiency. Patients treated with topical or intralesional corticosteroids may benefit from treatment with minoxidil (1% solution) at a dose of 5 to 20 mg tablets concurrent with topical preparations: as needed to control ulcers and then taper and maintain control with topical corticosteroids. Prednisone minimum dose: alternate-day concurrent with topical preparations as needed to control oral ulcers.
The numerous diseases that affect the oral cavity can pose difficult diagnostic and therapeutic challenges. Some simplification can be attained by dividing oral diseases into three groups based on management perspective. The first group includes conditions such as dental caries and periodontitis that are directly associated with the teeth and are the dentist’s treatment responsibility. The second group consists of conditions that do not cause symptoms, present little risk of adverse consequences, or are so rarely encountered that they represent more of a novelty than a clinically significant consideration. The third group consists of a relatively short list of conditions that produce pain or pose the risk of serious complications and require treatment other than dental care. The diseases of this third group are compared in the Current Diagnosis box and were selected to frame this therapeutic overview because patients may seek treatment from the physician rather than the dentist.

Disseminated Odontogenic Infection
With few exceptions, disseminated bacterial infections of odontogenic origin represent a dramatic, acute exacerbation of a chronic, asymptomatic infection. A variety of dental conditions are possible causes, such as a periodontal abscess, an abscess within the supportive bone resulting from the pulpal necrosis of a carious tooth, or an infection of the gingiva surrounding a partially erupted third molar. The patient often describes a history of one or more prior acute episodes of bacterial infection symptoms from the site followed by resolution. The degree of swelling, lymphadenopathy, pain, and fever is proportional to the risk of potential complications such as sepsis. Of particular concern is evidence of rapid progression of diffuse swelling into the floor of the mouth and neck because of the risk of respiratory distress (i.e., Ludwig’s angina) or superiorly from the anterior portion of the maxilla because of the possibility of cavernous sinus thrombosis.

Definitive dental treatment to eliminate the underlying infectious source is the treatment goal after the acute, disseminated infection has been controlled. Penicillin is still considered the empiric antibiotic choice for disseminated odontogenic bacterial infections in individuals with no history of adverse reaction, and clindamycin (Cleocin) is used for those hypersensitive to penicillin. Many patients mistakenly assume that empiric antibiotic treatment can eliminate the infection in the same sense that antibiotic treatment can cure bacterial sinusitis or pharyngitis. The patient should be informed that improvement of an acute odontogenic infection after antibiotic treatment is not curative and that dental care to eliminate the underlying cause is necessary. One or more courses of antibiotics without elimination of the source increase the probability of the emergence of more virulent, antibiotic-resistant pathogens. More aggressive treatment, including intravenous antibiotics and surgical drainage in a hospital setting, must be considered in cases of rapid progression or extensive swelling, particularly if the anterior maxilla or submandibular areas are involved and in instances of compromised host resistance.

### TABLE 1
Clinical Suspicion Factors for Oral Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>MORE SUSPICIOUS</th>
<th>LESS SUSPICIOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causative factors</td>
<td>Alcohol and tobacco use</td>
<td>Frictional cause (e.g., sharp tooth)</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;40 years (younger much less likely)</td>
<td>&lt;40 (probability increases if immunocompromised)</td>
</tr>
<tr>
<td>Surface appearance</td>
<td>Altered and heterogeneous</td>
<td>Unaltered or homogeneous</td>
</tr>
<tr>
<td>Peripheral delineation</td>
<td>Vague borders</td>
<td>Sharp borders</td>
</tr>
<tr>
<td>Distribution</td>
<td>Isolated</td>
<td>Multifocal</td>
</tr>
<tr>
<td>Pain (ulcers)</td>
<td>Painless or less pain than expected for lesion size</td>
<td>Pain (inflammatory)</td>
</tr>
<tr>
<td>Location</td>
<td>Tongue, oropharynx, floor of mouth</td>
<td>Gingiva, hard palate, buccal mucosa (less likely)</td>
</tr>
<tr>
<td>Palpation</td>
<td>Indurated, non tendent</td>
<td>Compressible, tender</td>
</tr>
<tr>
<td>Clinical course</td>
<td>Unchanging (weeks), progressive (months)</td>
<td>Variable (within weeks), static (months or years)</td>
</tr>
</tbody>
</table>
The combination of induration, altered surface appearance, lack of tenderness to palpation, and progressive enlargement over a period of weeks or months suggests malignancy.

Definitive diagnosis of most oral lesions requires a biopsy, and this is indicated if oral SCC is considered a significant differential diagnostic possibility. Exfoliative cytology is much less reliable as a screening method in the assessment of malignant and premalignant oral disease compared with lesions of the uterine cervix. The harsh nature of the oral environment from food, tobacco use, and other habits limits the appreciation of cytologic features. The diagnosis of oral candidiasis and some viral lesions can be made by exfoliative cytology. Table 1 lists features that prompt increased suspicion of oral cancer and the need for definitive diagnosis by biopsy. As with any differential diagnosis, one or two corresponding features may not be compelling unless dramatic. A greater number of findings that suggest oral SCC indicate a stronger justification for biopsy. The decision to obtain a biopsy of an oral lesion should be made with consideration of the substantial positive impact that early detection has on a disease with an otherwise unfavorable prognosis.

Necrotizing Ulcerative Gingivitis

Necrotizing ulcerative gingivitis (NUG) is a characteristic, potentially destructive infection of the dental supportive tissues caused by a predominance of fusiform bacteria and spirochetes. Some combination of psychologic stress, compromised immune function, malnutrition, or other condition of diminished host resistance dramatically increases the risk of NUG. This is suggested by the colloquial phrase trench mouth used to refer to this infection, because it was frequently observed among debilitated soldiers during World War I. It has also been called Vincent’s infection and acute NUG (ANUG).

Acute onset of poorly localized, severe dental pain and a putrid taste are typically the patient’s chief complaints. Onset usually corresponds with a significant alteration in the general health or emotional status, although a more chronic course of variably pronounced symptoms can be expected with protracted conditions such as acquired immunodeficiency syndrome (AIDS). Visual features of NUG include necrotic deterioration of the gingiva with pronounced peripheral erythema and a superficial pseudomembrane. The tissue around the mandibular anterior teeth is most severely affected in most cases, and the gingiva often appears “punched out” from between the teeth. The gingival necrosis produces the characteristic fetid breath that is far more pungent than that caused by typical gingivitis. The putrid odor in combination with the acute onset and poor localization of pain is usually a more reliable basis for diagnosis than visual findings. Additional features, such as fever and cervical lymphadenopathy, are proportional to the severity of the oral findings.

Treatment of NUG consists of the combination of supportive care, antimicrobial measures, and improvement in the underlying compromising health conditions. Supportive care is nonspecific and includes rest, fluid intake, and a soft but nutritious diet. Warm saline, dilute hydrogen peroxide, and chlorhexidine gluconate (Peridex) are effective antimicrobial rinses. Penicillin and metronidazole (Flagyl) are the empiric systemic antibiotics of choice. Ultimate combination of thorough dental cleaning of the teeth with debride ment of the necrotic soft tissue and improved oral hygiene. Resolution of NUG, including complete healing of the gingival tissue, is strikingly rapid in most instances if this is accomplished and underlying health status improves. Persistence or recurrence of NUG after debridement suggests the possibility of human immunodeficiency virus (HIV) infection or another undiagnosed compromising condition.

Oral Candidiasis

Oral candidiasis is a superficial fungal infection of the oral mucosa that is clinically similar to vaginal candidiasis in many respects. With isolated exceptions, the infection is caused by the fungus Candida albicans, which can be identified in the mouths of approximately 50% of healthy adults. The risk of oral candidiasis is increased by one or more factors of compromised host resistance: decreased local resistance, compromised immune function, or uncontrolled systemic disease. Frequently encountered examples of decreased local resistance include poor oral hygiene, xerostomia, wearing dentures that provide an organism reservoir or limit hygiene, and recent antibiotic therapy that has altered the normally competitive oral bacteria. The combination of one or more of these local factors with a systemic condition that causes compromised immune status or constitutional compromise dramatically increases the risk of clinical apparent infection. Common examples include AIDS, corticosteroid therapy, severe anemia, and poorly controlled diabetes mellitus.

Oral candidiasis lesions can have four distinct appearances. The most characteristic form is the pseudomembranous, curdlike globules of thrush that wipe off with cotton gauze, leaving a sore, erythematous mucosal surface. The erythematous or atrophic form of oral candidiasis produces a thin, “beefy” appearance often affecting the dorsum of the tongue or mucosa that supports a denture. The third type of lesion is the formation of fissures similar to those of tinea pedis that usually are at the corners of the mouth and are referred to as angular cheilitis. The fourth is a hyperplastic form that produces a patchy, white thickening of the surface epithelium that does not rub off and that appears similar to the hyperkeratosis of chronic frictional irritation. Oral candidiasis often produces more than one lesion form simultaneously in different areas of the mouth, which may be a confirmational finding. Patients often describe little discomfort or only a mild burning sensation from affected sites.

The clinical course of the infection may be acute, chronic, or cyclic in severity, depending on the nature of the underlying causes. The combination of clinical appearance, suspected compromised host status, and improvement after empiric treatment provides an adequate basis for the diagnosis. Exfoliative cytology provides definitive evidence of the infection in more equivocal situations.

Antifungal treatment eliminates oral candidiasis in most instances, but recurrences or a chronic, subclinical course can be expected if the predisposing condition remains unchanged. This implies that treatment of superficial oral candidiasis may not be justified in such instances if the affected individual is asymptomatic, because the only realistic treatment goal is elimination of symptoms. That decision must be weighed against the possibility of spread to the esophagus.

Options for routine topical treatment of oral candidiasis include clotrimazole (Mycelex) troches or nystatin (Mycostatin) pastilles, and use should continue for 1 week after resolution of symptoms. Several considerations can complicate effectiveness. Patients with xerostomia have difficulty dissolving the troches or pastilles and prefer a nystatin rinse. Concurrent management of the dry mouth (discussed later) increases the effectiveness of topical antifungal treatment for candidiasis. Limiting the Candida organism reservoir in the denture acrylic for those who wear dentures can be accomplished by soaking overnight in most commercial denture soaking solutions, mouthwashes such as Listerine, or chlorhexidine gluconate. These products are adequately fungicidal, and keeping the denture overnight disrupts adherence and colonization of candidal organisms. Some patients are more compliant about managing the denture problem by applying a thin layer of nystatin ointment1 or clotrimazole cream (Lotrimin)2 to the denture before wearing. Direct application of these preparations also promotes rapid resolution of angular cheilitis. Systemic administration of ketoconazole (Nizoral) or fluconazole (Diflucan) is an alternative for patients who cannot manage topical treatment or for severely immunocompromised individuals in the interest of controlling oral symptoms and minimizing the risk of spread to the esophagus.

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1 Not FDA approved for this indication.
Xerostomia
Xerostomia is defined by the patient’s subjective perception of “dry mouth” rather than by an objective parameter. The amount of saliva is decreased, and its character typically is altered to a more viscous, ropey consistency. The condition is common because salivary function is adversely affected by so many routinely encountered influences, including many frequently prescribed medications, smoking, methamphetamine abuse, several common systemic diseases, and tumoricidal irradiation exposure. In addition to these influences, primary Sjögren syndrome is characterized by chronic dry eyes and dry mouth caused by autoimmune-mediated tissue disorder such as rheumatoid arthritis.

The subjective response of different individuals to a mild or moderate degree of oral dryness varies considerably. Many patients who appear to produce adequate saliva complain of dryness, whereas others who seem unusually dry during oral examination have no complaints. Most patients with an advanced degree of dryness find the continual “cotton mouth” sensation and other consequences to be a significant quality-of-life issue. Decreased saliva production causes difficulty chewing and swallowing, as well as painful abrasion of the mucosa by coarse foods. Beyond the physical irritation, limited saliva alters the sense of taste and the enjoyment of food. Saliva contributes to oral health by providing antimicrobial components such as lactoperoxidase and IgE antibodies, and it has a significant flushing and cleansing function. Xerostomia causes a rampant and rapidly progressive pattern of dental decay that is particularly destructive even for previously caries-resistant individuals. This is compounded if the patient compensates for the dryness by drinking sucrose-rich soft drinks or sucking on hard candy. Similarly, periodontitis tends to progress rapidly despite normally effective treatment if saliva production is limited. Xerostomia is also associated with complaints of generalized soreness of the mouth caused by frequent and persistent episodes of oral candidiasis.

Management of xerostomia is challenging and often frustrating for the patient and the clinician. The treatment for severe, irreversible xerostomia, as in cases of head and neck radiotherapy, is essentially symptomatic. Different patients prefer different combinations of compensation methods. Sipping water throughout the day is the single most effective and simplest way to counter loss of saliva. Some patients report additional improvement with the use of commercially available saliva substitutes, although many do as well with water and ice chips. Most patients soon learn to avoid abrasive foods, irritating commercial mouth rinses that contain alcohol, and highly flavored toothpastes in favor of less irritating alternatives. Use of a humidifier at night is often beneficial. Comprehensive dental treatment should be recommended to limit the progression and severity of dental caries and periodontitis. Smoking and compensation by drinking sucrose-rich soft drinks, sports drinks, drinks that contain caffeine, and highly acidic citric juices should be discouraged.

Additional options beyond the previous recommendations are available for those who have some residual salivary function. Drinking ample water moistens the mucosa and maintains general hydration, which maximizes the residual saliva production. Sugar-free gum or hard candy significantly stimulates saliva flow. Alternative medications that are equally effective therapeutically but less likely to cause xerostomia may be substituted in some cases to treat conditions such as hypertension.

Several cholinergic salivary are available, including cevimeline (Evoxac), pilocarpine (Salagen), and Bethanechol (Urecholine). Titration of dosage is usually necessary to optimize saliva flow while minimizing frequent adverse effects such as excessive sweating and gastritis. Many patients discontinue treatment because of these and less common side effects that become more troublesome than the xerostomia. Contraindications such as glaucoma and the risk of serious complications such as arrhythmia must also be considered.

**Aphthous Stomatitis**
Recurrent aphthous stomatitis, colloquially known as canker sores, is a common condition of complex immune-mediated pathogenesis. Patients describe recurring episodes of painful ulcers that often follow triggering events such as minor tissue abrasion, eating certain foods, or episodes of emotional stress. The phrase *minor aphthous stomatitis* differentiates the most common, mild form of the disease from the more severe *major* and *herpetiform variations*. Most authorities believe these categorizations are somewhat artificial distinctions within a continuum of a single process. Similar ulcers are a feature of Behçet’s syndrome but are of minor diagnostic and treatment significance compared with the other manifestations of this rare, multisystem condition.

The clinical features of minor recurrent aphthous stomatitis are characteristic. One or more painful ulcers develop soon after a short prodromal period of burning or itching at the affected site. The superficial ulcers exhibit a uniform, yellowish white, pseudo-membranous surface with an erythematous peripheral halo at the sharply delineated ulcer margin. Typical size is 1 to 2 cm, and lesions affect only unbound oral mucosal surfaces of the lips, cheeks, floor of the mouth, or soft palate. This distribution specifically excludes the bound surfaces of the gingiva, hard palate, and the dorsum of the tongue. This feature is valuable for differentiating aphthous stomatitis from the intraoral recurrent herpetic lesions (discussed later) that affect only bound surfaces. Aphthous lesions typically heal within 7 to 10 days, and most patients describe a long clinical course of symptom-free periods of various durations interrupted by episodes of ulcer formation. Lesion-free periods of weeks, months, or even years typically distinguish recurrent aphthous stomatitis from autoimmune conditions such as erosive lichen planus (discussed later) that produce a continuous course of oral ulcers.

The major form of recurrent aphthous stomatitis produces ulcers of similar appearance, but the lesions are larger, require a longer healing time, often heal with scarring, and form so frequently that at least one ulcer is usually present. The herpetiform variant is characterized by a cluster of numerous smaller (1–3 mm) ulcers that often coalesce into a single, large lesion, and the ulcers are described as exceptionally painful. The clustering distribution explains the somewhat misleading herpetiform designation for this nonviral condition. This form of aphthous stomatitis may affect keratinized and nonkeratinized surfaces, which in addition to the clustering distribution may lead to confusion with recurrent herpes simplex lesions.

Minor recurrent aphthous stomatitis is more irritating than severe, and treatment beyond symptomatic management is usually not justified. Patients should learn to avoid their particular trigger event as much as possible, and many find relief during outbreaks from over-the-counter preparations such as Orabase with benzocaine 20% or by rinsing with soothing, coating products such as bismuth subsalicylate (Kaopectate). Rinses containing a variety of ingredients, such as tetracycline, aloe, and chlorhexidine gluconate, have been reported to promote ulcer healing in some cases. Treatment with corticosteroids (see Current Therapy box), however, is more consistently effective and is justified for major and herpetiform variants, as well as for particularly severe or frequent outbreaks of minor aphthous lesions.

**Orofacial Herpes Simplex Infection**
Most herpes simplex infections of the oral mucosa are caused by herpes simplex virus type 1 (HSV-1). A much smaller proportion of oral cases results from the type 2 herpes simplex virus that typically causes genital lesions. Transmission occurs by direct contact or contaminated saliva, and serologic studies demonstrate that as much as 90% of the population has been infected by age 50.

The initial infection, referred to as acute herpetic gingivostomatitis or primary herpes, usually affects children and causes acute
onset of cervical lymphadenopathy, chills, and fever similar to many acute viral infections. The distinguishing manifestation is the formation of multiple, painful oral vesicles that rapidly rupture. The resulting ulcers most prominently affect the gingiva, lips, and tongue, but may occur on any oral surface. Primary herpetic lesions in adults are more likely to cause complaints of pharyngitis rather than oral ulcers, which makes distinguishing it from other systemic viral infections unlikely. The severity of primary herpes varies from virtually subclinical or indistinguishable from nonspecific viral infections to debilitating. The distinguishing oral lesions are probably seen only in severe cases because relatively few seropositive individuals recall the oral ulcers of the primary infection when questioned. Symptoms resolve within 5 days to 2 weeks, depending on the severity of the manifestations, and significant complications such as encephalitis or keratoconjunctivitis are rare.

The HSV-1 virus becomes latent within the sensory neurons that supply the primary infection site. Episodes of recurrent lesions may develop after the primary infection, a pattern similar to the recurring genital lesions caused by HSV-2. The frequency, severity, and course of these outbreaks vary widely among individuals, and at least one half of HSV-1-seropositive individuals rarely or never suffer recurrent lesions. Those who do often associate occurrence with causative events, such as sun exposure of the exposed lip, abrasion of the surface, or an illness such as a nonspecific viral infection. This explains the colloquial terms cold sore and fever blister used to describe the most common presentation affecting the exposed lip, which is referred to as herpes labialis.

The typical episode begins with a prodromal sensation of burning or itching at the site near the vermilion border, followed by formation of one or more vesicles within 24 hours. The vesicles soon rupture, forming a coalesced crust that heals after 7 to 10 days. A few individuals suffer similar recurrent herpes lesions of the intraoral mucosa. Intraoral herpes lesions produce features of pain, onset, recurrent course, and healing time that are similar to those for aphthous stomatitis, which may present some differential diagnostic uncertainty. The diagnosis can be made in most cases based on the affected surface. Aphthous lesions are usually limited to the unbound mucosa of the lips, cheeks, soft palate, and floor of the mouth, whereas the intraoral ulcers of recurrent herpes simplex infection are limited to the bound mucosa of the gingiva and hard palate.

Treatment of primary herpes simplex infection for immunocompetent individuals is supportive and symptomatic, as for any acute viral infection. In viral infections associated with significant oral discomfort, a rinse consisting of a 1:1 mixture of diphenhydramine (Benadryl) and 12.5 mg/mL of Kapectate is used to relieve some symptomatology, and topical agents such as herpetic labial ointment (Abreva) cream may limit the severity and duration of lesions. The FDA recommends that systemic antiviral medication such as acyclovir (Zovirax) and valacyclovir (Valtrex) be reserved for immunocompromised individuals, with the goal of decreasing the duration and severity of symptoms. Administration of the antiviral agent must be started during the initial stage of the infection to be effective.

Most individuals affected by secondary herpetic lesions suffer relatively few episodes, and no treatment is warranted. Patients prone to frequent lip lesions after sun exposure soon learn the preventive value of sunscreen lip balms, but the advice may be helpful to those who have not made the association. For patients who experience numerous secondary herpetic episodes, topical antiviral treatment with penciclovir (Denavir) cream or docosanol 10% (Abreva) cream may limit the severity and duration of the lesions, but applications must begin during the prodromal stage to be effective. Systemic administration of valacyclovir (Valtrex) can be used therapeutically during the prodromal stage or prophylactically. FDA recommendations limit the use of systemic acyclovir for recurrent orofacial herpetic lesions to immunocompromised patients for prophylaxis and treatment of individual outbreaks at the onset of prodromal symptoms.

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1Not FDA approved for this indication.
Diseases of the Mouth

patients with skin lesions, and many individuals exhibit oral lesions without skin abnormalities. The oral lesions appear as a lacy network of white, hyperkeratotic lines that bilaterally affect the buccal mucosal surfaces, although any intraoral surface may be affected. This is referred to as the reticular presentation of oral lichen planus, and no treatment is warranted because the white lesions are asymptomatic. The erosive form of lichen planus is less common but is of greatest therapeutic concern because affected patients seek pain relief. Ulcers tend to form in the same oral sites for a given patient and cyclically vary in severity as ulcers concurrently heal somewhat in some areas and progress elsewhere. Buccal mucosa and gingiva are the typically affected sites, but any intraoral surface may be affected.

One helpful distinguishing visual feature of ELP lesions from other autoimmune oral ulcers is that the zone between the ulcer and unaffected mucosa often exhibits a fine pattern of white lines that suggests the reticular form of the disease. This appearance is enhanced by drying the saliva with cotton gauze. The term desquamative gingivitis is used to describe the clinical presentation if the erosive lesions most dramatically affect the gingiva, which is often the case. The gingiva appears uniformly erythematous and delicately thin, with isolated ulcers. Bulla formation after lateral pressure on this atrophic surface (i.e., Nikolsky’s sign) results from the compromised epithelial-connective tissue interface. The patient often complains of sore, bleeding “gums,” but the atrophic appearance and Nikolsky’s sign are helpful in distinguishing similar complaints from the much more commonly encountered gingivitis and periodontitis caused by poor oral hygiene.

MMP has also been referred to as cicatrical pemphigoid and benign MMP. The typical presentation of MMP is a chronic course of primarily gingival vesicles and bullae that rapidly degenerate into ulcers that fit the desquamative gingivitis description, although any intraoral area may be affected. The white, hyperkeratotic striations seen at the periphery of the ulcers caused by ELP are absent or less conspicuous with MMP. In contrast to ELP, if nonoral lesions of MMP are present, they affect the conjunctiva and genital mucous membrane surfaces rather than the skin. Occurrence of ocular lesions eventually approaches nearly 25% of affected individuals during the protracted disease course, and these lesions may cause blindness in severe cases.

Of the four characteristic forms of pemphigus, only PV causes oral lesions to any clinically significant degree. Approximately one half of PV patients develop oral ulcers before the appearance of skin lesions. Oral ulcers may affect any intraoral surface and appear superficial with an irregular shape. Initial vesicle or bulla formation is unusual with oral PV, in contrast to MMP, and the peripheral striations described with ELP are absent. The oral ulcers caused by PV tend to show slow progression without healing over time, in contrast to the cyclic variation of concurrent healing and lesion formation characteristic of ELP and MMP.

Several less common conditions can cause oral ulcers with a protracted clinical course. Bullous pemphigoid typically develops after age 60, but the condition is uncommon, skin lesions are the prominent feature, and less than one third of patients exhibit oral ulcers. Lupus erythematosus can cause oral ulcers very similar to those of ELP, but this occurs infrequently and only well into the course of the disease after the diagnosis has been established. Approximately 20% of individuals affected by erythema multiforme experience recurrences, but the course of oral lesions is much more episodic than continuous, and the characteristic target skin lesions often suggest the diagnosis. Graft-versus-host disease produces oral lesions similar to those of ELP, but the cause is obvious.

The oral ulcers caused by all of the conditions in this group respond to corticosteroid medications in the recommended therapeutic approach as described in the Current Therapy box. Several pivotal issues about these conditions and treatment with corticosteroids are important for successful management:

• The possibility of candidiasis and recurrent herpes simplex infection should be excluded on the basis of clinical course and features before empiric treatment of oral ulcers because corticosteroids worsen these infectious conditions.
• The patient should understand that the therapeutic goal is to control the oral ulcers rather than to cure the disease. Optimal treatment for ELP using corticosteroids, for example, converts the ulcers to the asymptomatic reticular form. Neither the patient nor the clinician should expect treatment to yield a completely normal tissue appearance.
• Oral candidiasis is a frequent complication of corticosteroid treatment, and this risk is increased with any concurrent condition such as xerostomia. Candidiasis can be detected early with periodic recall evaluation and by exfoliative cytology in suspected situations. Understanding the typical oral candidiasis symptoms increases the patient’s awareness of the need to return for treatment.
• Empiric topical corticosteroid treatment should be discontinued for 2 weeks if a biopsy becomes necessary for a definitive diagnosis.

Every effort should be made to identify and discontinue use of causative or irritating agents. Examples such as the link of acidic foods with aphthous ulcers are obvious to the patient, but many are more subtle. One example is cinnamon flavoring agents in many foods and toothpastes. Others are irritating to the mucosa but are mistakenly perceived as beneficial. Hydrogen peroxide, phenol preparations, and alcohol-based mouth rinses that “seem to be doing some good” because they are painful and consequently assumed to be killing bacteria are examples, and they should be avoided by patients with oral ulcers.

Corticosteroid Treatment of Immune-Mediated Oral Ulcers
Corticosteroid management of oral ulcers is similar to the approach for immune-mediated skin lesions. The therapeutic goal is lesion and symptom control, because disease cure or spontaneous remission is unlikely. This should be understood by the patient to avoid unreasonable expectations. Healing of ulcers should be achieved with as little corticosteroid medication as possible. Topical corticosteroids should be tried first, limiting systemic administration to “bursts” as needed to control outbreaks of refractory ulcers followed by maintenance with topical treatment. Long-term systemic corticosteroid administration should be considered only as a last resort. The severity of lesions in these conditions typically varies with time, which means that the need for treatment beyond topical control also varies. Understanding several issues unique to the oral cavity can increase treatment effectiveness:

• Application of the topical corticosteroid after eating and at bedtime and avoiding frequent snacks promote adherence, absorption, and effectiveness.
• Application of preparations with a cotton swab minimizes the risk of onychomycosis from routine application with the fingers.
• Low- and intermediate-potency topical corticosteroid preparations such as hydrocortisone (Hytone) and betamethasone valerate (Valisone) tend to be less than optimally effective in the oral environment. Initial trial with a higher-potency preparation is justifiable because significant systemic absorption through the oral mucosa is minimal. The use of ultrapotent topical corticosteroids is reserved for persistent ulcers if some systemic absorption is acceptable.

References
Established, onycholysis can result in pain and loss of function seen in a range of inflammatory and traumatic diseases. Once attached to the nail bed, with a specialized configuration of epidermis that serves the purpose of minimizing the risk of separation of the nail from the nail bed. Such lifting is called onycholysis and is seen in a range of inflammatory and traumatic diseases. Once established, onycholysis can result in pain and loss of function of the digit.

**Physiology**

Fingernails grow at approximately 3 mm a month, with a faster rate on the dominant hand, on larger digits, in men, in pregnant women, and possibly in warmer weather. The rate diminishes with age from about 45 years. It is slower in toenails, with a rate of approximately 1 mm a month, which can mean that it takes 12 months or more for a big toenail to grow out fully. This has significance for the assessment of the outcome of treatment interventions. It can take several months before a result can be assessed, and in the instance of treatment of onychomycosis it can mean that the treatment has been stopped before the benefits have been fully appreciated.

**Function**

Fine manipulation, picking up small objects, or scratching an itch or a sticky label are all common uses of a nail. All these functions can be lost in nail disease. Where many nail diseases are associated with soft tissue inflammation of the digit tip or nail fold, there can also be pain that limits function further.

**DISEASES OF THE NAILS**

Method of

David de Berker, MRCP

**Anatomy**

The nail plate arises from the nail matrix and grows out attached to the nail bed (Figure 1). The plate is inert and physiologically comparable to the stratum corneum as a structure composed of modified corneocytes containing a high proportion of keratins specific to the hair and nail differentiation that provide the hard and flexible characteristics of the appendage. The matrix is clinically visible as the lunula or half moon in the radial digits, particularly in the thumb. It usually is concealed by the proximal nail fold in the form of the cuticle. The lateral nail folds provide a soft tissue boundary to the nail sides. Distally, the nail is firmly attached to the nail bed, with a specialized configuration of epidermis that serves the purpose of minimizing the risk of separation of the nail from the nail bed. Such lifting is called onycholysis and is seen in a range of inflammatory and traumatic diseases. Once established, onycholysis can result in pain and loss of function of the digit.

**Clinical Features and Diagnosis**

Fungal invasion of nail alters the color and integrity of the nail. It may also alter attachment to the nail bed and the shape of the nail. The main color change is the development of shades of yellow or orange. Diagnosis relies on laboratory confirmation by obtaining a sample of nail and subungual debris for microscopy and mycological culture to provide the identity of the fungus, from which its role and likely sensitivities can be determined. Nail plate histology and polymerase chain reaction assay can be used as second-line tests.

Superficial white onychomycosis can manifest as small white powdery islands within the surface of the nail plate or as larger confluent areas. Scraping with a semisharp blade can demonstrate that it is limited to the dorsal aspect of the nail, and this sample can be sent to mycology for confirmation of the pathogen. It is a form of onychomycosis more common in children, who as a rule do not often suffer onychomycosis.

Proximal white subungal onychomysis is a variant of onychomycosis seen relatively more often on the fingernails and in people with immunosuppression, either through medications or as part of disease such as HIV. The infection manifests as a white appearance arising proximal to the rim of the proximal nail fold and beneath the nail plate. With time, as the nail grows out, there may be disturbance of the dorsal nail plate, and disease may progress to the distal free edge with nail destruction.

**CURRENT DIAGNOSIS: ONYCHOMYCOSIS**

- Make an objective diagnosis with KOH, culture, or clipping for periodic acid–Schiff.
- Onychomycosis is much more common on the toenails than the fingernails.
- The most common organisms are *Trichophyton rubrum* and *Trichophyton mentagrophytes*.
- *Candida* only rarely causes onychomycosis. It is primarily a colonizer where the local environment is conducive.
- Nondermatophyte molds (e.g., *Aspergillus* and *Fusarium* spp) are unusual causes of onychomycosis in the United States. Repeat tests showing the same organisms and ruling out other causes are required before initiating treatment.

**Diseases**

**Onychomycosis**

Onychomycosis is the infection of the nail plate and nail bed with fungus. Pathogenic fungi can damage the nail plate and its attachments. Fungus can also be present in an altered nail but not be the cause of the altered appearance in that it is biologically normal for fungus to occupy cracks in a damp space where there is organic material. Dermatophyte fungi (e.g., *Trichophyton* sp.) are more likely to be pathogenic than nondermatophytes, also referred to as molds (e.g., *Fusarium* sp.). *Candida* sp. also commonly colonizes rather than gives rise to an active onychomycosis with nail changes. However, when a nondermatophyte becomes established as a pathogen, it is often more difficult to eradicate than a dermatophyte and may well manifest with associated biological or occupational factors in the patient (e.g., working with soil, wet work).

**Figure 1.** Surface anatomy of the nail.
All three forms of infection can combine or progress to result in a nail that is almost or entirely overtaken with fungal infection, creating a variant known as total dystrophic onychomycosis.

Current Therapy: Onychomycosis

- Oral treatment should be reserved for patients with mycological confirmation, with emphasis on those at risk for complications (diabetes, immunosuppressed patients, those at risk for secondary bacterial cellulitis).
- Topical treatment is disappointing when used in isolation, except in cases of superficial white onychomycosis. When used in combination with oral therapy, it can increase the cure rate by about 10%.
- Oral treatment is more successful than topical treatment. Terbinafine (Lamisil) 250 mg PO once a day for 6 weeks for a fingernail and 3 months for a toenail in adults is the first-line treatment. Itraconazole (Sporanox), dosed 200 mg daily or 200 mg twice daily pulsed 1 week per month, is the next most successful agent.
- Newer antifungals are not established, and laser treatment is not fully evaluated.
- Nondermatophytes are not always pathogenic, but when they are, they can be difficult to effectively treat.
- Patients are at high risk for recurrence. Post-treatment prevention of tinea pedis is important to prevent reinfection.

Treatment

All national guidelines on the management of onychomycosis require that the clinical diagnosis be confirmed by microscopy of the nail for fungi and preferably also by mycological culture before commencing systemic treatment. It is common to see patients who have been treated for nonfungal disease with antifungal treatment, which wastes patients’ time and money and puts them at needless risk of serious adverse effects if they take oral therapy. Polymerase chain reaction assays are available as an alternative to routine microscopy but remain unable to determine the difference between a pathogenic and saprophytic role.

The main oral treatment for dermatophyte fungi is terbinafine (Lamisil). Itraconazole (Sporanox) is the main alternative. The concomitant treatment with a topical antifungal agent such as amorolfine 5% (Curanail, Loceryl) or ciclopirox 8% (Penlac) can increase the rate of success, which in a trial environment is between 50% and 80% depending on accepted end points. There is a significant relapse or reinfection rate in the following 5 years, and some patients choose to use a topical therapy intermittently on the nail to attempt to avoid this. Ongoing intermittent treatment of tinea pedis is also likely to help prevent relapse.

Topical therapy alone has a smaller chance of success in dermatophytes, but it can be effective, especially if combined with thorough debridement by the dermatologist or with the help of a podiatrist with a nail Burr and curette. Topical therapy can also be undertaken in combination with surgical or chemical avulsion (50% urea paste in yellow soft paraffin), and this is of value in non-involved nail.

Podiatrists with a nail Burr and curette. Topical therapy can also be undertaken in combination with surgical or chemical avulsion (50% urea paste in yellow soft paraffin), and this is of value in non-involved nail.

Clinical Features and Diagnosis

A personal or family history of psoriasis assists in interpretation of the signs. Sometimes, nail psoriasis occurs in isolation, and clinical signs alone provide the diagnosis or may be supported by a nail unit biopsy. The presence of fungus does not rule out an underlying diagnosis of psoriasis, especially on a big toenail, where fungus has been noted in 27% of psoriatic nails. Nail psoriasis has features that reflect the focus of disease within the nail unit.

Treatment

Treatment requires close attention to hand care, which entails avoiding manicure or work practices that are likely to exacerbate the problem. Typical issues are the clearance of debris from beneath the nail with a sharp instrument that elicits the isomorphic reaction with further psoriasis. Manipulation of the cuticle does the same, and having long nails results in leverage on the nail plate with minor trauma to exacerbate onycholysis. So the rules are:
- No clearance of debris except with a gentle soft nail brush
- No trimming or manipulation of the cuticle
- All nails to be as short as possible.
- General hand care with protection from solvents and wet work and use of plenty of emollient

Where potent topical steroid is to be used (Table 1), it is best applied at night only and for 2 to 3 months. Nail steroid injections have the theoretical risk of rupture of the tendon of the distal interphalangeal joint if undertaken frequently and so are usually done up to several months apart; my practice is to provide a ceiling of four injections per digit. As a rule, all systemic agents work, including biologicals, but their use is rarely justified by nail disease alone. It can be argued that cyclosporine (Sandimmune) in 3-month pulses is good for younger people with no kidney problems, methotrexate (Trexall) might suit older people, and acitretin (Soriatane) may suit those with hypertrophic nail disease. But most choices will be determined by the additional characteristics of the patient and the psoriasis elsewhere.

Idiopathic Onycholysis

Onycholysis is the separation of the nail from the nail bed, with a cleavage that commences at the free edge and progresses proximally.

Current Diagnosis: Onycholysis

- Primary onycholysis and chronic paronychia are diagnoses of exclusion.
- Onychomycosis, psoriasis, lichen planus, and drug reactions all must be ruled out before diagnosis.
- Primary onycholysis and chronic paronychia are more common on the fingernails than the toenails, in women, in adults, in those who use nail cosmetics, and in those who have recurrent exposure to moisture or chemicals.
- Both primary onycholysis and chronic paronychia represent breakdown in the normal barrier of the nail apparatus.
- Onycholysis results from breakdown of the onychocorneal band or nail bed–nail plate connection. Chronic paronychia results from breakdown of the cuticle and nail folds.
- In both scenarios, moisture, contact irritants, contact allergens, colonizing yeast, and bacteria invade the exposed nail apparatus and contribute to a cycle of inflammation.
**Diseases of the Skin**

**Candida**

Candida onycholysis presents with the nail bed. In this instance the contact is the margin of attachment shared with the wrench, the easier it is to exert a torsion force on the point presented by the overhanging margin of the nail. The principle is lysis further through the mechanics of creating a large lever represented by the overhanging margin of the nail. The principle is shared with the wrench in your tool set: The longer the arm on sensibilities to have long nails, which then exacerbates the onycholysis. It is common for people with such cosmetic material out with a sharp object. This then creates more pathology, a bigger split, and the accumulation of more debris managed by physical manipulation. It is common for people with such cosmetic sensibilities to have long nails, which then exacerbates the onycholysis further through the mechanics of creating a large lever represented by the overhanging margin of the nail. The principle is shared with the wrench in your tool set: The longer the arm on the wrench, the easier it is to exert a torsion force on the point of contact. In this instance the contact is the margin of attachment with the nail bed.

Clipping for mycology is usually undertaken and sometimes reveals *Candida* sp. This is not causal, but is a colonizing microbe in the warm onycholytic space.

**Clinical features and diagnosis**

Most patients with onycholysis also have psoriasis. However, for some with problems of nail attachment, the cause is multifactorial and it might not be possible to provide a unifying diagnosis. A subtype of onycholysis occurs in people who undertake manicure vigorously and have long nails. Such people are troubled by the debris beneath a nail and significantly damage the area by scraping material out with a sharp object. This then creates more pathology, a bigger split, and the accumulation of more debris managed by physical manipulation. It is common for people with such cosmetic sensibilities to have long nails, which then exacerbates the onycholysis further through the mechanics of creating a large lever represented by the overhanging margin of the nail. The principle is shared with the wrench in your tool set: The longer the arm on the wrench, the easier it is to exert a torsion force on the point of contact. In this instance the contact is the margin of attachment with the nail bed.

Clipping for mycology is usually undertaken and sometimes reveals *Candida* sp. This is not causal, but is a colonizing microbe in the warm onycholytic space.

**Treatment**

Treatment principles are shared with psoriasis (see earlier). The presence of *Candida* sp. on mycology might tempt the clinician to try itraconazole (Sporanox) systemically. However, it rarely helps, although the removal of one factor in the pathology can help other treatments to improve the situation. Success mainly requires avoidance of all physical exacerbating factors and clipping back the separated nail to treat the exposed nail bed with moderate-potency topical steroid. Antiseptic soaks can help if clipping back is not an option or there is significant microbial colonization.

**Lichen planus**

Lichen planus of the nail has features in common with psoriasis in that it can involve all the different structures of the nail unit and give rise to a range of features accordingly. The area of greatest concern is when it manifests with features of scarring, which can cause permanent loss or splits in nails, with considerable cosmetic and physical handicap.

**Clinical Features and Diagnosis**

In common with its presentation on the skin, nail lichen planus can be hypertrophic, with thickened nails, or it can be atrophic, with patterns of pronounced pitting that coalesce and eventually fragment the nail. In some instances the disease is very focal and the matrix pathology results in complete loss of nail production, with scarring sequelae. If this occurs with normal matrix remaining on either side, a pterygium may be the outcome, with a scar and nail split being bordered by viable nail spurs like wings. This is normally irreversible, and any suggestion of this pattern of disease should prompt rapid and usually systemic treatment. The potential for side effects with systemic therapy, which may be prolonged, means that I favor a diagnostic biopsy when there is any doubt or when presentation is with nail disease alone. Sometimes, clinical corroboration with mucosal, skin, or scalp disease allows certainty without a biopsy. Biopsy is best taken of nail bed, matrix, and nail fold to ensure it is representative and does not miss the diagnosis.

**Treatment**

The general protective and topical steroid therapies used in psoriasis can apply in lichen planus. If systemic therapy is needed, oral or intramuscular steroid injection can be used and represent flexible

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**TABLE 1** Nail Psoriasis: Clinical Features and Diagnosis

<table>
<thead>
<tr>
<th>CLINICAL FEATURE</th>
<th>FOCUS OF DISEASE</th>
<th>TREATMENT MODALITY</th>
<th>OPTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitting</td>
<td>Proximal matrix</td>
<td>Potent topical steroid to nail fold</td>
<td>Clobetosone dipropionate&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tazarotene to nail fold</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Steroid injection</td>
<td>Triamcinolone acetonide (Kenalog)</td>
</tr>
<tr>
<td>Onycholysis</td>
<td>Nail bed</td>
<td>Clip back and treat topically</td>
<td>Steroid and or vitamin D analogues</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antiseptic finger soaks for secondary infection e.g., <em>Candida</em> and <em>Pseudomonas</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic therapy</td>
<td>Cyclosporine (Sandimmune), methotrexate (Trexall), fumaric acid esters, acitretin (Soriatane), biologicals</td>
</tr>
<tr>
<td>Salmon patch or oily patch</td>
<td>No topical therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transverse ridging and undulations</td>
<td>Proximal nail fold</td>
<td>Potent topical steroid, vitamin D analogues</td>
<td>See pitting</td>
</tr>
<tr>
<td>Subungual hyperkeratosis</td>
<td>Nail bed</td>
<td>Steroid injection</td>
<td>Triamcinolone acetonide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Steroid injection</td>
<td>Triamcinolone acetonide</td>
</tr>
<tr>
<td>Nail shedding</td>
<td>Matrix and nail bed</td>
<td>Systemic therapy</td>
<td>Cyclosporine, methotrexate, fumaric acid esters, acitretin, biologicals</td>
</tr>
</tbody>
</table>

<sup>2</sup>Not available in the United States.
and effective therapy. The duration of the treatment means that monitoring of blood pressure, glucose, and weight may be indicated and bone protection might be needed. Regimens vary, but oral prednisolone 0.25 to 0.5 mg/kg for 4 to 6 weeks, tapering in the 2 weeks following, normally reverses active disease. It also allows assessment of what may be the irreversible scarred element, although nail growth rate means that this judgment should wait until a further 4 to 6 weeks after the end of treatment. Acitretin (Soriatane) and ciclosporine (Sandimmune) also can be used in lichen planus and may be better where patient morbidity does not allow prolonged or repeated oral steroids. Injected steroids may be used to address areas of focal scarring but seldom result in full cure.

Eczema
Eczema of the nail folds or nail bed may be associated with eczema elsewhere on the hand or foot and can cause nail unit disturbance in a manner similar to psoriasis. Special patterns of eczema can be relevant for allergic contact sensitivity.

Clinical Features and Diagnosis
The most common pattern of nail changes in eczema is where the nail fold is inflamed as part of an irritant hand eczema or as part of atopic eczema. This acts as a focus of inflammation that in turn disturbs matrix function owing to their adjacency. The nail then suffers transverse ridges and alterations of color, which reflect the fluctuating inflammation. Where the eczema is more directed at the digit tip, the nail bed is more likely to be involved, which in turn results in onycholysis. Both patterns often manifest most in the dominant hand because trauma, or simply use, increases the likelihood of pathology.

Occupational factors can be important both for analysis of the cause and for helping patients manage the global situation because they can suffer degrees of incapacitation. Where the occupation plays a part in the pathology, such as irritants in a health care or food-preparation worker, it may be necessary to review career choices. Hairdressers, beauticians, and engineers in certain fields come into contact with a wide range of contact sensitizers. The use of nail cosmetics alone can be relevant. Consider patch testing.

Treatment
Treatment is as for eczema elsewhere and shares many of the points made for managing psoriasis of the nail unit:

- Avoidance of irritants, trauma, nail manipulation, and frequent wetting
- Use of copious thick emollient
- Topical steroid tailored to severity
- Hand protection

Infective and chronic paronychia can be a complicating factor in nail unit eczema and requires additional systemic antibiotics in some instances.

Paronychia
Paronychia means inflammation of the proximal or lateral nail folds. There can be an infective component, and there is often a traumatic or eczematous background pathology.

Clinical Features and Diagnosis
An acute paronychia manifests as a focus of redness, pain, and sometimes a point of purulent collection and discharge in the nail fold. There may be a history of preceding trauma or, in children, of nail biting.

Chronic paronychia is seen with a raised, bolstered proximal nail fold, loss of cuticle, and transverse ridges in the nail extending up the nail plate, indicating many months of fluctuating inflammation. There is an account of episodic pain and sometimes discharge of pus. Antibiotics or antifungals alone do not settle the pathology.

Treatment
Acute paronychia is primarily infective and will subside after management of the bacterial infection and the associated wound or inflamed focus. Chronic paronychia has substantial crossover with an irritant hand eczema, and management is as for hand eczema. The low level of infection is secondary to the loss of cuticle and loss of barrier function in a digit that has substantial exposure to microbes. Where wet work is a factor, Candida sp. may be found, but short-term eradication with systemic therapy does not resolve the chronic problem. Management is with potent steroid, sometimes under tape occlusion. Evening (10 minutes) antiseptic soaks can help diminish the risk of infective exacerbation, but once a cuticle has re-formed and the nail fold is flat, the risk has passed. If there is a failure to respond to this regimen, the diagnosis might need challenging. Periungual squamous cell carcinoma can manifest in this manner and requires lateral longitudinal biopsy for assessment.

Ingrown Toenail
An ingrown nail represents a conflict between the shape of the nail and the soft tissues surrounding it. This conflict can be highlighted by an episode or period of trauma such as sport or new shoes, or may be a sustained anatomical state. It is compounded by cutting the nail short at the distolateral corner such that the nail fold overlaps the end of the nail. Symptoms arise through the soft tissue inflammation, which can sometimes be complicated by bleeding or infection. Treatment is directed at the acute inflammation and subsequently at the anatomy if needed.

CURRENT THERAPY: INGROWN TOENAIL

- Infantile disease should be treated with warm soaks with antiseptic followed by massage of the nail and distal phalangeal tuft.
- Adolescent and adult disease should be addressed with correct nail plate cutting and shoes. For mild disease, twice daily antiseptic soaks, topical steroids, 20% to 40% topical urea cream (Keralac, Carmol), and cotton wisps or dental floss

CURRENT DIAGNOSIS: INGROWN TOENAIL

- Common risk factors include incorrect nail cutting, wide feet, narrow-toed shoes, lateral plate malalignment, and lateral nail fold hyper trophy.
- Neonates and infants demonstrate distal nail ingrowing, which is separate in pathogenesis and treatment from the disease in adolescents and adults.
- Ingrown nails can be graded on a scale from I to III, with I being erythema and swelling with drainage from the nail fold and III being associated with exuberant overgrowth of granulation tissue over and around the ingrown nail plate.

Clinical Features and Diagnosis
Ingrowing can occur at any nail margin, with the most common site being the lateral nail fold in the big toe of someone in the second or third decade of life. At this site, it is the angle of the distal and lateral nail that becomes embedded in the lateral nail fold to create a puncture wound. The inflammation that follows creates a more bulky lateral nail fold and a positive feedback loop such that resolution typically requires medical intervention.

In a newborn or in a nail regrowing after loss, ingrowing can occur at the free edge as it meets the distal digit pulp. Proximally, an incompletely shed nail may be displaced upwards to embed into the ventral aspect of the proximal nail fold, with a pattern of pain and inflammation that matches ingrowing at other sites. This is called retronychia. All variants can evolve to create a mass resembling a pyogenic granuloma coupled with ooze and potential for secondary infection and local cellulitis.
under the aggravating part of the lateral nail plate will decrease inflammation, improve symptoms, and normalize the nail plate without surgery.

- For more advanced cases, use twice-daily warm soaks and oral antibiotics (with signs of infection), followed by lateral plate avulsion and lateral matricectomy (either chemical or surgical).

Treatment
Mild acute ingrowing can be treated with antiseptic soaks, potent topical steroid, and oral antibiotic if infection is suspected. Causal footwear or activities should be avoided and shoes with a high toe box to accommodate the tips of the toes should be worn. It may be possible to insert a pledget of cotton, wool or similar between the embedding edge of nail and the damaged soft tissue. Advice on square end nail cutting to avoid an overshort nail is important. If this conservative approach does not work, surgery is indicated. This is normally ablation of the lateral 3 to 4 mm of nail matrix and can be done with 85% aqueous phenol to create a chemical burn or with excision. The latter requires considerable skill for a reliable outcome because the apex of the horn of the matrix is difficult to access, and a remnant, if left, results in a spicule of nail regrowth that will continue to cause problems. Phenol, however, tends to find the entire exposed matrix because it is a liquid flowing into a crevice and does not need precise placement.

Distal embedding normally settles with conservative measures, and proximal ingrowing with retronychia requires avulsion. Avulsion is not the treatment for lateral or distal ingrowing because it results in recurrence of the problem as the nail regrows in most instances.

Single Digit Dystrophy
Dystrophy of a single nail is relatively common.

Clinical Features and Diagnosis
Dystrophy in a single digit can have any appearance, but the important thing for the clinician is that single-digit dystrophies include the uncommon but significant category of skin cancer. The most common of these is in situ squamous cell carcinoma (SCC), but the main other diagnosis is melanoma, either with a longitudinal melanonychia or as amelanotic melanoma with a lesion resembling a pyogenic granuloma. Both SCC and melanoma are infamous for having a late diagnosis in the digit, and the reason for this is lack of awareness shared by patient and clinician.

Following exclusion of inflammatory dermatoses by history and body examination and of onychomycosis by multiple clippings, the area should be biopsied for histology of matrix and nail bed. The classic biopsy is the lateral longitudinal biopsy, although this procedure, because there is a further risk of false reassurance of a negative biopsy if the sample is too small or directed at the wrong area of the nail unit.

Treatment
Where malignancy is detected, treatment is normally surgery.

References
Erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) were previously thought to represent a spectrum of one disorder and therefore have been traditionally grouped together. Current understanding of these disease entities allows us to separate EM from the latter two disorders. EM usually represents a hypersensitivity reaction to human herpes simplex virus type 1 or 2 (HSV-1, HSV-2) reactivation. SJS and TEN are severe, life-threatening drug hypersensitivity reactions that represent a spectrum of mucosal and cutaneous involvement. Exceptions are discussed in the following paragraphs.

Erythema Multiforme

Diagnosis

EM is an abrupt, self-limited, but often recurrent eruption of symmetrically distributed papules, plaques, and targetoid erythematous to dusky red lesions that are fixed and have a predilection for the extensor and acral surfaces. Many patients also have oral erosions or targetoid lesions. Vesicles and bullae may evolve from the target lesions. Eye or genital involvement is not typical. Symptoms may include burning or pruritus. The skin heals without scarring, but transient hyperpigmentation is commonly seen.

Young adults are most commonly affected. EM is rare in the young and elderly. There should not be a prodrome or systemic illness associated with the eruption, although some patients report vague flulike symptoms. The eruption most commonly follows clinical or subclinical HSV-1 or HSV-2 reactivation. EM can uncommonly be associated with mycoplasma, histoplasmosis, or Epstein-Barr virus infection. An EM-like drug eruption and other similar clinical entities exist.

The clinician should consider the following in the differential diagnosis: subacute cutaneous lupus erythematosus; urticaria and urticarial vasculitis; gyrate erythema; multiple, fixed drug eruptions; granuloma annulare; polymorphous light eruption; and multiple forms of acute cutaneous small vessel vasculitis. Although EM is a clinical diagnosis, skin biopsy with interpretation by a dermatopathologist and appropriate laboratory work-up are helpful when indicated.

Treatment

Patients with isolated episodes or first episodes of erythema multiforme should be treated symptomatically, reassured, and educated about HSV and EM. HSV reactivation typically precedes the onset of EM by 3 to 14 days; antiviral medications are not beneficial after the eruption has commenced.

Symptomatic measures to reduce burning and pruritus include oral antihistamines (diphenhydramine [Benadryl] 25 to 50 mg PO every 6 hours as needed, weight-based dosage in children) and mid-potency topical corticosteroids (triamcinolone acetonide cream [Kenalog] 0.1% twice daily applied to affected skin; avoid the face). For oral involvement, gentle oral hygiene (saline rinses, very soft toothbrush, 0.2% chlorhexidine gluconate [Corsodyl] or the 0.12% concentration [Peridex] in the United States) and topical anesthetics (2% viscous lidocaine [Xylocaine Viscous] applied as pea-sized amount every 2 hours as needed) can help alleviate symptoms. A short burst of oral corticosteroids may be helpful for severe involvement of the oral mucosa (prednisone 0.5 to 1 mg/kg/day for 4 to 5 days).

Patients who suffer from multiple recurrences of EM may be treated prophylactically with oral antiviral medications. When patients can identify the onset of the preceding HSV reactivation, episodic treatment initiated at the onset of the HSV prodrome may significantly reduce the severity and duration of the following EM. Treat with valacyclovir (Valtrex) 500 mg twice daily for 7 days. When patients have multiple recurrences (>6 per year) or cannot identify the preceding HSV activation, treat with valacyclovir 500 mg daily or acyclovir (Zovirax) 400 mg twice daily for at least 6 months. Some patients may achieve a remission at this point, and some may require further suppressive therapy.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Diagnosis

SJS and TEN are rare, severe, potentially fatal drug hypersensitivity reactions characterized by extensive denudation of skin or mucosal epithelium, or both, and they are accompanied by systemic illness. These entities are best considered on a diagnostic spectrum: SJS has less than 10% body surface area (BSA) with epidermal detachment and two or more mucosal surfaces involved; SJS/TEN overlap has 10% to 30% BSA with detachment and mucosal surfaces typically involved; and TEN has more than 30% detachment, and mucosal surfaces are usually involved. SJS is characterized by an EM-like eruption of the skin of variable severity (see earlier description of EM) and extensive mucosal erosions of at least two sites (i.e., lips or oral tissue, ocular tissue, and genital mucosa). TEN has a skin eruption characterized by dusky red plaques that rapidly progress to denuded, coalescing plaques with a shiny red base. Epidermal detachment can be elicited by placing lateral pressure on a dusky plaque (i.e., Nikolsky's sign).

The accompanying systemic illness usually correlates with the severity of the overall clinical picture. SJS or TEN has an initial flulike prodrome followed by various degrees of fever, lymphadenopathy, systemic toxicity with dehydration and electrolyte imbalance, toxic hepatitis, leukocytosis, anemia, proteinuria, and microscopic hematuria. Less commonly, there is involvement of the nasal, esophageal, pulmonary, and gastrointestinal mucosas; arthritis; myocarditis; and nephritis.

A causal drug can usually be identified. The eruption follows drug exposure by 1 week to 2 months. It is crucial that all potential causative drugs be discontinued immediately (Box 1). Other factors are thought to less frequently induce SJS (Box 2).

The clinician should consider autoimmune bullous disease (i.e., pemphigus, pemphigoid, paraneoplastic pemphigus, and linear IgA bullous dermatosis [LABD]), staphylococcal scalded skin syndrome (SSSS), bullous lupus Kawasaki disease, acute generalized exanthematous pustulosis, and acute graft versus host disease in

<table>
<thead>
<tr>
<th>Box 1</th>
<th>Drugs Commonly Associated with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis*</th>
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<tbody>
<tr>
<td>• Sulfonamide antibiotics (trimethoprim-sulfamethoxazole [Bactrim])</td>
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<tr>
<td>• Aminopenicillins</td>
<td></td>
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<td>• Quinolones</td>
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<td>• Cephalosporins</td>
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<tr>
<td>• Tetracyclines</td>
<td></td>
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<tr>
<td>• Acetaminophen (Tylenol)</td>
<td></td>
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<tr>
<td>• Carbamazepine (Tegretol)</td>
<td></td>
</tr>
<tr>
<td>• Phenobarbital</td>
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<tr>
<td>• Valproic acid (Depakene)</td>
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<tr>
<td>• Nonsteroidal anti-inflammatory drugs (NSAID, oxicam group)</td>
<td></td>
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<tr>
<td>• Allopurinol (Zyloprim)</td>
<td></td>
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<tr>
<td>• Corticosteroids</td>
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</table>

*Many other drugs are reported to induce Stevens-Johnson syndrome and toxic epidermal necrolysis.
the differential diagnosis. Biopsy of early lesional skin (with epi-
dermis still attached) may reveal necrolysis and interface derma-
tis and can help to rule out SSSS. Biopsy of perilesional, noninvolved skin for direct immunofluorescence can help to rule out autoimmune bullous disease.

### Treatment

It is essential to immediately identify the offending agent and dis-
continue it. If several possible agents exist, they must all be imme-
diately discontinued. Prompt discontinuation is associated with a
35% reduction in mortality per day (Table 1).

Supportive care is the mainstay of treatment of SJS or TEN. If
systemic illness is significant or if the BSA involved exceeds
10% to 20%, the patient should be cared for in an intensive care
unit or burn unit setting whenever possible.

Essential supportive care includes thermoregulatory equipment,
monitoring, and replacement of fluid and electrolytes as indicated.
A controlled-pressure thermoregulated bed is helpful. All care
should be performed under sterile conditions, and isolation pre-
cautions are necessary to reduce infection risk. Wound care should be
performed under the supervision of a dermatologist or burn
specialist. Goals of wound care are to minimize manipulation
and further denudation of skin, promote healing, reduce infection
risk, and increase comfort. Isotonic saline can be used to cleanse
involved skin once daily. Silicon or biologic dressings or skin
equivalents may be left in place, but the surfaces and surrounding
skin should be cleansed. Vaseline gaze may be used for limited
BSA and in pressure sites. Mucosal surfaces, orifices, and crusts
should be cleansed with saline several times daily, and mupirocin
(Bactroban) ointment should be placed around orifices and in
macerated areas twice daily.

An ophthalmologist should be consulted to manage ocular in-
volvement and help prevent the adhesions and scarring. Eyelids
should be cleansed three times daily with saline and antibiotic
ointment subsequently applied to the cornea. Antibiotic drops should be
instilled to protect the cornea. Gentle oral care with 0.2% chlor-
hexidine gluconate (0.12% in the United States) should be admin-
istered three to four times daily.

Pain control and nutritional support are imperative. Lines
should be placed through noninvolved skin when possible and
changed every 3 days with culture of the catheter tips. Routine cul-
tures from involved skin and sputum can help to monitor for infec-
tion and guide treatment when necessary. Clinical infection should
be treated quickly and aggressively.

There are no generally accepted evidence-based standards for
specific therapy for SJS or TEN. When patients are stable with lim-
ited skin and mucosal involvement and do not seem to be progres-
sing to worse disease, supportive care with close observation is most
appropriate. If the patient has extensive or rapidly progressing dis-
ease, immunosuppressive therapy should be considered, weighing
the risks and benefits, and started without delay if it is to be pursed.

Evidence from several case series and other reports supports the
use of intravenous immunoglobulin (IVIG)¹ in TEN, but there also
exists contradictory evidence from limited controlled trials that
IVIG is not beneficial. If used, it should be started as early as possible
in an attempt to halt progression to further BSA involvement. A
dose of 1 g/kg for 3 consecutive days is recommended. Cyclosporine
was evaluated in 29 patients with SJS/TEN in an open-label trial.
Progression of epidermal detachment and death rate were less than
predicted in the group treated. Cyclosporine was given orally at 3
mg/kg/day for 10 days, then tapered over the next month. Signifi-
cant cyclosporine toxicities were noted. Some other case reports
and case series support the use of cyclosporine (Sandimmune, Neo-
ral)¹ to reduce disease progression, but no randomized trials have
been conducted to prove its efficacy. Conflicting reports about
the use of corticosteroids exist, and some evidence points to in-
creased mortality associated with their use. However, evidence to
the contrary was found in a retrospective analysis that showed re-
duced mortality associated with corticosteroid use. The rarity of SJS
or TEN combined with the variability in patient and institutional
factors and the bias inherent in retrospective studies has resulted
in a paucity of evidence to support any specific therapy. Ultimately,
treatment decisions must be made on an individual basis.

### SCORTEN: Predicted Mortality in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

<table>
<thead>
<tr>
<th>PROGNOSTIC FACTOR</th>
<th>PRESENT</th>
<th>ABSENT</th>
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<tbody>
<tr>
<td>Age &gt;40 y</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Heart rate &gt;120 beats/min</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Malignancy present</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Day 1 BSA &gt;10%</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Serum urea &gt;10 mmol/L</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Serum HCO₃ &lt;20 mmol/L</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Serum glucose &gt;14 mmol/L</td>
<td>1</td>
<td>0</td>
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<tr>
<th>SCORTEN sum*</th>
<th>Predicted Mortality</th>
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<tbody>
<tr>
<td>0–1</td>
<td>3.7%</td>
</tr>
<tr>
<td>2</td>
<td>12.1%</td>
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<tr>
<td>3</td>
<td>35.8%</td>
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<tr>
<td>4</td>
<td>58.3%</td>
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<tr>
<td>5 or higher</td>
<td>90%</td>
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</table>

*SCORTEN is a severity-of-illness score developed for toxic epidermal necro-
lysis (TEN).

¹Not FDA approved for this indication.

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Fungal infections of the skin, hair, and nails are some of the most common infections worldwide, with special prominence among children, the elderly, men, and immunocompromised hosts such as those with diabetes, cancer, or HIV infection. Fungal infections of the skin can be divided into four general categories. Superficial fungal infections are caused by dermatophytes such as those from the *Trichophyton, Microsporum,* and *Epidermophyton* genera. Cutaneous infections include tinea corporis, candidiasis, and onychomycosis. Subcutaneous (e.g., mycetoma, sporotrichosis) and systemic fungal infections (cryptococcosis, blastomycosis) that manifest in the skin are less common.

Diagnosing superficial fungal infections is generally based on clinical characteristics and response to empiric treatment. In unclear or recalcitrant cases, confirmation of diagnosis can be attempted by potassium hydroxide (KOH) preparation or histologic examination of scrapings, examination of scrapings under Wood’s light, or culture. Fungal elements, however, are sometimes difficult to detect by microscopy, and tinea species grow poorly on routine culture media. Growth of dermatophytes is best performed on specific mycologic media at laboratories experienced in fungal isolation. However, depending on the specific fungal disease, the optimal site to obtain scrapings varies and affects the yield on culture.

Differential diagnosis depends on the location of the suspected fungal infection and specific clinical characteristics. Most commonly, discrimination must be made from eczema, contact dermatitis, acneiform eruptions, folliculitis of other cause, skin maceration, psoriasis, lichen planus, or trauma.

**Tinea Pedis**

Tinea pedis (also called athlete’s foot) is most commonly caused by *Trichophyton rubrum.* It is spread by contact with infected desquamated skin and is more prevalent among men than women or children. Infection may be asymptomatic or cause various degrees of interdigital itching and cracking, erythema, scaling, and, rarely, blisters. The scaling occasionally causes an extensive moccasin sole appearance, one manifestation of dry-type tinea pedis. The disease can become extensive in immunocompromised patients, especially those with AIDS.

**Tinea Cruris**

Tinea cruris (also called “jock itch”) is most commonly caused by *T. rubrum* or *Epidermophyton floccosum.* Occurring more commonly during summer months, tinea cruris manifests with unilateral or bilateral medial thigh and/or scrotal redness, itching, and scaling, generally with a sharp border and occasionally with papules and pustules near the leading edge. There are no satellite lesions as with candidiasis of the skin.

**Tinea Corporis**

Also called ringworm, tinea corporis is now relatively uncommon in the United States, being seen more commonly in tropical parts of the world. However, cases still occur in this country, especially among the homeless, HIV-infected persons, and inner city children and their caregivers. Clusters have also occurred among athletes who have skin-to-skin contact, such as wrestlers. Typical cases are caused by *T. rubrum* and appear ringlike, well demarcated, and scaly, with central clearing and little inflammation. Lesions may be hyperpigmented in darker-skinned persons. Lesions commonly, infection derives from animal sources such as cows, dogs, and cats and is caused by *Trichophyton verrucosum* or *Microsporum canis.* Animal-associated species tend to cause a more nodular and inflammatory form of tinea corporis that is especially seen in children. Kerions are characteristic large pustular lesions caused by these dermatophytes.

**Candidasis**

*Candida* species are normal flora of the mouth and vagina, especially in settings such as antibiotic exposure, dry mouth, excessive skin moisture, and extremes of age and in immunocompromised hosts, and can cause disease on skin and mucosal surfaces. In the mouth or vagina, candidiasis is suggested by white plaques, cheesy exudates, and erythema. Candidiasis of the mouth can also occur in other forms such as erythematous plaques, angular cheilitis, acute or chronic atrophic lesions (the latter in the setting of dentures), or chronic hypertrophic plaques. Candidiasis of the skin most
commonly occurs in moist or occluded areas such as the groin, buttocks (especially under diapers), and axillae, but it can involve any area including the nails (described earlier). Satellite lesions help to differentiate skin candidiasis from tinea or other conditions.

**Treatment**

Treatments for fungal infections are shown in Table 1.

**References**


**KELOIDS**

**Method of**

Woraphong Manuskiatti, MD

**CURRENT DIAGNOSIS**

- Clinical characteristics: a raised, firm scar, possibly painful or pruritic, and extending beyond wound borders
- Histologic characteristics: thick bundles of hyalinized collagen arranged in dense swirls or nodules

Keloids are a common dermatologic condition, especially in dark-skinned persons. The incidence of keloids in persons of European descent is reported to be less than 1%, whereas the incidence in persons of sub-Saharan African ethnicity and Latin Americans...
Pathogenesis
Keloids represent abnormal wound healing in response to cutaneous surgery, physical trauma, or inflammatory responses. The pathogenesis of keloids has yet to be determined and may be multifactorial. Studies have demonstrated both overproduction of collagen and increased procollagen levels, as well as decreased levels of collagenase in keloidal tissue. Proposed mechanisms for the cause of keloid formation include tension and vessel occlusion, as well as genetic, hormonal, and immune-mediated mechanisms. Currently, much of the research attention has focused on the immunoregulation of collagen production and deposition.

Prevention
Prevention should be the first rule of keloid therapy. Avoiding all unnecessary wounds in any patient, whether keloid-prone or not, remains an evident solution. Nonessential surgical and cosmetic procedures should not be performed in patients with histories of forming keloids and in anatomic sites prone to keloid formation including the mid-chest, shoulder, back, and posterior neck. All postoperative and cutaneous trauma sites should be treated with appropriate antibiotics to prevent infection. All surgical wounds should be closed with normal tension. If possible, incision should not cross joint spaces and skin excisions should be horizontal ellipses in the same direction as the skin tension lines.

Treatment
Several forms of treatment have been used with varying degrees of success. No single therapy has been shown to be superior. Often, use of multiple modalities is necessary to successfully treat the lesions. The selection of therapeutic options typically depends on the scar’s size, location, and depth and on the patient’s age, past responses to treatment, and economic status (Table 1).

Medical Therapies
Corticosteroid Injections
Intralesional corticosteroid injections have been the mainstay therapy for treatment of keloids. Corticosteroids decrease excessive scarring by reducing synthesis of collagen and glycosaminoglycan and by reducing inflammatory mediators and fibroblast proliferation during the wound-healing process. The most commonly used corticosteroid is triamcinolone acetonide (Kenalog, 10-40 mg/mL), which, depending on the size and location of the lesions, is administered intralesionally at 2- to 4-week intervals over the course of months to years. Response rates vary from 50% to 100%, with a recurrence rate of 50%. Intralesional corticosteroid injections also reduce symptoms of pruritus and tenderness. Results are improved when corticosteroids are combined with other therapies such as excision and cryosurgery. Complications of repeated corticosteroid injections include atrophy, telangiectasia, and hypopigmentation at and around the injection sites (Figure 1).

5-Fluorouracil
Treatment of keloids with intralesional 5-FU injection (Adrucil)1 combined with corticosteroids has been shown to be as effective as intralesional corticosteroids alone, but the latter is much more likely to cause adverse effects. 5-FU appears to work by decreasing keloid fibroblast proliferation. Injections are given once a week at the beginning and then adjusted up or down according to the treatment response. Side effects of intralesional 5-FU include spots of purpura, burning sensation during injection, and localized superficial tissue slough.

Imiquimod
A study on the effect of postoperative application of imiquimod 5% cream (Aldara)1 on the surgically excised keloids for a period of 8 weeks noted a lower recurrence rate than that of excision alone. Theoretically, imiquimod induces production of interferon and thus downregulates collagen synthesis. Reported side effects include local skin irritation and mild hyperpigmentation.

<table>
<thead>
<tr>
<th>TABLE 1 Common Therapeutic Regimens for Keloids</th>
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<tr>
<td><strong>TREATMENT MODALITY</strong></td>
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<tr>
<td>Intralesional corticosteroids</td>
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<tr>
<td>Intralesional 5-FU plus TAC</td>
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<tr>
<td>Imiquimod (Aldara)1</td>
</tr>
<tr>
<td>Onion extract (e.g., Mederma)</td>
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<tr>
<td>Excision (Scalpel or CO2 laser excision)</td>
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<tr>
<td>Cryosurgery</td>
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<td>Pressure therapy</td>
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<tr>
<td>Pulsed dye laser</td>
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<tr>
<td>Silicone gel sheeting</td>
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1Not FDA approved for this indication.

Abbreviations: 5-FU = 5-fluorouracil; TAC = triamcinolone acetonide.
Onion Extract

Extract of Allium cepa, or onion extract, is an active ingredient in a number of topical scar treatment products (e.g., Mederma). Onion extract exhibits anti-inflammatory, bacteriostatic, and collagen downregulating properties and improves collagen organization. It is recommended that onion extract be applied three times daily for 8 weeks for new scars (after wound closure) and three times daily for 2 to 6 months on old scars. However, most documented clinical studies of onion extract have shown that onion extract does not improve hypertrophic and keloid scarring.

Surgical Therapies

Primary Excision

Surgical excision of keloids without adjunctive therapy has persistently shown poor results, with a high rate of recurrence (45% to 100%). Decreased recurrence rates are consistently reported with excision in combination with other postoperative treatment modalities, such as intralesional corticosteroids, radiation, pressure therapy, silicone gel sheeting, or imiquimod cream. Surgical techniques to minimize tissue trauma, closing with minimal tension, and using buried sutures when necessary for layered closure are recommended in order to decrease the possibility of recurrence.

Cryosurgery

Freezing keloids with a cryogen such as liquid nitrogen affects the microvasculature and causes cell damage. This occurs via intracellular crystallization, leading to tissue anoxia with subsequent tissue necrosis and sloughing, followed by tissue flattening. Cryosurgery alone results in keloid flattening in 51% to 74% of the patients after two or more sessions performed at 3- to 4-week intervals. Limitations to this procedure include postoperative pain, slow healing, and hypopigmentation (especially in dark-skinned patients).

Physical Modalities

Radiation Therapy

Radiation may be used as a monotherapy or combined with surgery to prevent recurrence of keloids following excision. Radiation therapy is thought to work by inhibiting fibroblast proliferation and neoangiogenesis in wound healing. When used as a monotherapy, radiation is not very effective and the recurrence rate of 30% to 100% is high. The risks of carcinogenicity associated with radiotherapy are controversial. Caution is advised when treating young children or when treating areas around the breasts and thyroid due to the increased radiosensitivities of these tissues.

Pressure Therapy

The mechanism involved in how pressure therapy reduces keloid formation is not well understood, but it is hypothesized that pressure induces tissue hypoxia, resulting in fibroblast degeneration and subsequent collagen degradation. It is generally recommended that the pressure be maintained between 24 and 30 mm Hg for 18 to 24 hours a day for at least 6 to 12 months for this therapy to be effective. Pressure therapy is commonly used in combination with other modalities such as silicone gel sheeting following surgical excision. The patient’s compliance is the limiting factor because the success of the therapy requires long-term pressure application.

Laser Therapy

At present, the common use of lasers to treat keloids is based on two different approaches. One technique is an application of carbon dioxide (CO₂) laser for nonspecific destruction of keloids. Keloid vaporization or excision by CO₂ laser alone results in high (40% to 90%) recurrence rate and provides no distinct advantage over scalpel excision. The CO₂ laser is now reserved to use for debulking of large keloids before initiating other treatment modalities. Another method is 585-nm or 595-nm pulsed dye laser for selectively damaging the microvasculature of the keloids (Figure 2). Multiple (more than two) pulsed dye laser treatment sessions have been shown to decrease scar height and erythema and to improve scar texture and dysesthesia.
Silicone Gel Sheeting
The mode of action of silicone gel sheeting remains unclear but is thought to occur through an increased scar hydration effect provided by the sheet, leading to antikeloidal effects. To be effective, the sheets must be applied for at least 12 hours daily for 2 to 3 months, with removal permitted for routine hygiene. Adverse events such as pruritus, rash, maceration, and odor can be managed by temporary interruption of treatment and regular washing of the sheet and the scar. The efficacy of silicone gel sheeting on hypertrophic and keloid scarring remains unclear and warrants rigorous evaluation. The ease of use of silicone gel sheeting and its lack of serious adverse effects make it an attractive alternative to invasive treatments, such as intralesional injection of corticosteroids, radiation, laser treatment, surgical excision, cryotherapy, and pressure therapy. Silicone gel sheeting may be especially useful in children and others who cannot tolerate the pain associated with other treatment modalities.

Miscellaneous Therapies
There are additional novel therapies; however, many treatments are anecdotal and require confirmation of their efficacy and safety through formal studies. Some of these therapies include topical vitamin E, retinoic acid (Retin-A) and tacrolimus (Protopic), intralesional verapamil (Isoptin) and bleomycin (Blenoxane), colchicine, and ultraviolet A1 phototherapy.

Conclusions
Therapeutic management of keloids remains a challenge because of their high rate of recurrence and lack of curative treatment. The most important point concerning keloid formation is prevention. Treatment approaches to keloids is depend not only on the size of the lesion but also on the age, location, and economic status of the patient. The use of several approaches in combination or sequentially, based on the patient’s individual requirements and responses, is recommended to maximize the therapeutic outcome.

References

1Not FDA approved for this indication.

CURRENT THERAPY

Acquired Melanocytic Nevi
Acquired melanocytic nevi are subdivided into junctional, compound, and intradermal types based on the location of the nevus cells. By definition, these lesions are not present at birth but can begin to appear in early childhood, usually after 6 to 12 months of age. Peak ages of appearance of melanocytic nevi are 2 to 3 years of age in children and 11 to 18 years in adolescents. Although nevi can appear at any age, it is relatively unusual for new melanocytic nevi to develop in middle-aged or older adults. With time, nevi can spontaneously regress. Consequently, patients in their ninth decade of life usually demonstrate few melanocytic nevi. An average white adult has 10 to 40 melanocytic nevi, but African Americans have far fewer, averaging only 2 to 8.

The number and location of melanocytic nevi have been shown to be associated with sun exposure, immunologic factors, and genetics. Consequently, melanocytic nevi are most numerous on the sun-exposed skin of the head, neck, trunk, and extremities, but they are only rarely found on covered areas such as the buttocks, female breasts, and scalp. Evidence suggests that patients with an increased number of melanocytic nevi (>50) might have an increased risk of melanoma.

Melanocytic nevi appear in a sequential fashion. Junctional melanocytic nevi arise during childhood as flat, dark macules. Histologically, an increase in single or nests of melanocytes are located...
at the dermoepidermal junction. With time, some of the junctional nests of melanocytes migrate into the dermis (compound melanocytic nevi). Clinically, compound melanocytic nevi are elevated and less heavily pigmented than junctional melanocytic nevi. Ultimately, all of the nevus cells migrate into the dermis (intradermal melanocytic nevi), resulting in the development of a tan or skin-colored domeshaped papule. Melanocytic nevi can be flat or elevated and even polypoid, papillomatous, or verrucous and can demonstrate a range of color from skin-tone to black, but they are characteristically uniform in color, symmetrical, well marginated, and usually smaller than 6 mm in diameter.

All melanocytic lesions of clinical concern should be examined with a dermatoscope, a hand-held instrument with a magnified lens and a light source similar to an ophthalmoscope. This instrument allows evaluation of colors and microstructures not visible to the naked eye, helps distinguish whether pigmented lesions are melanocytic or nonmelanocytic and helps distinguish whether melanocytic pigmented lesions are likely to be malignant. Used by an experienced dermatologist with proper training, the dermoscope improves diagnostic accuracy by 20% to 30%.

It is unnecessary to surgically remove all melanocytic nevi because they are benign neoplasms of melanocytes. However, indications for removal include ABCD (asymmetry, irregular border, variegation or change in color or change in diameter), symptoms (e.g., pruritus), evidence of inflammation or irritation, cosmetic issues, and patient anxiety. Melanocytic nevi on acral, genital, or scalp skin that appear benign do not require surgical removal. Shave biopsies are appropriate therapy for lesions considered clinically benign. However, if a lesion is being removed because of concern regarding the possibility of malignancy, an excisional biopsy (biopsy of choice) or incisional biopsy (including a deep scoop) that extends to the subcutaneous tissue is indicated. All melanocytic lesions should be submitted to a dermatopathologist for histologic review. A history of recent sun exposure or trauma should be conveyed to the dermatopathologist because such external trauma can induce reactive atypical histologic findings.

**Recurrent Melanocytic Nevi**

Recurrent melanocytic nevi are melanocytic nevi that have previously been incompletely removed (either iatrogenically or traumatically) and have recurring weeks to months later. Irregular brown pigmentation is clinically noted within the scar site. If the original biopsy demonstrated a benign melanocytic nevus, re-treatment is unnecessary unless the aforementioned indications are present. However, these nevi can demonstrate pseudomelanomatous histologic features. Therefore, if the pigmented area is excised, the dermatopathologist should be notified of the clinical history and, if possible, the slides from the original biopsy should be obtained and reviewed to ensure that the lesion is not histologically misdiagnosed.

**Halo (Melanocytic) Nevi**

Halo (melanocytic) nevi are melanocytic nevi in which a white rim or halo has developed. This phenomenon most commonly occurs around compound or intradermal nevi and is histologically associated with a dense, bandlike inflammatory infiltrate. The white halo area is histologically characterized by diminished or absent melanocytes and melanin. Approximately 20% of patients with halo nevi also exhibit vitiligo.

Although a halo can develop around many lesions in the skin, the most important differential diagnosis is between a halo nevus and melanoma with a halo. The halo and the central melanocytic nevus of halo nevi are symmetrical, round or oval, and sharply demarcated. Halo nevi most commonly occur in adolescence as an isolated event, but approximately 25% to 50% of affected persons have two or more.

The clinical course of halo nevi is variable. With time, the halo can repigment while the central nevus persists. Alternatively, the melanocytic nevus can regress completely and leave a depigmented macule that can persist or repigment over months or years.

Halo nevi do not require surgical excision unless atypical clinical features suggest the possibility of an atypical melanocytic lesion. It is advisable (particularly in adults, in whom halo nevi are less common) to perform a complete cutaneous examination with and without the aid of a Wood’s lamp to rule out any associated atypical pigmented or regressed lesions. All patients should be warned to use sunscreens or protective clothing because of the increased risk of sunburn in the depigmented halo region.

**Congenital Melanocytic Nevi**

By definition, congenital melanocytic nevi (CMN) are present at birth. Arbitrarily, they have been classified into small (<1.5 cm), medium (1.5–20 cm) and large (>20 cm) lesions. Terms such as bathing trunk or garment-type nevi refer to CMN that cover a significant portion of the cutaneous surface.

The approximate incidence of small congenital nevi is 1% of all live births. Large congenital nevi are rare and reported in only 1 in 20,000 births. Histologically, some congenital nevi have distinguishing histologic features (melanocytic nevus cells that extend into the deeper dermis as well as the subcutis and melanocytic nevus cells arranged peripherally, angiocentrically, within nerves, and interposed between collagen bundles). However, these features have been identified in some acquired melanocytic nevi and are absent in some congenital nevi (especially small ones). In addition, the history obtained from the patient or their parents is often inaccurate. Consequently, it can be very difficult in some cases to distinguish a small congenital nevus from an acquired nevus.

Congenital nevi can give rise to dermal or subcutaneous nodular melanocytic proliferations. The vast majority of these lesions, particularly in the neonatal period, are biologically benign, despite a worrisome clinical presentation and atypical histologic features. Genetic analysis has shown that benign melanocytic proliferations within congenital nevi express aberrations qualitatively and quantitatively different from those seen in melanoma.

The primary significance of congenital nevi is related to the potential risk for progression to melanoma. Essentially, the larger the nevus, the greater the risk of progression to melanoma. Historically, even small nevi were estimated to exhibit a lifetime melanoma risk of 5%. However, recent prospective studies suggest that small and medium congenital nevi are associated with a low risk that may approximate the risk of acquired nevi. Conversely, large congenital nevi have a lifetime risk of melanomatosus progression of approximately 6.3%. Up to two thirds of melanomas that arise in these giant congenital nevi have a nonepidermal origin, thus making clinical observation for malignant change difficult. Approximately 50% of these melanomas occur in the first 5 years of life, 60% in the first decade, and 70% before 20 years of age. Patients with large congenital nevi, especially those that involve posterior axial locations (head, neck, back, or buttocks) and are associated with satellite congenital nevi, are at increased risk for neurocutaneous melanosis (melanosis of the leptomeninges).

For large congenital nevi that involve a posterior axial location, magnetic resonance imaging (MRI) is indicated. If clinical symptoms or MRI indicate neurocutaneous melanosis, excision of the large nevus should be postponed until 2 years of age (the median age of neurologic symptoms). Patients with neurocutaneous melanosis have a greater than 50% mortality rate within 3 years. The risk and morbidity of multiple, staged excisions of a large CMN is not appropriate in patients with symptomatic neurocutaneous melanosis. All other large CMN are candidates for excision as soon as general anesthesia is considered a relatively safe risk. Other issues that need to be considered before undertaking staged excisions include cosmetic issues, functional outcome, and psychosocial issues. The staged excisions are usually started after 6 months of age for nevi on the trunk and extremities and later for those on the scalp to allow closure of the fontanelle. If removal is not undertaken, follow-up with monthly self-examination, photography, dermoscopy, confocal laser microscopy, and computer assistance are recommended. For small congenital nevi, routine excision is not always recommended because the risk of melanoma is lower, and if it occurs, it
usually arises within the epidermis after puberty. If the lesions are not excised, follow-up by alternating visits to a dermatologist and primary care physician along with serial photography are indicated. Inasmuch as small congenital nevi typically enlarge with the growth of the child and can change in appearance with time, educating families on benign, predictable changes in contradistinction to potentially alarming changes is extremely important. If a lesion enlarges or changes suddenly or if parental anxiety or cosmetic issues arise, excision should then be contemplated for even small congenital nevi. Elective excision is best done when the patient is approximately 8 years old. With the use of topical anesthetic cream EMLA (eutectic mixture of local anesthetics: 2.5% lidocaine plus 2.5% prilocaine) or topical 4% lidocaine (ELA-Max), children of this age are usually cooperative and unschooled by the procedure.

**Blue Nevi**

Blue nevi occur primarily on the face and scalp, in addition to the dorsal surfaces of the hands and feet, as well-circumscribed, slightly raised or dome-shaped bluish papules that are usually less than 1 cm in diameter. Although these lesions are usually acquired in childhood and adolescence, rare congenital lesions have been reported. Histologically, blue nevi demonstrate a combination of intradermal spindle or dendritic melanin-pigmented melanocytes and melanophasges with dermal fibrosis. The blue appearance of these lesions is a function of both the depth of the melanin in the dermis and the Tyndall phenomenon: longer wavelengths of light penetrate the deep dermis and are absorbed by the lesional melanin, and shorter wavelengths (e.g., blue) are reflected back. Blue nevi that are clinically stable and that do not demonstrate atypical features do not require removal.

**Spitz Nevi**

Nevi of large spindle and epithelioid cells (Spitz nevi) are relatively uncommon. In Australia, an annual incidence of 1.4 per 100,000 people has been recorded. Most Spitz nevi are noted in children and adolescents: One third occur before the age of 10 years, one third between the ages 10 to 20 years, and one third past the age of 20 years. Rarely, lesions can occur in patients older than 40 years. Seven percent of Spitz nevi have been reported as congenital.

Four clinical types of Spitz nevi are recognized: light-colored soft Spitz nevi that can resemble a pyogenic granuloma; light-colored hard Spitz nevi that can resemble a dermatofibroma; dark Spitz nevi that must be distinguished from other melanocytic lesions, including melanoma; and disseminated or agminated Spitz nevi. Spitz nevi are typically smaller than 6 mm in diameter and dome shaped, with a smooth pink or tan surface and sharp borders. Although they can occur anywhere on the cutaneous surface except mucosal or palmar plantar areas, they are most commonly seen on the face (especially in children) and legs (especially in women). Spitz nevi in adults are usually more heavily melanized than those in children.

Dermatoscopy or epiluminescent microscopy (examination of lesions with enhanced light and a dermatoscope) helps magnify the images in vivo and can assist in establishing the clinical diagnosis of some Spitz nevi. Histologically, the lesion can demonstrate features similar to those of melanoma, which earned the lesion its original designation by Sophie Spitz as a melanoma of childhood. Because Spitz nevi can be histologically difficult to distinguish from melanoma, if a biopsy is performed on a lesion because of parental, cosmetic, or transitional concern, complete excision with clear margins is recommended. Spitz nevi show fundamental genomic differences compared with MM, consistent with the generally benign behavior of these lesions. Spitz nevi typically demonstrate no or only a very restricted set of chromosomal aberrations (i.e., 11p gain in a subset of Spitz nevi).

**Dysplastic Melanocytic Nevi**

Dysplastic melanocytic nevi, or Clark’s nevi, or nevi with architectural disorder and cytologic atypia can occur sporadically as an isolated lesion or lesions or as part of a familial autosomal dominant syndrome. When such lesions occur sporadically, they are considered a marker for a patient who is at increased risk of melanoma (6% risk versus an approximate 0.6% risk in the normal white population in the United States). In association with a family history or personal past medical history of melanoma, patients with dysplastic melanocytic nevi should be considered to have a significant risk of melanoma. One first-degree family member with melanoma is associated with a lifetime risk of melanoma of 15% for the patient with dysplastic melanocytic nevi. Two or more first-degree family members with melanoma place a patient with dysplastic melanocytic nevi at a lifetime risk of developing melanoma that approaches 100%. Less commonly, dysplastic melanocytic nevi can progress to melanoma. Such progression has been documented by serial photography. However, these data are confounded by the fact that clinically and histologically, dysplastic melanocytic nevi may be difficult to distinguish from an early melanoma.

Dysplastic melanocytic nevi are clinically distinguished from common acquired melanocytic nevi by a diameter usually larger than 6 mm, irregular border, asymmetry, and variable color with possible shades of brown, red, pink and black; dysplastic melanocytic nevi can be flat with or without a raised center (fried egg appearance). The lesions begin to appear in mid-childhood and early adolescence. New lesions can appear throughout the patient’s life. In addition to the back and extremities, these lesions can occur on sun-protected areas, including the scalp, buttocks, and female breasts. Dysplastic melanocytic nevi can be few or numerous, with hundreds of lesions.

Histologically, dysplastic melanocytic nevi show both architectural disorder: extension of the junctional component beyond the dermal component (shouldering); bridging of nests between adjacent rete ridges; papillary dermal concentric and lamellar fibroplasia; and a variable lymphocytic infiltrate with vascular ectasias. They also show cytologic atypia of melanocytes: increased nuclear size, hyperchromasia, dispersion or variation of nuclear chromatin patterns, and presence of nucleoli. Although there is some discordance in the histologic grading of dysplastic melanocytic nevi among expert dermatopathologists, there is some evidence to support the use in clinical practice of a two-tier grading system: Grade A are dysplastic melanocytic nevi with mild or moderate cytologic atypia and grade B are dysplastic melanocytic nevi with severe cytologic atypia. The probability of having a personal history of melanoma in any given dysplastic melanocytic nevi patient correlates with the grade of cytologic atypia in dysplastic melanocytic nevi. In addition, the presence of severe cytologic atypia in dysplastic melanocytic nevi correlates with a significantly greater risk of melanoma development (19.7%) compared with moderate (8.1%) or mild (5.7%) cytologic atypia.

Management of these patients is difficult. Dysplastic melanocytic nevi are not uncommon. Reportedly, as many as 4.6 million people in the United States have one or more sporadic dysplastic melanocytic nevi. Familial dysplastic melanocytic nevi are estimated to involve 50,000 patients in the United States. The risk of melanoma for these patients is probably on a continuum and correlated with their family history of melanoma or dysplastic melanocytic nevi, personal history of melanoma, number of acquired melanocytic and dysplastic lesions, and history of sun exposure. Removal of all dysplastic melanocytic nevi is inappropriate inasmuch as the chance of any single lesion becoming malignant is small and, in addition, the melanoma can arise de novo.

Management includes patient education and total body photography for comparison at future skin examinations. Patients should avoid the sun and use sunscreens and protective clothing. These patients should have regular biannual or quarterly examinations of the entire integument, including the oral, genital, and perianal mucosa, the scalp, and an ophthalmologic examination. Comparison with the previous total body photographs and use of the dermatoscope can be helpful. Any lesions that are suspicious for melanoma should be excised. Examination of first-degree family members (parents, siblings, and children) of patients with melanoma or dysplastic melanocytic nevi is recommended to identify other persons at high risk.
References


Bauer J, Bastian BC. Distinguishing melanocytic nevi from melanomas by DNA copy number changes: Comparative genomic hybridization as a research and diagnostic tool. Dermatol Ther 2006;19:40–9.


Melanoma
Method of Vesna Petronic-Rosic, MD, MSc

CURRENT DIAGNOSIS

- ABCDEs:
  - Asymmetry of lesion
  - Border irregularity, bleeding, or crustng
  - Color change or variegation
  - Diameter larger than 6 mm or growing lesion
  - Evolving: surface changes or symptomatic
- “The ugly duckling” sign
- Total-body photography and dermatoscopy
- Excisional biopsy with narrow margins
- Interpretation by physician experienced in the microscopic diagnosis of pigmented lesions
- Molecular analyses (rarely)
- Appropriate staging work-up
- Genetic testing when appropriate (rarely)

CURRENT THERAPY

- Early diagnosis and appropriate surgical therapy is the gold standard.
- Complete excision must be achieved with appropriate margins based on tumor thickness.
- Sentinel lymph node biopsy may be offered to patients with melanoma larger than 1 mm, with clinically unaffected regional nodes, and without distant metastases.
- Dissection of the lymph node basin may be offered to patients with micronodal or macronodal metastases.
- Adjuvant therapy may be considered for stage III disease.
- Stage IV treatment depends on location and extent of metastatic disease and may include surgical resection, chemotherapy, biological therapy, or radiation therapy.

Melanoma is a malignancy of pigment-producing cells (melanocytes). Melanocytes are located predominantly in the skin, but they are also found in the eyes, ears, gastrointestinal tract, leptomeninges, and oral and genital mucous membranes.

Epidemiology

Even though melanoma accounts for less than 5% of skin cancer cases, it causes most skin cancer deaths. U.S. incidence figures estimate that there were about 108,230 new cases of melanoma in 2007: 48,290 in situ (noninvasive) and 59,940 invasive (33,910 in men and 26,030 in women). The American Cancer Society’s most recent estimates for melanoma in the United States for 2009 are 68,720 new cases with 8,650 deaths. Overall, the lifetime risk for developing melanoma is about 1 in 50 for whites, 1 in 1000 for blacks, 1 in 200 for Latin Americans. At current rates, 1 in 63 Americans will develop an invasive melanoma over a lifetime.

Risk Factors

A large number of nevi is the strongest risk factor for melanoma in persons of European ancestry. Atypical mole syndrome is another risk factor. Exposure to ultraviolet light is a major risk factor, especially in persons who have fair hair and skin, who have solar damage, who had sunburns and short sharp bursts of sun exposure in childhood, and who used tanning beds. Tanning beds appear more detrimental when used before age 20 years. Familial risk factors include mutations in CDKN2A, which are associated with increased risks for both melanoma and pancreatic cancer. Organ transplant recipients have an increased risk for melanoma. Genodermatoses with a defect in DNA repair (such as xeroderma pigmentosum) increase risk for melanoma.

Pathophysiology

Transformation of normal melanocytes into melanoma cells likely involves a multistep process of progressive genetic mutations that alter cell proliferation, differentiation, and death and affect susceptibility to the carcinogenic effects of ultraviolet radiation. Primary cutaneous melanoma can develop in preexisting melanocytic nevi, but more than 60% of cases likely appear de novo.

Melanomas arising in skin that is chronically sun damaged show molecular features that distinguish them from melanomas arising in skin that is not sun-damaged. These features might determine tumor behavior and potential response to new targeted drugs. About 70% of melanomas arising in skin that is not sun damaged carry BRAF mutations. Genetic studies have shown that 50% of familial melanomas and 25% of sporadic melanomas may be due to mutations in the tumor suppressor gene p16. Linkage studies have identified chromosome 9p21 as the site of the familial melanoma gene.

Prevention

Early detection of thin cutaneous melanoma is the best means of reducing mortality. Patients with a history of melanoma should be educated regarding sun protective clothing and sunscreens, skin self-examinations for new primary melanoma, possible recurrence within the surgical scar, and screening of first-degree relatives, particularly if they have a history of atypical moles.

Clinical Manifestations

Early signs of melanoma include the ABCDEs:
- Asymmetry of lesion
- Border irregularity, bleeding, or crustng
- Color change or variegation
- Diameter larger than 6 mm or growing lesion
- Evolving: surface changes or symptomatic

The “ugly duckling” sign is also useful to recognize lesions that look or feel different compared to surrounding moles. Lentigo maligna (melanoma in situ) begins as an irregular tan-brown macule that slowly expands on sun-damaged skin of elderly persons. Long-term cumulative sun exposure confers the greatest
risk. Progression to invasive lentigo maligna melanoma is estimated to be 30% to 50%.

Supraventricular spreading melanoma, the most common type in light skin, represents approximately 70% of all melanomas. Peak incidence is in the fourth and fifth decade. Supraventricular spreading melanoma can arise in a preexisting melanocytic nevus that slowly changes over several years; it most commonly affects intermittently sun-exposed areas with the greatest nevus density (upper backs of men and women and lower legs of women). Pigment varies from black and blue-gray to pink or gray-white, and the borders are irregular. Absence of pigmentation often represents regression.

Nodular melanoma represents 15% of all melanomas. The median age at onset is 53 years. Clinically, a uniform blue-black, blue-red, or red nodule usually begins de novo and grows rapidly. About 5% are amelanotic. The most common sites are the trunk, head, and neck.

Acral lentiginous melanoma accounts for 10% of melanomas overall but is the most common type among Japanese, African Americans, Latin Americans, and Native Americans. The median age is 65 years, with equal gender distribution. It occurs on the palms or soles or under the nails, and it is on average 3 cm in diameter at diagnosis. Clinically, the lesion is a tan, brown-to-black, flat macule with color variegation and irregular borders. It does not appear to be linked to sun exposure.

**Diagnosis**

Excisional biopsy with narrow margins is recommended for diagnosis. Incisional biopsy is acceptable when suspicion for melanoma is low, the lesion is large, or it is impractical to perform a complete excision. It is believed not to be detrimental if subsequent therapeutic surgery is performed within 4 to 6 weeks. Dermatoscopy and total body photography are adjunctive noninvasive diagnostic techniques. Routine laboratory tests and imaging studies are not required for asymptomatic patients with primary cutaneous melanoma 4 mm or less in thickness for initial staging or routine follow-up. Indications for such studies are directed by a thorough medical history and complete physical examination.

Histologic interpretation should be performed by a physician experienced in the microscopic diagnosis of pigmented lesions. Molecular analyses for evidence of gene mutations, DNA copy number abnormalities, or changed protein expression are useful adjunctive tools in the assessment of histologically ambiguous primary melanocytic tumors.

The new revised American Joint Committee on Cancer (AJCC) staging system (Tables 1 and 2) includes simplified tumor-thickness thresholds of 1.0, 2.0, and 4.0 mm. Although tumor thickness and ulceration continue to define T2, T3, and T4 categories, T1b melanomas are defined by a tumor mitotic rate of 1/mm² or greater or ulceration, rather than Clark level of invasion. N1 and N2 categories remain for microscopic and macroscopic nodal disease respectively, with sentinel node biopsy recommended for pathologic staging. M staging continues to be determined both by site of distant metastasis and serum concentration of lactate dehydrogenase, but in patients with regionally isolated metastases from an unknown primary site, disease will be categorized as stage III rather than stage IV, because the prognosis corresponds to that of stage III disease from a known primary site.

Five-year and 10-year survival rates based on the TNM classification range from 97% and 93% for patients with T1a N0 M0 melanomas to 53% and 39%, respectively, for patients with T4b N0 M0 melanomas.

**Differential Diagnosis**

The differential diagnosis includes melanocytic nevus, angioma, pigmented basal cell carcinoma, pyogenic granuloma, seborrheic keratosis, Kaposi’s sarcoma, and hematoma (especially for acral lentiginous melanoma).

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**Table 1** Tumor, Node, and Metastasis (TNM) Staging Categories for Cutaneous Melanoma

<table>
<thead>
<tr>
<th>Tumor (T)</th>
<th>Thickness (mm)</th>
<th>Ulceration Status/Mitoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>T1</td>
<td>≤1.00</td>
<td>a: without ulceration and mitosis &lt;1/mm²</td>
</tr>
<tr>
<td>T2</td>
<td>1.01–2.00</td>
<td>a: without ulceration</td>
</tr>
<tr>
<td>T3</td>
<td>2.01–3.00</td>
<td>a: without ulceration</td>
</tr>
<tr>
<td>T4</td>
<td>≥4.00</td>
<td>a: without ulceration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nodes (N)</th>
<th>Number of Metastatic Nodes</th>
<th>Nodal Metastatic Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>N1</td>
<td>1</td>
<td>a: Micrometastasis</td>
</tr>
<tr>
<td>N2</td>
<td>3</td>
<td>a: Micrometastasis</td>
</tr>
<tr>
<td>N3</td>
<td>4+ metastatic nodes or matted nodes or in transit metastases/satellites with metastatic nodes</td>
<td>c: In transit metastases/ satellites without metastatic nodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metastases (M)</th>
<th>Classification</th>
<th>Site</th>
<th>Serum LDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>M1a</td>
<td>Distal skin, subcutaneous or nodal metastasis</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastasis</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastasis</td>
<td>Any distant metastasis</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

*Note: Micrometastases are diagnosed after sentinel lymph node biopsy. Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically. Abbreviations: is = in situ; LDH = lactate dehydrogenase; NA = not applicable.*

**Treatment**

Early diagnosis combined with appropriate surgical therapy is currently the only curative treatment. The recommended margins are:

- **Melanoma in situ:** 0.5 cm
- **Melanoma less than 1 mm:** 1 cm
- **Melanoma 1 to 2 mm:** 1 to 2 cm
- **Melanoma greater than 2 mm:** 2 cm

The recommended deep margin is muscle fascia. Wider margins and Mohs micrographic surgery can reduce risk of contiguous subclinical spread for the desmoplastic variant of melanoma.

Sentinel lymph node biopsy provides accurate staging information for patients with clinically unaffected regional nodes and without distant metastases. In cases of positive sentinel node biopsy or clinically detected regional nodal metastases (palpable,
positive cytology or histopathology), radical removal of lymph nodes of the involved basin is indicated. There is clinical trial evidence suggesting that the survival outcome for patients who are sentinel node positive is improved if immediate regional lymphadenectomy is done.

For resectable local or in-transit recurrences, excision with a clear margin is recommended. For numerous or unresectable in-transit metastases of the extremities, isolated limb perfusion or infusion with melphalan may be considered.

Radiotherapy is indicated in select patients with lentigo maligna melanoma, as an adjuvant in select patients with regional metastatic disease, and for palliation, especially in bone and brain metastases.

Numerous adjuvant therapies have been investigated for the treatment of localized cutaneous melanoma following complete surgical removal. Adjuvant interferon (IFN) alfa-2b (Intron A) is the only adjuvant therapy approved by the FDA for high-risk melanoma that affects outcome after surgery. No survival benefit has been demonstrated for adjuvant chemotherapy, nonspecific (passive) immunotherapy, radiation therapy, retinoid therapy, vitamin therapy, or biologic therapy.

Various experimental melanoma vaccines show promise in the adjuvant setting, although caution is needed because four phase III trials (E1694, MIAIT-III [Canvaxin], MIAIT-IV, and EORTC 18961) showed a deleterious effect of the experimental vaccine compared with control intervention. Considerable effort is now being focused on selecting patients on the basis of molecular profiling and on combining agents targeting melanoma-specific aberrations in signaling and apoptotic pathways to overcome the many resistance mechanisms in melanoma cells.

### Pathology Staging for Cutaneous Melanoma and Survival Rates

<table>
<thead>
<tr>
<th>STAGE</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>5-YEAR SURVIVAL</th>
<th>10-YEAR SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>88%</td>
<td>55%</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
<td>97%</td>
<td>95%</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
<td>96%</td>
<td>90%</td>
</tr>
<tr>
<td>II</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
<td>87%</td>
<td>78%</td>
</tr>
<tr>
<td>III</td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
<td>68%</td>
<td>53%</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Pathology staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial (i.e., sentinel node biopsy) or complete lymphadenectomy. Pathologic stage 0 or stage I A patients are the exception; they do not require pathologic evaluation of their lymph nodes.

### Complications

Metastasis may occur locally in the regional lymph node basins, or they can occur distally in the skin (away from the melanoma scar), the remote lymph node(s), the viscera, and skeletal and central nervous system sites.

### Monitoring

Most metastases occur in the first 1 to 3 years after treatment of the primary tumor, and an estimated 4% to 8% of patients with a history of melanoma develop another primary melanoma, usually within the first 3 to 5 years following diagnosis. The risk of new primary melanoma increases in the setting of multiple dysplastic nevi and family history of melanoma. Consider cancer genetics consultation in patients with three or more melanomas in aggregate in first-degree or second-degree relatives on the same side of the family, families with three or more cases of melanoma or pancreatic cancer on same side of family, and (in low-incidence countries) patients with three or more primary melanomas.

Frequency of monitoring is as follows: For patients with melanoma smaller than 1 mm: every 3 months for 1 year, then every 6 to 12 months for 4 years, then annual examinations thereafter. For patients with melanoma larger than 1 mm: every 3 months for 1 to 2 years, then every 6 months until the fifth year, then annual examinations thereafter.

Follow-up visits for all patients should include a thorough history, review of systems, complete skin examination, and examination of lymph nodes. In patients at high risk for metastatic disease or with an abnormal examination, appropriate imaging studies, laboratory studies, or biopsies may be indicated. Evidence to support the use of routine imaging and laboratory studies in asymptomatic patients with a normal physical examination remains controversial and is left to the discretion of the physician.

### References


### PAPULOUSQUAMOUS ERUPTIONS

Method of Tam T. Nguyen, MD

**CURRENT DIAGNOSIS**

- Psoriasis can be clinically described as erythematous plaques with silvery white scales.
- Severity is rated as mild (<5% body surface area [BSA]), moderate (5%–10% BSA), or severe (>10% BSA).
- Most cases are mild chronic plaques involving the extensor surfaces.
- Involvement of scalp and palmar and plantar surfaces is classified as severe.
- Psoriasis is commonly comorbid with several conditions, including cardiovascular disease, depression, and metabolic disorders.
CURRENT THERAPY

- Class I/II (super-potent) topical steroid is the mainstream treatment of mild to moderate psoriasis.
- For moderate- to severe cases, systemic treatment with methotrexate is the gold standard.
- Narrowband UVB remains a safe treatment option for all patients including children and pregnant women.
- Several immunomodulators or biologicals including etanercept have been proved very effective therapy. Biologicals can be given as monotherapy or in combination with other modalities for very recalcitrant cases.
- Treatment of comorbid conditions is paramount.

Epidemiology
Psoriasis, a common chronic idiopathic inflammatory disorder, affects 2% to 3% of Americans. The number of persons affected by this condition has more than doubled from 1970 to 2000. It is a chronic disorder that can involve many organ systems including skin, mucosa, the gastrointestinal tract, and joints. Although the onset of psoriasis can occur at any age, there is a bimodal distribution peaking in young adults in their early 20s and again in persons in their 50s. There is an equal prevalence among male and female patients, but the incidence is higher in men among younger adult populations.

Risk Factors
There is a strong family history and association with HLA-Cw6, HLA-B13, and HLA-B27. Psoriatic genes appear to be located on four key genes called pSOR1-4, which show an autosomal dominant pattern. In addition to the genetic etiology, environmental triggers, such as drugs, infection, and stress, also have a role in the pathogenesis of the psoriasis. Psychogenic stress from home and school is especially common in pediatric cases. Lithium and β-blockers are two well-known triggers of psoriasis. Certain conditions, such as Crohn’s disease and multiple sclerosis, predispose patients to developing psoriasis.

Pathophysiology
Even though the exact mechanism is unknown, psoriasis is a disease of T cells that leads to abnormal epidermal differentiation and hyperproliferation. Normal skin has epidermal turnover of about 21 to 28 days, but psoriatic skin turns over every 3 to 4 days. Several cytokines, including IL-12 and IL-23, are part of the immune-mediated disease.

Diagnosis
Although most psoriatic lesions have characteristic scaly and silvery plaques, the lesions can be misleading. Refer to Box 1 for the differential diagnosis. Psoriasis has several subtypes including erythrodermic, pustular, and vulgaris. Psoriasis vulgaris has several subtypes including chronic plaque, guttate (Figure 1), and inverse psoriasis. More than 80% to 90% of psoriasis cases are the chronic plaque psoriasis. Therefore, this chapter focuses on this subtype.

Severity of psoriasis is classified based on the body surface area (BSA) involved. There are several severity instruments, such as Koo-Menter Psoriasis, for assessing the severity. One of the best validated tools is the Psoriasis Area Severity Index (PASI). These instruments are used to classify the condition according to coverage of body surface area (BSA) as either mild (≤5% of BSA), moderate (5%–10% of BSA), or severe (>10% of BSA). Body surface area can be estimated using the rule of 9s. Each upper extremity and the head is 9%, and the chest, back, and each lower extremity are 18%. For children, similar rules apply, except that each lower extremity is 13.5%. When the lesions involve difficult regions such as hands, feet, face, scalp, and genitalia, they are treated as severe regardless of the amount of BSA they cover.

Fortunately, more than 70% to 75% of cases are classified as mild to moderate, and there is no need for blood work. However, when psoriasis is associated with comorbidities, such as depression and heart disease, or when systemic medications cause serious side effects, it may be reasonable to get basic laboratory tests such as a complete blood count with platelet (CBC), chemistry, liver function tests (LFTs), cholesterol panel, hepatitis B and C, uric acid, and erythrocyte sedimentation rate (ESR). For patients at high risk, consider HIV testing. Also, consider evaluating for tuberculosis with a PPD test. These laboratory tests are even more crucial when considering treating with immunosuppressants like methotrexate (Trexall) and biological agents. Liver biopsy should be done if methotrexate is used at a cumulative dose of 3.5 to 4 g. Equally important, patients’ quality of life needs to be assessed, which can be done with an instrument called the Dermatology Life Quality Index (DLQI).

Differential Diagnosis
The differential diagnosis of psoriasis is lengthy and can be tricky. Box 1 lists the differential diagnosis of psoriasis.
Clinical Manifestations
Most presentations of psoriasis are asymptomatic. When symptomatic, the most common clinical manifestation is pruritus. Other possible symptoms include fever and malaise, especially for more extensive disease. When psoriasis involves the joints, patients can have pain and stiffness in the involved joints; many of these cases involve the distal interphalangeal joints. On physical examination, the lesions are well-circumscribed dark pink to red plaques with silvery to white scales (Figures 2 and 3). Scales can be absent in certain locations, such as the intertriginous area (gluteal folds) (Figures 4 and 5). The margins are sharp and distinct, especially over extensor surfaces such as the elbows and knees (see Figure 2). Lesions also can involve the sacral area, nails, scalp, and the genitalia. If psoriasis forms under a nail, onycholysis (lifting of the nail plate) can occur with pitting and subungual keratosis.

When the scales are removed, several distinctive minute blood droplets appear; called the Auspitz sign. Use caution when removing the scales because it can be painful. When new lesions form at a site of trauma, it is called the Koebner phenomenon. Diagnosis can be made clinically. However, when in doubt, biopsy the lesion, which will show a thickened epidermis with an absent granular cell layer. The stratum corneum is hyperkeratotic, with classic infiltration of neutrophils.

If this inflammatory process affects the joints, psoriatic arthritis ensues. Although this article does not discuss psoriatic arthritis, it is important to recognize when it occurs. Unlike rheumatoid arthritis, the distal interphalangeal (DIP) joints are regularly involved, but it can affect any joints. Psoriatic arthritis only occurs in 4% to 42% of patients with psoriasis. Diagnosis can be made with the CASPAR criteria, which evaluates five possible presentations, including having psoriasis, nail dystrophy, negative rheumatoid factor, dactylitis, and radiographic evidence.

Figure 2. Chronic plaque psoriasis on the extensor surfaces.

Figure 4. Chronic plaque psoriasis with limited scales.

Figure 3. Chronic plaque psoriasis with classic silvery scales.

Figure 5. Chronic plaque psoriasis without scales.
Treatment Corticosteroids remain the mainstay for psoriasis therapy; they reduce inflammation, decrease mitosis, and reduce erythema. Because most cases are mild to moderate, the first-line therapy to consider is topical corticosteroids. Even for severe cases that require systemic treatment, topical steroids should still be considered as a first-line adjuvant therapy. Because psoriatic lesions are thickened, it is critical to go directly to super-potent steroids (class I), such as clobetasol (Clobex) (refer to Box 2 for steroid potency). When the localized lesions are lichenified and do not respond to potent topical corticosteroids, using steroid-impregnated tapes (flurandrenolide tape [Cordran]), which function as an occlusive wrap, can help. However, for areas of thinner skin, such as mucosa and lesions on the face, use less-potent topical steroids. Use caution when using class 1 steroids owing to all the potential side effects, including skin atrophy, hypopigmentation, telangiectasia, striae, and potential systemic absorption. In addition to the possible side effects, tachyphylaxis (reduced efficacy with prolonged use) can occur. Therefore, it is crucial to limit the use of potent topical steroids to less than 12 weeks.

One way to reduce the use of topical steroids is by using the vitamin D3 analogue class, such as calcipotriene (Dovonex). This class of drugs inhibits epidermal proliferation and stimulates cellular differentiation. It is considered as effective as medium-potency corticosteroids, without the side effects. However, one drawback is that it takes about 8 weeks to be effective. Therefore, it should not be used for acute psoriatic eruptions. More often it is used in combination with topical steroids. It is generally well tolerated topically, but about 10% of patients experience burning and itching or hypercalcemia.

Other topical applications include tazarotene (Tazorac) and anthralin (Driitho-Creme HP 1%, Driitho-Scalp 0.5%). Tazarotene is an acetylenic retinoid and can be as effective as high-potency topical corticosteroids. However, its use is limited owing to the side effects of erythema, burning, pruritus, and peeling. Therefore, it is best to combine it with corticosteroids to reduce the irritation. In addition, tazarotene can stain clothing, and it is less popular owing to the side effects (redness and irritation on skin as well as staining) and the feel and smell of the solutions. However, it is a good alternative to topical corticosteroids.

For a limited number of thickened lesions, consider intralesional steroid injections, such as a single intralesional injection of a mid-potency steroid (e.g., triamcinolone acetonide or Kenalog-10, 5–10 mg/mL). Most injected plaques clear completely and remain in remission for months. However, as with other steroid injections, side effects of skin atrophy and telangiectasis can occur. Therefore, the face and intertriginous areas should not be injected because of the increased risk of side effects.

For severe and recalcitrant cases, systematic medications are needed. One of the gold standards in the United States and many other countries is methotrexate (Trexxal) because it is available as a generic. Its exact mechanism is unknown; initially it was believed to inhibit proliferation, but more-recent studies describe an antiinflammatory property. The most common serious side effect of this drug is hepatotoxicity (as many as 33% of patients show some liver disease). Therefore, it is crucial to screen for alcohol dependence, liver disease, and obesity. Standard practice is to check baseline CBC and liver function enzymes, and then repeat these laboratory tests after 1 month of therapy. Methotrexate is highly teratogenic; hence it is absolutely contraindicated in pregnancy. After stopping the medication, men should wait at least 3 months and women should wait one ovaular cycle before attempting to conceive.

There are two methods for initiating methotrexate. Most patients start at an initial dose of 7.5 mg (3 tabs of 2.5 mg) weekly; in pediatric cases dosage is 0.2 to 0.7 mg/kg weekly. Others start at a higher dosage of 0.4 to 0.5 mg/kg weekly. Unfortunately, there is no current study to compare the two methods. With either dosing regimen, do not exceed 30 mg per week. Methotrexate depletes the body’s storage of folic acid, so it is important to supplement folic acid 1 mg daily except the day when methotrexate is taken. The methotrexate can be titrated upward every 2 to 4 weeks.

Unlike methotrexate, which can take several weeks before it becomes effective, cyclosporine (Sandimmune), a calcineurin inhibitor, is rapidly effective for severe cases. It is dosed at a low dose of 2 to 5 mg/kg/day divided into two doses and increased slowly every 2 to 4 weeks. Maintenance dosage is about 3 to 5 mg/kg/day. A main concern for this drug is nephrotoxicity. As long as the use of cyclosporine is limited to 1 year, it is generally safe. However, kidney function still needs to be monitored regularly. Cyclosporine has been associated with an increased risk of squamous cell carcinoma, especially when the patient has a history of psoralen plus ultraviolet A (PUVA) therapy.

Although not FDA-approved, azathioprine (Imuran) has been a successful systemic medication for psoriasis. Generally, it is initially dosed at 0.5 mg/kg. If there is cytopenia, then the dosage can be increased by 0.5 mg/kg/day every 4 to 6 weeks as needed. Another dosing method is based on thiopurine methyltransferase (TPMT) levels. If the TPMT is less than 5.0 U, do not use azathioprine. If the level is between 5 and 13.7 U, the maximum daily dose should be 0.5 mg/kg/daily. If the TPMT level is between

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Box 2 Classification of Topical Steroids, with a Few Samples from Each Class

**Class 1: Super Potent**
- Clobex lotion, 0.05%
- Cormax cream or solution, 0.05%
- Diprostone gel or ointment, 0.05%
- Olux foam, 0.05%

**Class 2: Potent**
- Elocon ointment, 0.1%
- Florone ointment, 0.05%
- Halog ointment/cream, 0.1%
- Lidex cream, gel, ointment, 0.05%

**Class 3: Upper Mid-Strength**
- Clobex lotion, 0.005%
- Cyclomulsion lotion, 0.1%
- Lidex-E cream, 0.05%
- Maxivite cream/oil, 0.05%

**Class 4: Mid-Strength**
- Aristocort cream, 0.1%
- Clobutinol cream, 0.05%
- Elocon cream, 0.1%
- Kenalog cream, ointment, spray, 0.1%

**Class 5: Lower Mid-Strength**
- DesOwen ointment, 0.05%
- Diprosone lotion, 0.1%
- Kenalog lotion, 0.1%
- Synalar cream, 0.025%

**Class 6: Mild**
- Derma-Smoothe/FS Oil, 0.01%
- DesOwen cream, 0.05%
- Synalar cream/solution, 0.01%
- Trediol cream, 0.05%

**Class 7: Least Potent**
- Topicals with hydrocortisone, dexamethasone, methylprednisolone, and prednisolone

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*May be compounded by pharmacists.*

*Not FDA approved for this indication.*
13.7 and 19.0 U, then the maximum daily dose may be increased to 1.5 mg/kg.

Acitretin (Soriatane) and isotretinoin (Claravis)\(^1\) are retinoids, which are vitamin A derivatives. Although acitretin is more commonly used, either may be used and requires a period of 3 to 6 months to achieve results. However, these retinoids are generally less effective than methotrexate and cyclosporine. Though they are less effective and a longer time is required for this class of agents to work, their main benefits include no malignancy potential and no immunosuppression. Therefore, these drugs are safe in patients with HIV and other immunosuppressive conditions. Unfortunately, acitretin and isotretinoin are highly teratogenic. Both male and female patients need to be drug free for 1 year for isotretinoin and 3 years for acitretin before they conceive. For other possible treatment agents, refer to Box 3.

In recent years, immunomodulators or biologicals have revolutionized the treatment course of psoriasis. Generally, criteria for this class of therapy are PASI greater than 10 and failure of other therapies or a contraindication to other therapies such as methotrexate. Most agents are limited to 1 to 2 years of use because most studies have not been evaluated beyond 2 years. Tuberculosis should be evaluated (PPD and possibly chest x-ray) before starting these biologics. All the medications in this class should be avoided in pregnancy. Alefacept (Amevive) and efalizumab (Raptiva) are T-cell inhibitors. Efalizumab (Raptiva) was withdrawn from the market in 2009 owing to reported cases of progressive multifocal leukoencephalopathy. Etanercept (Enbrel) is a tumor necrosis factor (TNF) inhibitor and should not be used in patients with multiple sclerosis. The three monoclonal antibodies include infliximab (Remicade), adalimumab (Humira), and golimumab (Simponi). A new drug in the class is ustekinumab (Stelara), which inhibits interleukin (IL)-12 and IL-23.

Etanercept (Enbrel) blocks TNF-\(\alpha\). It is generally dosed at 50 mg SC twice weekly for 12 weeks and then 50 mg weekly. Patients can self-administer the drug; laboratory monitoring is not required. There are limited data beyond 2 years. Etanercept\(^1\) is the preferred drug for children. Infliximab (Remicade) blocks both soluble and bound TNF-\(\alpha\). Its dosage is 3 to 5 mg/kg IV on weeks 0, 2, and 6, and then every 6 to 8 weeks. Medication generally is infused over 2 hours. It is crucial to have a PPD (but not chest x-ray) before treatment. It is approved for 1 year. In a comparative study, infliximab has been shown to improve lesions in 66% to 76% of cases. It is initially dosed at 45 to 90 mg SC at weeks 0 and 4, depending on body weight. Maintenance is every 12 weeks.

When these therapies are contraindicated, one alternative is phototherapy. This is the reason many patients report decreased symptom severity during the summer months due to the natural UV light. Phototherapy started with photochemotherapy with oral or topical psoralens combined with UVA light (PUVA). Although phototherapy is very effective for psoriasis, even in very thick lesions, recent studies have shown an increased risk of skin cancer. Therefore, PUVA has become less popular since the advent of UVB radiation treatment, especially with narrow band UVB (NB-UVB). NB-UVB is equally effective as PUVA and does not have the risk of skin cancer. The exact mechanism is unknown, but it is believed to affect DNA and to suppress IL-17 and IL-23, creating photoproducts that interfere with cell cycle progression. NB-UVB is first-line course of therapy for pregnant and pediatric patients. There are two methods for initiating NB-UVB phototherapy: the skin type protocol, which is easier to execute, and the minimum erythema dose (MED), which is more detailed but more accurate. Refer to Table 1 for treatment protocols. Both protocols generally require 30 to 35 treatments with the optimal frequency of three times a week.

Given all the treatment options (refer to Box 4), the choice of the treatment regimen depends on several factors. First, the severity of the psoriasis must be determined as well as the social and emotional impact of the condition. Another consideration is financial, including the insurance coverage, copayment, and deductibles. The lowest-cost treatment is methotrexate, and alefacept is the highest. The patient’s conveniences and preferences should be discussed. If the severity is only mild to moderate without much emotional impact, topical steroid and vitamin D analogue should be considered the first options. Other topicals include tar (Medator, Balnetar, Psorent), anthralin (Dritho-Creme HP, Dritho-Scalp), and tretinoin (Retin-A).\(^1\) If the degree is severe and/or the patient has emotional impact, systemic medications should be used. Most insurance plans will probably require that the patient try at least one oral medication before employing the biologicals. If systemic therapy is used, consider combining it with phototherapy (if possible). If there is no improvement within 2 to 4 months, the regimen should be changed to biologicals. Other combinations may be employed for better resolution.

For healthy patients, any of these therapies may be tried. Unfortunately, there are limitations with children, pregnant women, and patients trying to conceive. For pediatric patients, topical agents should be tried first, followed by UVB monotherapy. If the plaques are still recalcitrant, either add methotrexate (Trexall)\(^1\) or phototherapy. If phototherapy is not available and topical agents have failed, consider using methotrexate or cyclosporine (Sandimmune).\(^1\) Other options for pediatric patients include adalimumab (Humira)\(^1\) and etanercept (Enbrel).\(^1\) For pregnant women and patients trying to conceive, first try topical agents followed by UVB (ideally narrowband). This combination remains the safest option. If stronger options are needed, the only class B drugs are systemic steroids, adalimumab, alefacept (Amevive), infliximab

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**Box 3** Other Treatment Modalities for Moderate to Severe Psoriasis

<table>
<thead>
<tr>
<th>Fumaric acid esters(^2)</th>
<th>First-line therapy in a couple of European countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyurea (Hydrea)(^1)</td>
<td>A good option because there is no liver or kidney toxicity; however, be cautious of bone marrow suppression</td>
</tr>
<tr>
<td>Leflunomide (Arava)(^1)</td>
<td>Mycophenolate mofetil (Cellcept)(^1) good choice for HIV patients and patients with immunobullous disorders</td>
</tr>
<tr>
<td>Retinoid acid metabolism–blocking agents: liarozole(^4) and tazarotene (Rombozale)(^5)</td>
<td>Sulfasalazine (Azulfidine)(^1)</td>
</tr>
<tr>
<td>Tacrolimus (Prograf)(^6)</td>
<td>6 thioguanine (Tabloid)(^1)</td>
</tr>
</tbody>
</table>

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1. Not FDA approved for this indication.
2. Not available in the United States.
**Complications**

Patients suffering from psoriasis cope with the physical appearance of their lesions as well as the associated mental anguish associated with many other chronic ailments. Furthermore, psoriasis is associated with other chronic diseases, such as abdominal obesity, metabolic syndrome, and atherogenic dyslipidemia. Patients with psoriasis are more likely to have coronary artery disease, elevated blood pressure, obesity, and insulin resistance. There is an increased risk of malignancy, such as lymphoma. Substance abuse and smoking are common among these patients as well.

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**References**


**TABLE 1**

**Methods for Initiating Narrow-Band Ultraviolet B (NB-UVB) Therapy and Subsequent Dosing of Phototherapy**

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>TYPE 1</th>
<th>TYPE 2</th>
<th>TYPE 3</th>
<th>TYPE 4</th>
<th>TYPE 5</th>
<th>TYPE 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose</td>
<td>130 mJ/cm²</td>
<td>220 mJ/cm²</td>
<td>260 mJ/cm²</td>
<td>330 mJ/cm²</td>
<td>350 mJ/cm²</td>
<td>400 mJ/cm²</td>
</tr>
</tbody>
</table>

**Subsequent Doses**

<table>
<thead>
<tr>
<th>Severe erythema</th>
<th>No treatment. When burn resolves, decrease by 50% of last dose and then increase dose by 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild erythema</td>
<td>Same dose Same dose Same dose Same dose Same dose Same dose</td>
</tr>
<tr>
<td>Barely perceptible erythema</td>
<td>— — — — — —</td>
</tr>
<tr>
<td>No erythema: increase dose by</td>
<td>1.5 mJ/cm² 2.5 mJ/cm² 4.0 mJ/cm² 4.5 mJ/cm² 6.0 mJ/cm² 6.5 mJ/cm²</td>
</tr>
</tbody>
</table>

**Dosing Schedule**

Optimal schedule 3 ×/wk (M, W, F) is the optimal schedule because less is not as effective and more does not improve the resolution. Subsequent treatments should not be less than 24 hours from the last treatment. For the treatment of eczema, no clear guideline to the frequency. Some use 5 ×/wk.

**Dose Adjustments for Missed Days**

<table>
<thead>
<tr>
<th>MISSED DAYS</th>
<th>DOSE ADJUSTMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–7</td>
<td>Increase doses per skin type</td>
</tr>
<tr>
<td>8–11</td>
<td>Same dose</td>
</tr>
<tr>
<td>12–14</td>
<td>Decrease by 2 treatments’ worth</td>
</tr>
<tr>
<td>15–20</td>
<td>Decrease by 25%</td>
</tr>
<tr>
<td>21–27</td>
<td>Decrease by 50%</td>
</tr>
<tr>
<td>28+</td>
<td>Start over</td>
</tr>
</tbody>
</table>

**Box 4**

**Treatment Options for Psoriasis**

**Topical**

Steroid Tar (e.g., Medotar, Balnetar, Psorent) Anthralin (Dritho-Creme Hp, Dritho-Scalp) Calcipotriene (Dovonex) Calcitriol (Rocalo) Adapalene (Differin) Tazarotene (Tazorac) Tretinoin (Retin-A) Calcineurin inhibitors (pimecrolimus [Elidel], tacrolimus [Protopic])

**Oral or Systemic**

Methotrexate (Trexall) Acitretin (Soriatane) Isotretinoin (Claravis) Cyclosporine (Sandimmune) Mycophenolate mofetil (Cellcept)

**Immunomodulators**

Alefacept (Amevive) Etanercept (Enbrel) Infliximab (Remicade) Adalimumab (Humira) Ustekinumab (Stelara)

**Phototherapy**

UVA UVB

1Not FDA approved for this indication.
PARASITIC DISEASES OF THE SKIN

Method of
Andreas Katsambas, MD, PhD, and Clio Dessiinoti, MD, MSc

CURRENT DIAGNOSIS

Parasitic diseases are a common cause of morbidity and mortality, particularly in tropical and developing countries. They may be caused by protozoa, helminths, or arthropods. Because of the immigration of persons from tropical and subtropical countries worldwide and the travel of people from industrialized to tropical regions, parasitic diseases may be found in temperate climates. Skin lesions may provide important diagnostic clues for parasitic infections, and they are reviewed in the following sections, along with updated treatment guidelines.

CURRENT DIAGNOSIS

Cutaneous Amebiasis
- Purulent, foul-smelling nodules, ulcers, cysts, sinuses
- Microscopic identification of Entamoeba histolytica in stool or biopsy samples
- Molecular methods

Cutaneous Leishmaniasis
- Ulcerated nodule (i.e., volcano sign)
- Identification of Leishmania parasites by direct examination or culture from the lesion aspirate or biopsy
- Montenegro skin test
- In vitro lymphocyte proliferation assay
- Polymerase chain reaction

Trypanosomiasis
- Chagoma: painful erythematous nodule
- Regional adenopathy
- Cardiomegaly, megaesophagus, megacolon
- Microscopic examination of Trypanosoma cruzi in blood, lymph node biopsy, or skin biopsy or culture

African Sleeping Sickness
- Trypanosome chancre: painful, inflammatory nodule
- Regional adenopathy
- Fever, generalized pruritic eruption with erythematous annular plaques
- Central nervous system involvement

- Microscopic identification of Trypanosoma brucei in chancre fluid, lymph node aspirates, blood, bone marrow, cerebrospinal fluid

Cutaneous Toxoplasmosis
- Roseola, urticaria, prurigo-like nodules
- Isolation of Toxoplasma gondii in the skin

Ascariasis
- Urticaria
- Identification of adult worm or eggs in stool

Cutaneous Larva Migrans
- Creeping eruption
- Intense pruritus

Cysticercosis
- Subcutaneous nodules
- Isolation of Taenia solium in skin lesion
- Serologic tests

Dracunculiasis
- Ruptured blister with protruding worm

Filariasis
- Lymphatic Filariasis
  - Fever with lymphangitis and lymphadenitis
  - Chronic pulmonary infection
  - Progressive lymphedema leading to massive tissue thickening, especially of the legs and scrotum (i.e., elephantiasis)
  - Microscopic identification of microfilariae in blood

Onchocerciasis (River Blindness)
- Subcutaneous nodules, dermatitis, “leopard skin,” “lizard skin,” lymphedema
- Identification of microfilariae in skin snips
- Blindness

Loaiasis (Calabar Swellings)
- Pruritus, localized subcutaneous swellings
- Serpiginous lesion on the conjunctivae
- Microscopic identification of microfilariae in blood

Schistosomiasis (Snail Fever)
- Pruritic papules, edema
- Fever, lymphadenopathy, diarrhea
- Bilharziasis cutanea tarda: pruritic, grouped papules
- Identification of the eggs in stool, urine, biopsy of affected tissues
- Enzyme-linked immunosorbent assay (ELISA) tests

Cercarial Dermatitis (Swimmer’s Itch)
- Extremely pruritic erythematous macules, papules, vesicles on body areas exposed to infested water

Human Scabies
- Pruritus worsening at night
- Papules, excoriations, nodules, burrows on genitals, interdigital spaces, axillae, wrists
- Microscopic identification of mites or eggs from burrows or papules

Pediculosis
- Pediculosis Capitis
  - Intense pruritus of the scalp
  - Nape dermatitis
  - Identification of lice and nits on the hair

Pediculosis Corporis (Vagabond’s Itch)
- Intense pruritus, erythema, urticarial lesions, papules, nodules, and excoriations
- Identification of lice and nits from clothing

Pediculosis Pubis
- Pruritus
- Blue macules
- Identification of lice and nits on pubic hair
CURRENT THERAPY

**Cutaneous Amebiasis**
- Metronidazole (Flagyl) 750 mg PO three times daily for 7 and 10 days, or
- Tinidazole (Tindamax) 2 g once PO daily for 5 days, followed by iodoquinol (Yodoxin) 650 mg PO three times daily for 20 days or paromomycin (Humatin) 25 to 35 mg/kg/day PO in three doses for 7 days

**Cutaneous Leishmaniasis**
- Sodium stibogluconate (Pentostam) 20 mg/kg/day IV or IM for 20 days, or
- Meglumine antimoniate (Glucantime) 2.5 mg/kg/day PO (up to 150 mg/day) for 28 days, or
- Topical paromomycin, a formulation of 15% paromomycin and 12% methylbenzethonium chloride in soft white paraffin (Lesheutan), applied twice daily for 10 days or
- Pentamidine (Pentam 300), 3 to 7 mg/kg/day PO or IM daily or every second day for four to seven doses

**Trypanosomiasis**

**Chagas' Disease (American Trypanosomiasis)**
- Nifurtimox (Lampit) 8 to 10 mg/kg/day PO in three or four doses for 90 to 20 days, or
- Benznidazole (Radanil, Rochagan), 5 mg/kg PO once, or
- Miltefosine (Impavido) 2.5 mg/kg/day PO (up to 150 mg/day) for 28 days, or
- Suramin (Germanin) 100 to 200 mg (test dose) IV, then 1 g IV after 3 days, 3.6 mg/kg/day for 3 days; repeat after 7 days

**West African Sleeping Sickness**
- Suramin (Germanin) 100 to 200 mg (test dose) IV, then 1 g IV on days 1, 3, 7, 14, 21
- For late disease with involvement of the central nervous system, melarsoprol (Mel-B) 2 to 3.6 mg/kg/day IV for 3 days; repeat after 7 days
- Miltefosine (Impavido) 2.5 mg/kg/day IV for 10 days, or
- For late disease with involvement of the central nervous system, eflornithine (Ornidyl) 400 mg/kg/day IV in four doses for 14 days

**Cutaneous Toxoplasmosis**
- Self-limited disease; treatment not needed in healthy, nonpregnant persons
- For pregnant women or immunocompromised patients: pyrimethamine (Daraprim) 25 to 100 mg/day PO for 3 to 4 weeks (plus leucovorin 10 to 25 mg with each dose of pyrimethamine) and sulfadiazine 1 to 1.5 g PO four times daily for 3 to 4 weeks

**Ascariasis**
- Albendazole (Albenza) 400 mg PO once, or
- Mebendazole (Vermox) 100 mg PO twice daily for 3 days or 500 mg once, or
- Ivermectin (Stromectol) 150 to 200 µg/kg PO once

**Cutaneous Larva Migrans**
- Ivermectin (Stromectol) 200 µg/kg PO once; a second dose may be needed, or
- Albendazole (Albenza) 400 mg PO once for 3 days
- Topical thiabendazole 10% to 15% applied three times daily for 5 to 7 days for a limited number of lesions

**Dracunculiasis**
- Slow extraction of the worm, which is facilitated by metronidazole (Flagyl) 250 mg PO three times daily for 10 days

**Filarial Filariasis**
- Diethylcarbamazine (DEC, Hetrazan) 6 mg/kg/day PO in three doses for 12 days, or
- Ivermectin (Stromectol) 200 µg/kg PO once together with albendazole (Albenza) 400 mg PO once; kills only the microfilaria, not the adult worms
- For patients with microfilaria in the blood, DEC as follows: day 1: 50 mg; day 2: 50 mg three times daily; day 3: 100 mg three times daily; days 4 through 14: 9 mg/kg in three doses

**Onchocerciasis**
- Ivermectin (Stromectol) 150 µg/kg PO once for 6 to 12 months, until asymptomatic
- DEC: contraindicated because it may lead to blindness

**Loiasis**
- DEC 6 mg/kg/day PO in three doses for 12 days
- For patients with microfilaria in the blood, DEC as follows: day 1: 50 mg; day 2: 50 mg three times daily; day 3: 100 mg three times daily; days 4 through 14: 9 mg/kg in three doses

**Schistosomiasis**
- Praziquantel (Biltricide) 40 mg/kg/day in two doses for 1 day (S. haematobium and S. mansoni) and 60 mg/kg/day in three doses for 1 day (S. japonicum, S. mekongi)

**Human Scabies**
- Permethrin (Eurax) applied twice daily for 10 minutes; second application 7 to 10 days later, or
- Benzyl benzoate 25% solution applied topically; second application 7 to 10 days later, or
- Lufenuron (Ivexa) applied once weekly for 3 weeks; second application 7 to 10 days later
- Malathion (Ovide) 0.5% lotion, applied for 10 hours; a second application 7 to 10 days later
- Lindane shampoo: for recalcitrant disease, not to be used in children
- Ivermectin (Stromectol) 200 µg/kg PO once: treatment of choice for crusted scabies

**Pediculosis**

**Pediculosis Capitis**
- Malathion (Oxine) 0.5% lotion, applied for 8 to 12 hours before being washed off; approved for children older than 6 years, or
- Permethrin (Nix) 1% lotion, washed off after 10 minutes; second application 7 to 10 days later; approved for children older than 2 years
- Pyrethrins with piperidyl butoxide (RID) applied for 10 minutes
- Benzyl benzoate 25% solution
- Lindane shampoo: for recalcitrant disease, not to be used in children
- Ivermectin (Stromectol) 200 µg/kg on days 1, 2, and 10

**Pediculosis Corporis**
- Disinfection of clothes

**Pediculosis Pubis**
- Same treatment as pediculosis capitis: three times daily

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1Not FDA approved for this indication.
2Not available in the United States.
3Available in the United States from the Centers for Disease Control and Prevention.

Diseases Caused by Protozoa

**Cutaneous Amebiasis**
Intestinal amebiasis is caused by Entamoeba histolytica, which may rarely invade the skin and cause cutaneous amebiasis. The disease is transmitted by ingestion of food or water contaminated with cyst forms of the parasite and through fecal exposure during sexual contact.

Cutaneous amebiasis develops at the site of the invasion of the parasites into the skin from an underlying amebic abscess, usually at the perianal area or the abdominal wall. Cutaneous findings...
include purulent, foul-smelling nodules, cysts, and sinuses, which are associated with regional adenopathy and dysentery. Skin lesions grow rapidly and may lead to death if left untreated.

Diagnosis of cutaneous amebiasis is confirmed by microscopic identification of *E. histolytica* in the stool and in aspirates or biopsy samples obtained during colonoscopy, during surgery, or from the border of an ulcer. Treatment of choice for extraintestinal amebiasis is oral metronidazole (Flagyl) 750 mg PO three times daily for 7 to 10 days or tinidazole (Tindamax). Tinidazole was FDA approved in 2004 for the treatment of intestinal amebiasis in adults (2 g/day for 3 days) and children older than 3 years, and it appears to be as effective as and better tolerated than metronidazole. Either treatment should be followed by iodoquinol (Yodoxin) 650 mg PO three times daily for 20 days or paromomycin 25 to 35 mg/kg/day PO divided in three doses for 7 days.

Leishmaniasis

Leishmaniasis results from the infection with intracellular protozoan parasites belonging to the genus *Leishmania*. Leishmania parasites are transmitted to humans and other mammalian hosts (e.g., dogs, rodents) during feeding by infected female phlebotomine sandflies that serve as vectors. The parasites exist as promastigotes in the midgut of sandflies and as amastigotes (i.e., Leishman-Donovan bodies) within macrophages of humans and other mammals. Based on the extent and the severity of involvement in the human host, leishmaniasis may be clinically classified as cutaneous leishmaniasis, diffuse cutaneous leishmaniasis, mucocutaneous leishmaniasis, and visceral leishmaniasis.

Cutaneous leishmaniasis (New World or Old World form) begins as a small erythematous papule at the site of the bite of the sandfly, which evolves into an ulcerated nodule with a raised and indurated border (i.e., volcano sign) (Figure 1). The lesions gradually heal with a depressed scar. Diffuse cutaneous leishmaniasis is characterized by widespread cutaneous involvement without visceralization. Mucocutaneous leishmaniasis (known as espundia in South America) affects the skin, the mucosa, and the cartilages of the upper respiratory tract (especially the nose and the larynx) and may result in severe disfigurement. Visceral leishmaniasis results from the involvement of the bone marrow, spleen, and the liver, and it may lead to death if left untreated. It manifests with fever, splenomegaly, pancytopenia, and wasting. Post–kala azar dermal leishmaniasis may appear within a year after visceral disease independent of treatment, and it is characterized by macules, papules, and nodules, which are usually hypopigmented.

Diagnosis of leishmaniasis is based on finding the parasites in the skin from the lesion aspirate or biopsy by direct examination or culture. The leishmanin (Montenegro) skin test shows past and current infections, and it detects the inflammatory response in the skin after injection of phenol-killed parasites into the dermis. A past or current infection is also documented by an in vitro lymphocyte proliferation assay that requires a drop of blood from a finger prick. Polymerase chain reaction (PCR) techniques may be used to identify different *Leishmania* species. Circulating antibody levels are not considered a useful diagnostic sign.

Cutaneous leishmaniasis is usually self-limited and may not require treatment. Treatment of cutaneous leishmaniasis is indicated in case of numerous lesions or when lesions affect the face to avoid scarring. Therapies include sodium stibogluconate (Pentostam) 20 mg/kg/day IV or IM for 20 days. Meglumine antimoniate (Glucantime) 20 mg/kg/day IV or IM for 20 days or miltefosine (Impavido) 2.5 mg/kg/day PO (up to 150 mg/day) for 28 days may be used. Alternatively, intralesional injections of antimonials 1 mg/kg once weekly, cryotherapy, local heat, oral ketoconazole (Nizoral), topical amphotericin B, pentamidine (Pentam) 2 to 3 mg/kg IV or IM daily or every second day for four to seven doses, or topical paromomycin (applied twice daily for 10–20 days) may be used.

The production of antileishmanial antibodies does not correlate with resolution of the disease. Infection and recovery are associated with lifelong immunity to reinfection by the same species of *Leishmania*, although interspecies immunity may also exist.

Trypanosomiasis

There are three types of trypanosomiasis:

- American trypanosomiasis or Chagas’ diseases, caused by *Trypanosoma cruzi*
- East African sleeping sickness, caused by *Trypanosoma brucei rhodesiense*
- West African sleeping sickness, caused by *Trypanosoma brucei gambiense*

American trypanosomiasis (i.e., Chagas’ disease) is caused by the parasite *T. cruzi*, and it is endemic in Central and South America. The disease is transmitted by the bite of infected “cone-nosed” insects, by transfusion of infected blood, by organ transplantation, and across the placenta. During the acute stage, Chagas’ disease manifests with a painful erythematous nodule, known as chagoma, which is associated with regional adenopathy. The chronic stage manifests with cardiomyopathy, megaesophagus, and mega-colon. Diagnosis is confirmed by microscopic identification of the parasite in fresh anticoagulated blood, in blood smears, by lymph node biopsy or skin biopsy, or by culture. Treatment includes benznidazole (Radanil, Rochagan) 5 to 7 mg/kg/day PO in two doses for 60 to 90 days or nifurtimox (Lampit) 8 to 10 mg/kg/day PO in three or four doses for 90 to 120 days.

African trypanosomiasis (i.e., East and West African sleeping sickness) occurs in Africa and is transmitted by the bite of infected male and female tsetse flies. It manifests with a highly inflammatory, painful, red or violaceous, indurated nodule surrounded by an erythematous halo, called trypanosome chancre, at the site of the inoculation of the parasites. There is regional adenopathy. Later, the chancre resolves spontaneously, and the patient has fever, malaise, a generalized pruritic eruption with erythematous annular plaques or urticarial lesions, and central nervous system (CNS) involvement with personality changes, apathy, somnolence, coma, and death. Diagnosis is based on the identification of trypanosomes by microscopic examination in chancre fluid, affected lymph node aspirates, blood, bone marrow, or in the late stages of infection, cerebrospinal fluid.

Treatment of East African sleeping sickness consists of suramin (naphthylamine sulfonic acid, Germanin) 100 to 200 mg (test dose) IV and then 1 g IV on days 1, 3, 7, 14, and 21. For late disease with CNS involvement, melarsoprol B (a trivalent organic arsenical, Mel-B) is used in the following dosage regimen: 2 to 3.6 mg/kg/day IV for 3 days; after 7 days, 3.6 mg/kg/day for 3 days; and the latter repeated after 7 days. For West African sleeping sickness, treatment of choice is pentamidine isethionate (Pentam 300) 

1. Not FDA approved for this indication.
2. Not available in the United States.
3. May be compounded by pharmacists.
Diseases Caused by Helminths

Ascariasis
Ascariasis is caused by Ascaris species, mainly *Ascaris lumbricoides*. It is transmitted by the ingestion of eggs in soil contaminated with human feces. Skin involvement of ascariasis manifests with urticaria. Diagnosis is based on finding the adult worm or eggs in the feces. Treatment includes albendazole (Albenza) at 400 mg PO once or mebendazole (Vermox) 100 mg PO twice daily for 3 days (or 500 mg once) or ivermectin (Stromectol) at 150 to 200 μg/kg PO once.

Cutaneous Larva Migrants
Cutaneous larva migrans is also known as creeping eruption, with the first term describing a syndrome and the second a clinical sign found in various conditions. The syndrome cutaneous larva migrans is caused when various nematode larvae (i.e., hookworms, such as *Ancylostoma braziliense*, *Ancylostoma caninum*, *Bunostomum phlebotomum*) of dogs, cats, and other mammals penetrate and migrate through the skin. Cutaneous larva migrans is transmitted by skin contact to soil contaminated with animal feces. In humans, larvae are unable to reach internal organs and eventually die. Cutaneous larva migrans manifests with intensely pruritic, papular lesions, which evolve as the larvae migrate to a characteristic linear, minimally elevated, serpiginous tract that moves forward in an irregular pattern. Diagnosis is easily made clinically and is supported by a travel history or by possible exposure in an endemic area.

Treatment of choice consists of ivermectin (Stromectol) at a single dose of 200 μg/kg. In case of treatment failure, a second dose usually suffices. Ivermectin has an excellent safety profile, without any notable adverse events, and it has been used in millions of individuals in developing countries during onchocerciasis and filariasis control operations. It is contraindicated in children who weigh less than 15 kg (or are younger than 5 years) and in pregnant or breast-feeding women. Alternatively, repeated courses of oral albendazole (Albenza) at 400 mg daily for 3 days may be used. Treatment with oral thiabendazole (Mintezol) 50 mg/kg daily for 2 to 4 days has been associated with adverse events such as dizziness, nausea, vomiting, and intestinal cramps, and it is therefore not recommended. In the absence of multiple or widespread lesions, topical treatments may be considered, such as topical thiabendazole at 10% to 15%, applied three times daily for 5 to 7 days, which has similar efficacy with oral ivermectin and no adverse events.

Lymphatic Filariasis
Lymphatic filariasis is caused by the nematode *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*, and it is transmitted by mosquitoes. Adult worms result in a chronic inflammatory cell infiltrate around lymphatic vessels, causing their dilatation, hypertrophy, and obstruction. Many patients are asymptomatic, but some may develop fever with lymphangitis and lymphadenitis, chronic pulmonary infection, and progressive lymphedema leading to massive tissue thickening, especially of the legs and scrotum (i.e., elephantiasis). The overlying skin is thickened. Diagnosis is based on microscopic identification of the microfilariae in the blood and affected tissues.

Treatment consists of diethylcarbamazine (DEC,Hetrazan) in the following regimen: 50 mg on day 1, 50 mg three times daily on day 2, 100 mg three times daily on day 3, and 6 mg/kg in three doses on days 4 through 14. Prophylaxis with DEC 500 mg/day for 2 days each month is effective against *W. bancrofti* infection for travelers in endemic areas.

Onchocerciasis
Onchocerciasis (i.e., Blinding filariasis) is caused by the filarial nematode *Onchocerca volvulus*, which is transmitted by the blackflies *Simulium*. It may manifest with subcutaneous onchocercal nodules, acute or chronic dermatitis, depigmentation (i.e., leopard skin), and skin atrophy (i.e., lizard skin), and in later stages, it may manifest with lymphadenopathy and lymphedema. The microfilariae have a predilection for the eyes, and the infection can lead to blindness (i.e., river blindness). Diagnosis is based on identification of microfilariae in skin snips.

1Not FDA approved for this indication.
2Not available in the United States.
3May be compounded by pharmacists.
Diseases of the Skin

**Loiasis**
Loiasis (i.e., Calabar swellings) is caused by the parasite *Loa loa*, which is transmitted by deerflies (*Chrysops*). Cutaneous manifestations include pruritus, urticaria, and Calabar swellings, which are erythematous, warm, subcutaneous swellings associated with the migration of the worm through the subcutaneous tissues. Occasionally, there is subconjunctival migration of the adult worm, producing a migrating serpiginous lesion on the conjunctivae. Diagnosis is confirmed by identification of microfilariae in the blood by microscopic examination. DEC is the treatment of choice in the following regimen: 50 mg on day 1, 50 mg three times daily on day 2, 100 mg three times daily on day 3, and 9 mg/kg/day in three doses on days 4 through 14. Ivermectin (Stromectol) may cause encephalopathy in patients with a heavy *L. loa* infection. Prophylaxis with DEC is effective for *L. loa* in adults who travel in endemic areas.

**Schistosomiasis**
Schistosomiasis (i.e., snail fever) in humans is caused mainly by the trematodes *Schistosoma haematobium*, *Schistosoma japonicum*, and *Schistosoma mansoni*. All trematodes have a life cycle that involves the snail as an intermediate host. The infective cercariae leave the snail, swim, and penetrate the human skin, causing a pruritic papular dermatitis. The disease is transmitted by exposure to contaminated water with live cercariae or by drinking infested water. Skin findings of acute schistosomiasis include pruritic schistosomal dermatitis due to a hypersensitivity response to the cercariae and edema of the face, extremities, genitals, and trunk. Schistosomal fever (i.e., Katayama fever), lymphadenopathy, and diarrhea may also develop. Late skin findings (i.e., bilharziasis cutanea tarda) appear in patients with visceral disease and include firm, pruritic, grouped papules. Secondary infection, ulceration, and development of squamous cell carcinoma may follow. Diagnosis is confirmed by identification of the eggs in the urine or stool, and enzyme-linked immunosorbent assay (ELISA).

Treatment includes praziquantel (Biltricide) 40 mg/kg/day in two doses for 1 day (for *S. haematobium* and *S. mansoni*) or 60 mg/kg/day in three doses for 1 day (for *S. japonicum*).

**Cercarial Dermatitis**
Cercarial dermatitis (i.e., swimmer’s itch) is caused by cercariae (i.e., larvae) of nonhuman schistosomes that penetrate the skin and die without invading other tissues. It is transmitted by contact with fresh or salt water contaminated with cercariae. It manifests with extremely pruritic, erythematous macules of sudden onset, which evolve into papules, vesicles, and urticarial lesions located on parts of the body directly exposed to the water, while sparing clothed areas. Cercarial dermatitis is a self-limited disease, and treatment is symptomatic with topical steroids and oral antihistamines.

**Diseases Caused by Arthropoda**

**Human Scabies**
Scabies is a common skin infestation caused by the mite *Sarcoptes scabiei*, which is an obligate human parasite. Scabies is transmitted by direct contact with an infested individual or by contact with bedding and clothing. The incubation period for scabies is about 3 weeks, and reinfection results in symptoms within 1 to 3 days. Scabies is characterized by pruritus that usually worsens at night.

Papules, nodules, excoriations, and burrows may be found. Lesions are usually located on interdigital spaces, wrists, ankles, axillae, waist, and genitals. Scabies manifests as red-brown nodules that represent a hypersensitivity response. In adults, the head is usually spared, whereas the involvement of the scalp, palms, and soles is common in infants.

Crusted or Norwegian scabies manifests with hyperkeratotic papules or plaques of the hands and feet (often with nail involvement) and an erythematous scaly eruption on the face, neck, scalp, and trunk. Because pruritus is often absent, this disease can be misdiagnosed as psoriasis, eczema, or an adverse drug reaction. Lesions contain thousands of mites and are highly contagious. Crusted scabies mainly affects immunocompromised patients (e.g., patients with human immunodeficiency virus infection), mentally retarded persons, or debilitated patients.

Diagnosis is based on the microscopic identification of mites or their eggs or feces from burrows or papules. Treatment should be applied from the neck down in adults, and in infants, application should include the scalp and face (avoiding the eyes and mouth). Treatment includes 5% permethrin (Elimite) applied for 10 hours and repeated after 1 week. A 2.5% benzyl benzoate solution is also efficacious in adults, and because of low toxicity, it is recommended in a lower concentration (10%) for children older than 4 months and for women during pregnancy. Sulfur ointments in petrolatum at concentrations of 6% to 10% may be used for scabies in children and pregnant women. Alternative treatments for scabies include crotamiton 10% (Eurax) applied once daily for 2 days, or ivermectin (Stromectol) as a single- or two-dose regimen of 200 μg/kg/dose can be used. Aggressive treatment with ivermectin at a single dose of 200 μg/kg, repeated after 2 weeks with or without topical 5% permethrin cream (two applications, 1 week apart) and keratolytics (5% salicylic acid ointment applied twice daily) is the treatment of choice for crusted scabies. All sexual and close personal and household contacts within the preceding 6 weeks should be treated simultaneously. Bedding and clothing should be decontaminated (i.e., machine washed and dried using the hot cycle or dry cleaned) or removed from body contact for at least 3 days, because the mite dies when separated from the human host.

**Pediculosis**
Pediculosis (i.e., lice) is a contagious dermatosis, caused by lice, which are blood-sucking, wingless insects and are obligate human parasites. Two species of lice infest humans causing three clinical forms of infestation: *Pediculus humanus capitis* (i.e., head louse), *Pediculus humanus corporis* (i.e., body louse), and *Phthirus pubis* (i.e., pubic louse). The body louse is the only louse that can carry human disease, including rickettsioses and epidemic typhus.

**Pediculosis Capitis**
Pediculosis capitis is caused by *P. humanus capitis*, and it is transmitted by close contact or by fomites with combs, brushes, towels, and hats. It manifests with pruritus (due to the saliva of the louse), excoriations, nape dermatitis, secondary bacterial infection, and cervical and suboccipital lymphadenopathy. Diagnosis is based on identification of lice and eggs or nits on the hair and on fluorescence of nits with Wood’s light. Visible nits are deposited on the hair shaft, close to the scalp. After adequate treatment, nits found at 1.0 to 1.5 cm from the scalp are not alive.

Treatment includes malathion (Ovide) 0.5% lotion applied for 8 to 12 hours or permethrin (Nix) 1% cream rinse applied to shampooed hair for 10 minutes. A second application with permethrin is recommended 1 week later to kill hatching progeny. Alternatively, pyrethrins with piperidyl butoxide (RID) can be applied and washed off after 10 minutes. Benzyl benzoate 25% solution is

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1 Not FDA approved for this indication.
2 Exceeds dosage recommended by the manufacturer.
3 Available in the United States from the Centers for Disease Control and Prevention.
4 Not FDA approved for this indication.
5 May be compounded by pharmacists.
mainly a scabicide, but it may also be used as a pediculicide. Ivermectin (Stromectol)\textsuperscript{1} can be used at a dose of 200 µg/kg on days 1, 2, and 10. Vinegar\textsuperscript{1} may be used to facilitate nit removal from the hair shaft, using a fine-toothed comb. Bedding, clothing, and headgear should be decontaminated (as for scabies) or removed from body contact for 2 weeks. Information for managing head lice can be found at the National Pediculosis Association web site (http://www.headlice.org).

**Pediculosis Corporis**

Pediculosis corporis (i.e., vagabond’s itch) is caused by *P. humanus corporis*, which lives and reproduces in the lining of clothes and leaves the clothing only for feeding from the skin. This disease is usually found among vagabonds. Transmission occurs mainly through contact with contaminated clothing or bedding. Clinical manifestations include pruritus, excoriations, and small, red macules that usually occur on the back. Clothes should be examined carefully for lice.

Treatment is the same as for pediculosis capitis. Dry heat or washing in hot water followed by ironing is effective in killing the lice and their ova in clothing. Items that cannot be washed should be removed from body contact for 2 weeks.

**Pediculosis Pubis**

Pediculosis pubis is caused by *P. pubis* and affects the pubic hair. However, if left untreated, it may also affect very hairy regions of the chest, abdomen, axillary region, and especially in children, the eyelashes, edge of the scalp, and eyebrows. Patients present with pruritus. Useful diagnostic signs include small, blue-gray macules on the trunk, thighs, and axillae (i.e., taches bleuâˆtres or maculae ceruleae) due to conversion of bilirubin to biliverdin by the saliva of the louse and a brown “dust” found on underclothing due to the excreta of the insects. *P. pubis* is transmitted mainly by sexual contact, but it also may be transmitted by clothing or from parents to children.

Patients with pubic lice should be evaluated for other sexually transmitted diseases. Treatment of pediculosis pubis is the same as for pediculosis capitis. Bedding and clothing should be decontaminated (as for scabies) or removed from body contact for 2 weeks. Attention should be paid to treating sexual partners within the previous month because they are a common cause of reinfection. For infested eyelashes and eyebrows, ophthalmic-grade petroleumatum ointment may be used two to four times daily for 10 days, and lice and nits should be carefully removed from the eyelashes, edge of the scalp, and eyebrows. Patients present with pruritus. Useful diagnostic signs include small, blue-gray macules on the trunk, thighs, and axillae (i.e., taches bleuâˆtres or maculae ceruleae) due to conversion of bilirubin to biliverdin by the saliva of the louse and a brown “dust” found on underclothing due to the excreta of the insects. *P. pubis* is transmitted mainly by sexual contact, but it also may be transmitted by clothing or from parents to children.

Patients with pubic lice should be evaluated for other sexually transmitted diseases. Treatment of pediculosis pubis is the same as for pediculosis capitis. Bedding and clothing should be decontaminated (as for scabies) or removed from body contact for 2 weeks. Attention should be paid to treating sexual partners within the previous month because they are a common cause of reinfection. For infested eyelashes and eyebrows, ophthalmic-grade petrolatum ointment may be used two to four times daily for 10 days, and lice and nits should be carefully removed from the eyelashes with forceps.

References

Diseases of the Skin

Melanocytes. Deposition of melanin in the epidermal layers visibly refers to decrease of melanin, melanocytes, or both in the production, melanocyte number, or both in the skin. Hypopigmentation refers to melanotic causes of skin color change, differentiating it from skin color changes due to blood, carotene, bilirubin, or other causes. Hyperpigmentation refers to an increase in melanin production, melanocyte number, or both in the skin. Hypopigmentation refers to decrease of melanin, melanocytes, or both in the skin. Depigmentation refers to the absence of both melanin and melanocytes. Deposition of melanin in the epidermal layers visibly appears as a yellow to brownish hue. Dermal deposition appears as blue or blue-gray, with mixed epidermal and dermal melanin deposition appearing gray or blue-brown.

Evaluation
A thorough history and visual inspection of the pigmentary disorder can provide useful clues to the diagnosis, particularly recognition of pigmentary patterns (diffuse, circumscribed, linear, or reticulated). Further examination may be achieved by using the Wood’s lamp to differentiate epidermal from dermal melanin.

General Recommendations for All Pigmentary Disorders
Broad-spectrum sunscreen with an SPF of 30 is recommended, in addition to wearing protective clothing. Avoiding prolonged sun exposure is also desired, if possible.

Hyperpigmentation
Ephelides

Description
Ephelides (freckles) are multiple, small (1–4 mm), light to dark brown macules with poorly defined margins that occur on sun-exposed areas of the body (face, upper back, arms). They are more commonly found in children (fading with age), fair-skinned persons, and those with red or blonde hair (especially those of Celtic ancestry). A relationship has been shown between painful sunburns in youth and development of ephelides, and the macules become darker with greater UV exposure. They are thought to be genetic in origin, following an autosomal dominant pattern, and are strongly associated with variants in the melanocortin-1-receptor (MC1R). Ephelides are significant because they are associated with an increased risk of melanoma and nonmelanoma skin cancer, perhaps serving as a marker for sun susceptibility.

Treatment
Although treatment is not necessary, modalities include either hydroquinone 4% (Claripel, Eldopaque Forte) or glycolic plus kojic acid combination (Brown Spot Night Gel) plus maximum ultraviolet A (UVA)-blocking sunscreen in the morning and tretinoin 0.1% cream (Retin-A) in the evening. Other therapies have included cryotherapy, lasers, and chemical peels.

Postinflammatory Hyperpigmentation

Description
Postinflammatory hyperpigmentation is a very common condition that occurs as a result of a previous or ongoing inflammatory process, most commonly acne vulgaris, atopic dermatitis, infections, and phototoxic reactions and as a result of treatment with topical medications, chemical peels, and lasers. Postinflammatory hyperpigmentation occurs more commonly in persons with darker skin.

1Not FDA approved for this indication.
pigmentation and appears as dark patches or macules with indistinct margins at the location of the inciting inflammatory event.

**Treatment**
Primary treatment is aimed at treating the inciting cause of the hyperpigmentation. Additional effective therapies include 4% hydroquinone alone or in combination with a topical steroid. Other combination treatments include mequinol 2% plus tretinoin 0.01% combination\(^1\) twice daily or fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%\(^1\) once daily. Treatment must be temporarily stopped if irritation occurs. Broad-spectrum sunscreen should also be employed.

**Hypopigmentation or Depigmentation**

**Pityriasis Alba**

**Description**
Pityriasis alba is a childhood or adolescent condition that affects all races. It begins as an erythematous macule with ill-defined borders. The erythema fades after a few weeks, leaving two or three round, well-defined, paler macules with overlying powdery white scale, ranging in size from 0.5 cm to 5 cm in diameter. These eventually transition to smooth, hypopigmented lesions, which are generally located on the face. The pathogenesis of this disorder is unknown.

**Treatment**
Pityriasis alba is thought to be a self-limited skin disease. However, general treatment guidelines include use of emollients and lubricant, use of sunscreen, and decreasing sun exposure. Lesions limited to the face may be treated with hydrocortisone 1% (Lanacort 10 Crème)\(^1\) or other mild, nonfluorinated steroid. More-potent steroids may be used for lesions on the body, including hydrocortisone valerate 0.2% (Westcort)\(^1\) or alclometasone dipropionate 0.05% (Aclovate).\(^1\) However, these can lead to atrophy if used over an extended period. Newer, safer, effective alternatives include tacrolimus 0.1% ointment (Protopic)\(^1\) twice daily. Side effects include a burning sensation that fades over time. Extensive disease that is not amenable to topical therapy might benefit from photochemotherapy (psoralen plus UVA [PUVA] or UVB alone).

**Vitiligo**

**Description**
Persons with vitiligo acquire sharply demarcated, depigmented macules in a localized or generalized distribution. These macules appear milky white as compared with the surrounding normally pigmented skin. Lesions can increase in size. There is no predilection for race or sex, and three quarters of patients generally present before the age of 30 years.

**Treatment**
General recommendations include the use of sunscreen, avoidance of the sun, and use of protective clothing. Treatments for localized vitiligo (<20% of body surface area) include cosmetics, a 2-month trial of topical treatment (potent or very potent corticosteroid or calcineurin inhibitor), excimer laser, or topical PUVA. Adults who have failed treatments for localized vitiligo may be considered for narrow-band UVB, oral PUVA, or surgical treatment, which includes split-skin grafting, transfer of suction blisters, or autologous epidermal suspensions added to dermabraded skin (followed by UVB). Surgical candidates should have localized, limited involvement and should not demonstrate lesion enlargement or Koebner phenomenon for 12 months prior to treatment. Patients with more than 20% body involvement may be considered for narrow-band UVB (311 nm) or oral PUVA. Those with greater than 50% body involvement or disfiguring facial involvement may be considered for complete depigmentation with monobenzyl ether of hydroquinone (Benoquin 20%), 4-methoxyphenol, or the Q-switched ruby laser (694 nm). Children are generally not offered surgical treatment, and oral PUVA is relatively contraindicated in children younger than 10 years.

**Idiopathic Guttate Hypomelanosis**

**Description**
This is an acquired, asymtomatic leukoderma with multiple, circular, smooth, small macules that have a porcelain white color. Black dots are occasionally observed within the macules. The macules increase in number with age, but they generally do not increase in size. They are most commonly located on sun-exposed areas of the upper and lower extremities.

**Treatment**
Treatments have included cryotherapy, dermabrasion, surgical minigrafting, and intralesional steroids; however, none of these have shown consistent acceptable results. Phototherapy has not been shown to be effective.

**Postinflammatory Hypopigmentation**

**Description**
Postinflammatory hypopigmentation is the result of an inciting inflammatory event leading to lesions that are off-white or tan, with ill-defined borders. This entity is noticed more commonly in those with darker skin.

**Treatment**
Hypopigmentation resolves with treatment of the underlying condition. Topical cosmetics may be useful. Topical corticosteroids and topical PUVA therapy may also be used in patients who have lesions in cosmetically distressing areas.

**References**

PREMAiNLIGANT CUTANEOUS AND MUCOSAL LESIONS

Method of Juliet Aylward, MD

CURRENT DIAGNOSIS

**Actinic Keratoses or Cheilitis**
- Flesh-colored, red, or pigmented lesions with thick or delicate keratotic scale
- Swelling, fissures, and scaling on lower lip
- Sun-exposed sites
Identification and clinical monitoring of premalignant skin lesions can reduce the morbidity and mortality of skin cancer for many patients with diverse histories and exposures. The link between precancerous and cancerous lesions and ultraviolet (UV) light exposure has been studied extensively. Some patients do not understand the importance of or choose not to adhere to sun-protection precautions and the prudent use of sunscreens. The cause of premalignant lesions also includes human papillomavirus (HPV) disease, arsenic exposures, and degeneration of benign nevi, birthmarks, and neoplasms.

Although certain exposures and conditions are associated with premalignant lesions, some groups of patients are at higher risk for precancerous and cancerous lesions. In many cases, these cancers are rapidly progressive, high grade, and aggressive. Patients who are at high risk are immunocompromised due to human immunodeficiency virus infection or acquired immunodeficiency syndrome, have heritable immunodeficiencies, have had effective immunosuppression of chronic lymphocytic leukemia, have undergone organ transplantation, or are on immunosuppressive medications. An increased susceptibility to infection with oncogenic HPV types may be important in the pathogenesis of malignancies in these patients. Genodermatoses associated with a higher risk of skin cancer include xeroderma pigmentosa, oclocutaneous albinism, Bazex syndrome, and nevoid basal cell carcinoma syndrome. A history of UV exposure and cigarette smoking further compounds the risk for many of these patients.

A variety of dermatoses and neoplasms have a demonstrated association with development of malignancies, although these benign conditions or lesions are not necessarily precancerous. In certain long-standing skin diseases, persistence or progression of characteristic lesions despite apparent appropriate treatment may herald development of skin cancer. Similarly, atypical appearance of or change in a previously stable lesion of a skin condition or in a previously stable neoplasm is suspicious. These conditions include Zoon balanitis or vulvitis, discoid lupus erythematosus, lichen planus, lichen sclerosus, lichen planopilaris, and chronic radiodermatitis. The neoplasms include nevus sebaceous, plexiform neurofibromas, and leuoplakia or erythroplakia. Scars, epitomized by the persistent scarring seen in dystrophic epidermolysis bullosa, and nonhealing wounds (e.g., burns, chronic ulcers) also may provide sites for malignant growth.

By recognizing these risk factors, predispositions, special populations, and associations, the practitioner can identify premalignant lesions in at-risk patients and recommend appropriate follow-up evaluation and treatment. This approach is essential for prevention and early detection of various types of cancers of cutaneous and mucosal surfaces. Lesions that progress, become symptomatic, become locally destructive or disfiguring, do not respond to appropriate treatment, or change their clinical appearance or behavior should be evaluated for malignancy. Biopsy and referral to a dermatologist are recommended.

**Actinic Keratoses or Cheilitis**

**Clinical Manifestations**

Precursors to squamous cell carcinoma in situ (SCCIS) and squamous cell carcinoma (SCC) can develop on cutaneous and mucosal surfaces subjected to intense, intermittent, or frequent sun exposure. They manifest as flesh-colored, red, or pigmented papules or plaques. Some are rather firm and indurated with a hard scale; others are thin and friable, with a more delicate scale or without scale, appearing shiny and atrophic. Clinical diagnosis is facilitated by light palpation of sun-exposed sites with the fingertips because the characteristic, gritty, sandpaper-like scale can be very prominent. Involvement can range from multiple or few discrete lesions to an ill-defined zone or field. Occurrence on the lip, often exclusively the lower lip, may be associated with pain, swelling, and fissures. Most lesions remain stable for years without progression or degeneration. The absolute risk is not known but is estimated at 0.1% to 10% per year. Lesions that persist after treatment or show rapid progression should raise suspicion for malignant degeneration. Suspicion should be elevated if mucosal lesions are ulcerated, and biopsy is recommended.

**Atypia in Melanocytic Nevi**

- "Fried egg" appearance with a papular center on a macular base
- Asymmetry, ill-defined borders, variegated color, diameter larger than 6 mm, ulceration, bleeding, pain, or pruriitus in a new or previously stable pigmented lesion

**Current Therapy**

**Actinic Keratoses or Cheilitis**

- Physical methods: curettage, liquid nitrogen, dermabrasion, ablative laser resurfacing
- Nonselective topical chemical agents: glycol acid 20%, tri-chloroacetic acid 10% to 30%
- Selective topical chemical agents: 5-fluorouracil (Carac, Efudex), diclofenac sodium (Solaraze), ingenol mebutate gel (Picato), imiquimod (Aldara, Zyclara), 5-aminolevulinic acid (Levulan Kerastick) or methyl aminolevulinate (Mativex) activated by a light source, and retinoids, including tretinoin (Retin-A), adapalene (Differin), and tazarotene (Tazorac)
- Oral agents: retinoids

**Arsenical Keratoses**

- Surgery and modalities used for actinic keratoses

**Porokeratoses**

- Surgery and modalities for actinic keratoses

**Human Papillomavirus Disease**

- Verrucous, hyperkeratotic lesions on palms and soles
- Fleshy, hyperkeratotic lesions or shiny, atrophic lesions or erosions in the anogenital region
- White, adherent, keratotic lesions on mucosal surfaces; may become verrucous and exophytic

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**Arsenical Keratoses**

- Surgery and modalities used for actinic keratoses

**Porokeratoses**

- Surgery and modalities for actinic keratoses

**Human Papillomavirus Disease**

- Blistering agents: liquid nitrogen, Cantharone (0.7% cantharidin), podophyllin 25% in tincture of benzoin (Podoco-25), purified podophyllotoxin 0.5% solution or gel (Condylox)
- Keratolytics: topical salicylic acid products (e.g., Compound W, Wart-Off, Dr. Scholl’s, Duofilm, Salactic, Mediplast, Sal-Acid), topical retinoids, and topical urea 10% to 40% (Carmol, Gordon’s)
- Physical methods: curettage, liquid nitrogen, surgery, ablative laser, electrofulguration, occlusive tapes such as duct tape
- Immunotherapy: imiquimod (Aldara), intralesional candida or mumps antigen injections
- Oral agents: cimetidine (Tagamet)
- Other: sinecatechins (Veregen and Polyphenon E)

**Atypia in Melanocytic Nevi**

- Close clinical observation and mole mapping
- Surgery, curettage, ablative laser

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1 Not FDA approved for this indication.
2 May be compounded by pharmacists.
Treatment

Limited mechanical removal of discrete lesions is possible with curettage. Liquid nitrogen applied with a cotton-tipped applicator or spraying device is a common and effective treatment for cutaneous and mucosal lesions. Lesions can be treated until they appear white or frozen; treatment is for 8 to 10 seconds on the lip and other delicate tissues. Thicker skin and thicker lesions require freeze times of 20 seconds or to the patient’s tolerance. After this, a second cycle may be used immediately. Some lesions may require two or three such treatments separated by 4 to 12 weeks before resolution. Posttreatment pain, swelling, and blistering can be limiting. Because this modality is nonselective, normal and atypical cells are affected equally.

Other destructive modalities may be beneficial for discrete lesions; these include dermabrasion and ablative lasers such as carbon dioxide (CO2) and erbium:yttrium—yttrium—aluminum—garnet (Er: YAG) lasers.

Treatment of individual lesions with chemical peeling agents such as glycolic acid 20% (e.g., Biomedic MicroPeel Solution) and trichloroacetic acid 10% to 30% can be effective and repeated. Carbon dioxide (CO2) and erbium:yttrium—yttrium—aluminum—garnet (Er: YAG) lasers.

Other chemical peeling agents such as salicylic acid 5% [Tretin-A], and 7% [Fluoroplex], 10% to 30% [Fluoroplex], and 5% cream [Efudex] for cutaneous surfaces and 1% [Fluoroplex], 2% [Efudex], and 5% solution [Efudex] for mucosal surfaces can be applied in various regimens, once or twice daily for 2 to 6 weeks as the patient tolerates. More delicate mucosal tissues should be treated once or twice daily for 1 to 3 weeks. Use is limited by development of irritation, pain, and skin breakdown. Because this is a selective chemical treatment, affected cells are targeted, and a more vigorous response should lead to more significant improvement. Inflammatory response is individual, and for patients who are not tolerating treatment well, application can be reduced to once to three times weekly. Breaks or time off during a treatment course can be introduced. The treatment course can be abbreviated if needed. An effective treatment course also may treat early or in situ lesions of SCC or basal cell carcinoma (BCC) in the field.

Other topical chemotherapeutic field treatments include diclofenac sodium 3% gel (Solaraze) applied once or twice daily for 8 to 12 weeks. The inflammatory response is attenuated and therefore may be better tolerated by patients. Concomitantly, improvement is less dramatic. A shorter course may be preferred, so ingenol mebutate (Picato) as 0.015% gel can be applied to the face and scalp for 3 consecutive days or can be applied as 0.05% gel to the trunk and extremities for 2 consecutive days. Imiquimod 5% cream (Aldara) may be applied daily for 3 to 6 weeks or twice daily for 3 days per week for 4 to 8 weeks. Another regimen is application once or twice per week for 4 to 8 months, used continuously or in alternating 1-month cycles. The daily dosing schedule and treatment course should be decreased by about one half for mucosal surfaces. The disadvantage is unpredictability of response. Imiquimod 2.5% and 3.75% cream (Zyclara) can be used each night for two 2-week treatment cycles separated by a 2-week no-treatment period for the face and scalp. Imiquimod also may treat early or in situ lesions of SCC and BCC in the field.

Photodynamic treatment is another selective treatment for individual lesions or field treatment. Application of 20% 5-aminolevulinic acid (ALA [Levulan Kerastick]) or 16% methylaminolevulinate (MAL [Metvix]) to affected areas is followed by activation by a light source. Treatment can be completed by the practitioner in 1 day. Before application, scale should be removed with acetone, chemical peel, or microdermabrasion. Alternatively, the patient can apply 5-fluorouracil cream or solution for 5 days or any topical retinoid [tretinoin [Retin-A], adapalene [Differin], or tazarotene [Tazorac]1) for 1 month. ALA is available as a cream and requires occlusion for 3 hours. To achieve the best response, two treatments should be given at 1-week intervals. The light source for activation of ALA is blue light (412–422 nm) and for activation of MAL is red light (570–670 nm). To treat discrete lesions with ALA or MAL, laser (385 or 595 nm) or intense pulsed light (560–1200 nm) may be used. Like 5-fluorouracil and imiquimod, photodynamic therapy may treat early or in situ lesions of BCC or SCC in the field.

Topical (tretinoin, adapalene, or tazarotene) and oral (acitretin [Soriatane])1 retinoids can decrease development of actinic keratoses and nonmelanoma skin cancer in at-risk individuals. Efficacy is relatively mild, but any topical retinoid can be used each night indefinitely as tolerated by the patient. Acne and early signs of aging improve with this regimen. Oral retinoids can be used daily or every other day at the lowest dose (acitretin 10 mg) producing clinical improvement. The dose should be titrated up (to 50 mg maximum) as needed and as tolerated. Benefits are conferred only with maintenance of retinoid therapy.

Arsenical Keratoses

Clinical Manifestations
The small, punctate, hyperkeratotic lesions of arsenical keratoses are seen on the palms and soles of patients exposed to arsenic through contaminated well water and various medications. Carcinoma may develop after 10 to 20 years and evolve from precancerous keratoses or on any skin surface.

Treatment
Although acute toxicity can be treated with chelation, it has little value in chronic exposure. As for actinic keratoses, treatment of arsenical keratoses includes cryotherapy, topical chemotherapy, photodynamic therapy, and retinoids.3 Discrete lesions can be treated with surgery or curettage.

Porokeratoses

Clinical Manifestations
The classic porokeratosis has a smooth, atrophic center surrounded by a grooved ridge of hyperkeratosis called a cornoid lamella. The plaque form (i.e., Mibelli’s porokeratosis) is large and progressive, often appearing early in life. The disseminated superficial type favors sun-exposed sites and manifests as numerous, small, annular papules. The linear type may be generalized or segmental and often manifests very early in life. Only the punctate keratotic papules seen in porokeratosis palmaris, plantaris et disseminate have no clinically evident cornoid lamellae. Malignant transformation occurs mostly commonly in the linear type, followed by the Mibelli type. It is rare in the disseminated type and has not been reported in the punctate type.

Treatment
Treatment modalities include those described for actinic keratoses and surgical excision may be beneficial.

Human Papillomavirus Disease

Clinical Manifestations
The clinical manifestations of precancerous HPV infection on cutaneous and mucosal surfaces are diverse. The initial appearance and clinical behavior of verrucous carcinoma (i.e., Buschke- Lowenstein tumor on the genitals and oral florid papillomatosis) is as plantar, genital, and mucosal HPV disease; verrucous hyperkeratotic papules and plaques on the plantar surface; fleshy or hyperkeratotic papules in the anogenital region; and white, adherent keratotic plaques or leukoplakia of the mucosal surfaces. The clinically benign appearance and behavior change may signal malignant degeneration. Lower-risk types HPV-6 and -11 or high-risk HPV-16 may be implicated.
HPV-8, -16, -31, and -33 may be the causative agents in premalignant anogenital squamous intraepithelial lesions. The preferred terms *vulvar intraepithelial lesions/neoplasia* (VIL/N), *anal intraepithelial lesions/neoplasia* (AIL/N), and *penile intraepithelial lesions/neoplasia* (PIIL/N) have replaced the confusing terminology Bowen’s disease, erythroplasia of Queyrat, and Bowenoid papulosis for these anogenital lesions. Dermatologists reserve the term *bowenoid papulosis* for discrete, fleshy, red-brown papules with a better prognosis that are seen in younger patients. Clinical appearance includes verrucous keratotic plaques, erosions, Bowenoid-papulosis–type lesions, erosions, and erythematous, well-demarcated plaques, which may be shiny on the glans penis.

Progressive verrucous leukoplakia may appear as benign leuko- plakia early—hyperplastic, thin, white plaques of the mucosal surface. These slowly progress to verrucous exophytic masses, many of which degenerate to SCC. HPV-16 infection has been associated with this multifocal premalignant condition.

Epidermodysplasia verruciformis (EDV) is a rare, inherited condition that predisposes to infection with the less common viral types of HPV-5, -8, -9, -12, -14, -15, -17, -19, -25 through -36, and -38 and with the more common types of HPV-3 and -10. This leads to flat verrucous papules on the extremities, face, and neck, which may be numerous and may coalesce. Lesions similar to fine versicolor may develop over the trunk. SCC develops in 30% to 60% of these patients, and HPV-5, -8, and -47 are identified in 90% of the lesions.

**Treatment**

Eradication of HPV infection is challenging and often requires months of treatment. Observation may be reasonable for certain lesions with clinically benign appearance and behavior, and spontaneous resolution may occur.

Lesions of nonmucosal sites, including the planar feet, can be treated by freezing with liquid nitrogen for 10 to 30 seconds for two cycles. This may need to be repeated every 3 to 6 weeks until resolution. Another blistering agent, Cantharone (0.7% cantharidin [Canthacur]) can be applied under occlusion for 6 to 24 hours. The advantage is painless application, but individual responses are unpredictable. Hyperkeratotic lesions, such as those on the planar surface, require more aggressive use of these modalities. Imiquimod (Aldara) applied daily can be beneficial, but it may require 6 months of treatment. Constant use of occlusive tapes such as duct tape has demonstrated efficacy and may be combined with any treatments. Between liquid nitrogen treatments or as adjunctive therapy, use of keratolytics such as topical salicylic acid products (e.g., liquid [Compound W, Wart-Off, Dr. Scholl’s, Duofilm], film [Salactic], plaster [Mediplast, Duofilm, Sal-Acid], compounded in ointment), topical retinoids, and topical urea or phenol may be compounded by pharmacists.

For treatment of lesions in the anogenital region, liquid nitrogen or as adjunctive therapy, use of keratolytics such as topical salicylic acid products (e.g., liquid [Compound W, Wart-Off, Dr. Scholl’s, Duofilm], film [Salactic], plaster [Mediplast, Duofilm, Sal-Acid], compounded in ointment), topical retinoids, and topical urea or phenol, may require 6 months of treatment. Observation may be reasonable for certain lesions with clinically benign appearance and behavior, and spontaneous resolution may occur.

**References**


A pressure ulcer is the visible evidence of pathologic changes in blood supply to the dermal and underlying tissues, usually because of compression of the tissue over a bony prominence.

A differential diagnosis of ulcer type is critical to treatment. Chronic ulcers of the skin include arterial ulcers, venous stasis ulcers, diabetic ulcers, and pressure ulcers. Pressure ulcers generally appear in soft tissue over a bony prominence. A classic presentation aids the diagnosis. For example, arterial ulcers occur in the distal digits or over a bony prominence, diabetic ulcers occur in regions of callus formation, and venous stasis ulcers occur on the lateral aspect of the lower leg. However, atypical presentations may occasionally obscure the etiology. The treatment of these various etiologies differs considerably. This discussion is limited to the treatment of pressure ulcers and should not be used to treat other types of ulcers.

Seven principles of management guide treatment of pressure ulcers. The chief cause of these ulcers is pressure applied to the tissues that compromises blood flow. Therefore, the first treatment principle is to relieve pressure. Pressure relief can be obtained by positioning the patient frequently at a fixed interval to relieve pressure over the compromised area. Turning and positioning may be difficult to achieve because of a patient’s self-positioning or medical treatments that interfere with the ability to position the patient. Because of this difficulty, a number of medical devices are designed in an attempt to relieve pressure. These devices can be classified as static or dynamic. Static devices include air-, gel-, or water-filled containers that reduce the tissue-surface interface. Dynamic devices use a power source to inflate compartments that support the patient’s weight or alternate the pressure on different areas of the body. Choose a static device when the patient has good bed mobility. Choose a dynamic device when the patient cannot self-position in bed.

At the present time, results of reported clinical trials do not favor one device over another. The choice should be based on durability, ease of use, and patient comfort. A simple check for so-called bottoming out should be done for all devices. Your hand should be inserted palm upward under the patient’s sacrum between the device and the bed surface. If there is not an air column between the patient and the bed surface, the device is ineffective and should be changed. No device is effective in reducing heel pressure, the second most common site for pressure ulcers. Bridging with pillows is effective in reducing heel pressure in immobile patients; patients with high bed mobility may require boot devices to elevate the heel off the bed surface. Patients who fail to improve or who have multiple pressure ulcers should be considered for a dynamic-type device, such as a low-air-loss bed or air-fluidized bed.

Studies in turning and positioning suggest an optimum interval of 4 hours while on a pressure-reducing device. More frequent turning schedules, including the often-suggested 2-hour interval, have not been demonstrated to prevent pressure ulcers. Recent prevention studies after hip fracture have failed to demonstrate effectiveness of turning or pressure reduction on ulcer incidence.

The second principle of pressure ulcer therapy is to assess pain. Pressure ulcers do not always result in pain, particularly in insenate patients. However, some pressure ulcers do result in pain and should be treated aggressively. Oral or parenteral pain medications should be used to control symptoms.

The third principle of ulcer therapy is to assess nutrition and hydration. Pressure ulcers occur in sicker individuals in whom nutrient intake may be reduced by coexisting illness. Increased intake of protein (1.2 to 1.5 g/kg/day) is associated with higher healing rates. Achievement of high protein intake may be difficult because of anorexia of aging or anorexia associated with coexisting diseases. Adequate calories, adjusted for stress (30 to 35 kcal/kg/day), should be prescribed. Adequate dietary intake should provide adequate vitamins and minerals. No difference in healing rates is associated with supertherapeutic doses of vitamin C or zinc. If adequate dietary intake is compromised, a supplemental vitamin/mineral prescription at RDA (recommended daily allowance) doses should be considered. Adequate hydration can be maintained by 30 mL/kg/day of water. The decision to institute enteral feeding in patients with pressure ulcers who are unable to maintain adequate oral intake should not be undertaken lightly. The decision to use enteral feeding must consider the patient’s wishes, overall goal of care, and the complications of enteral feeding. Recent studies surprisingly observed that the use of percutaneous gastroscopy feedings increased the incidence of pressure ulcers and was associated with poorer healing, perhaps because of adverse patient selection.

The fourth principle of pressure ulcer management requires removing necrotic debris. Phagocytosis removes necrotic debris naturally. Accelerating the rate of removal may shorten healing time. Options include sharp surgical débridement, mechanical débridement with gauze dressings, application of exogenous enzymes, or autolytic débridement under occlusive dressings. Choose surgical débridement if the ulcer is infected. Surgical débridement is the fastest method but may remove some viable tissue, cause discomfort, and is the most expensive method, especially if done in an operating room. Applying moist gauze that is allowed to adhere to the ulcer bed by drying is a form of débridement. When the dry dressing is removed, nonselective tissue removal occurs. This method can be associated with discomfort, may delay healing while débridement is in progress, and is often defeated when the dressing is remoistened before removal. Enzymatic débridement can digest necrotic material. Only one enzymatic preparation is currently available in the United States: collagenase. Enzyme preparations are nonselective, possibly resulting in some damage to fibroblasts, epithelial cells, or granulation tissue. Enzymatic débridement is slower, can be associated with discomfort, and should be limited in duration until a clean wound bed is obtained. Autolytic débridement is achieved by allowing autolysis under an occlusive dressing. Both enzymatic and autolytic débridement may require 2 to 6 weeks to achieve a clean wound bed. A total of five clinical trials did not show that enzymatic débridement increased the rate of complete healing in chronic wounds compared to control treatment. Unless clinically infected, heel ulcers are better left underebrided because they occur in poorly vascularized tissues.

The fifth principle of pressure ulcer management is to maintain a moist wound environment. Maintaining a moist wound environment is associated with more rapid healing rates compared to dressings that are allowed to dry. Continuously moist saline gauze is the historical standard dressing for stage II through IV pressure ulcers. Care must be taken to change the gauze frequently to prevent drying because this may delay healing. Newer wound dressings provide a low moisture vapor transmission rate (MVTR), a measure of how quickly the dressing allows drying. A MVTR of less than 35 g of water vapor per square meter per hour is required to maintain a moist wound environment. Woven gauze has a MVTR of 68 g/m²/hour, and impregnated gauze has a MVTR of 57 g/m²/hour. By comparison, hydrocolloid dressings have a MVTR of 8 g/m²/hour. Dressings with low MVTR provide a healing environment that encourages granulation tissue formation and epithelialization.

The use of occlusive-type dressings is more cost effective than gauze dressings primarily because of a decrease in nursing time for dressing changes. A meta-analysis of five clinical trials comparing a hydrocolloid dressing with a dry dressing demonstrated that treatment with a hydrocolloid dressing resulted in a statistically significant improvement in the rate of pressure ulcer healing (odds ratio: 2.6).

Oclusive dressings can be divided into broad categories of polymer films, polymer foams, hydrogels, hydrocolloids, alginates,
and biomembranes. Each has advantages and disadvantages. No single agent is perfect. The choice of a particular agent depends on the clinical circumstances. Nonpermeable polymers can be macerating to normal skin. Polymer films are not absorptive and may leak, particularly when the wound is highly exudative. Most films have an adhesive backing that may remove epithelial cells when the dressing is changed. Hydrogels are hydrophilic polymers that are insoluble in water but absorb aqueous solutions and are available in amorphous gels or sheet dressings. They are poor bacterial barriers and are nonadherent to the wound. Because of their high specific heat, these dressings are cooling to the skin, aiding in pain control and reducing inflammation. Most of these dressings require a secondary dressing to secure them to the wound. Hydrocolloid dressings are complex dressings similar to ostomy barrier products. They are impermeable to moisture and bacteria and highly adherent to the skin. Hydrocolloid dressings have an accelerated healing of 40% compared to moist gauze dressings. Hydrocolloid dressings are particularly suited for areas subject to urinary and fecal incontinence. Their adhesiveness to surrounding skin is higher than some surgical tapes, but they are nonadherent to wound tissue and do not damage epithelial tissue in the wound. The adhesive barrier is frequently overexposed in highly exudative wounds. Hydrocolloid dressings should be used cautiously over tendons or on wounds with eschar formation. Alginate complexes polysaccharide dressings that are highly absorbent to exudative wounds. This high absorbency is particularly suited to exudative wounds. Alginate dressings are nonadherent to the wound, but if the wound is allowed to dry, damage to the epithelial tissue may occur with removal. Alginate may be used under other dressings to absorb exudate. These biomembranes are very expensive and not readily available.

Stages I and II pressure ulcers can be managed with a polymer film or hydrocolloid dressing. Stage III and IV pressure ulcers may be treated with a film or hydrocolloid dressing. In addition, some stage III and IV wounds with dead space or tunneling may require a wound filler, such as a calcium alginate or an amorphous hydrogel, to obliterate dead space and decrease potential for anaerobic colonization.

Vacuum-assisted closure is used in both acute and chronic wounds. Only two randomized, controlled trials in pressure ulcers are reported. In both trials, vacuum-assisted closure was not superior (despite a higher cost) to treatment with a hydrogel or moistened gauze.

Electrotherapy is used for stages III and IV pressure ulcers unresponsive to conventional therapy. Several clinical trials suggest that electrosurgery is likely to be marginally effective. Hyperbaric oxygen, ultrasound, infrared, ultraviolet, and low-energy laser irradiation have insufficient data to recommend their use currently. No data support the use of a systemic vasodilator, hemorheologics, oxygen, ultrasound, infrared, ultraviolet, and low-energy laser irradiation. The use of these agents in a pressure ulcer should be limited to use in infected ulcers and strictly limited in duration.

The seventh principle of pressure ulcer management is to control infection. Quantitative microbiology alone is a poor predictor of clinical infection in chronic wounds. All pressure ulcers are colonized with bacteria, usually from skin or fecal flora. The presence of microorganisms alone (colonization) does not indicate an infection in pressure ulcers. The diagnosis of infection in chronic wounds must be based on clinical signs. Consensus panels on diagnosis of infection in pressure ulcers suggest that advancing cellulitis is the most reliable sign. Edema, odor, and purulent exudate are much more nonspecific. In the presence of clinical signs of infection, enteral or parenteral antibiotics should be used. In ulcers that are not progressing toward healing, an empirical trial of topical antimicrobials may be considered, although the data are inconclusive.

References

PRURITUS ANI AND VULVAE
Method of
Lynee Margesson, MD, FRCP, and F. William Danby, MD, FRCP
Anogenital pruritus is a common symptom that affects the genitals or anus, or both. Pruritus ani affects 1% to 5% of the population and is more common in men. Pruritus vulvae is a common vulvar complaint affecting up to 10% of women. Genital pruritus in men is less common. Pruritus in these areas can be acute or chronic, and it can range from minor to debilitating.

Finding the cause of the pruritus is of utmost importance to manage these patients effectively. The most common causes are outlined in Box 1. Because the cause of pruritus is often multifactorial, always consider a combination of conditions, especially when both areas are involved, such as in contact dermatitis, the metabolic diseases, sweating, and some of the dermatoses.

In the vulvar area, the most common cause is acute candidiasis. Irritant contact dermatitis is next and often results from oversea- lous cleansing habits or exposure to topical irritants such as urine, feces, sweat, and topical medications. Among the chronic conditions, the most common causes are lichen simplex chronicus and lichen sclerosus. Psoriasis and lichen planus are seen less often. Patients may have a combination of infection, contact dermatitis (usually irritant), and dermatoses. Pruritus of the penis alone is unusual, and the most common causes are scabies and monilial balanitis. Scrotal itch may result from a primary irritant (often in atopics) or allergic contact dermatitis, scabies, and tinea cruris, even though the dermatophyte rarely involves the scrotum itself. Pubic lice cause pruritus of the entire hairy genital area.

In the anal area, dietary factors (through nickel allergy or irri- tant contact dermatitis from foods through fecal soiling) account for most cases of anal pruritus. As in the vulva, this is confounded by excessive cleansing and irritation and less frequently by allergic reactions to topical medications. Underlying anorectal diseases
### Box 1 Causes of Anogenital Pruritus

**Idiopathic In Up To 25% of All Cases**

**Acute Pruritus**

- *Candida*, dermatophytosis
- Herpes simplex virus, human papillomavirus, molluscum contagiosum
- *Staphylococcus aureus*, *Streptococcus*
- Pinworms, scabies, pediculosis

**Dermatoses**

- Contact dermatitis: irritant (e.g., poor hygiene), allergic
- Drug eruptions
- Atopic dermatitis/eczema
- Psoriasis

**Chronic Pruritus**

- Lichen simplex chronicus
- Contact dermatitis (irritant, allergic)
- Lichen sclerosus
- Lichen planus
- Psoriasis
- Hailey-Hailey

**Neuropathy**

- Vulvar and anal intraepithelial neoplasia
- Squamous cell carcinoma
- Extramammary Paget’s disease

**Anal-Specific Causes**

- Dietary factors
- Hemorrhoids and rectal prolapse
- Anal fissures
- Fistulae
- Proctitis
- Inflammatory bowel disease
- Metabolic factors: diabetes; renal failure; celiac disease; iron deficiency anemia; hyperthyroidism; hypovitaminoses A, B, C, D
- Sweating

### Box 2 Investigations for Anogenital Pruritus

- CBC (infection or parasite), plasma glucose
- Culture—bacteria, *Candida*, dermatophyte
- Wet prep of vaginal secretions for *Candida*, bacterial vaginosis, trichomoniasis
- Culture all balanitis for yeast and bacteria
- Adhesive tape testing for pinworms
- Potassium hydroxide testing of skin and vaginal secretions for yeast, scabies, dermatophytles
- Patch testing for allergic contact dermatitis
- Skin biopsy for dermatoses, tumors
- Anal or gastrointestinal disease—anoscopy, proctoscopy, colonoscopy
- Prostate cancer—prostate-specific antigen (PSA) and digital rectal examination (DRE)

### Box 3 Treatment of Anogenital Pruritus

**Nonspecific Measures**

- Patient support and education
- Stop all irritants (e.g., overwashing, scratching, infection, unnecessary topical preparations)
- Topical anesthetics (e.g., 5% lidocaine ointment bid to qid [may sting]); AVOID benzocaine (Vagisil).
- Cool compresses, soaks, gel packs (not frozen); keep in refrigerator in self-sealed plastic bag.
- Bland emollients (plain petrolatum or zinc oxide ointment) to soothe open fissured or eroded tissue.

**Specific Measures**

- Eliminate protease-containing laundry detergents
- Eliminate local secondary bacterial and yeast infection
- Stop scratching—use nighttime sedation (hydroxyzine [Sinequan]) 10–100 mg)/citalopram (Celexa) 20–40 mg each morning
- Reduce inflammation—topical corticosteroid ointments
  - Mild disease: 1%–2.5% hydrocortisone ointment with or without pramoxine (Pramason)
  - Moderate disease: triamcinolone 0.1% (Kenalog) ointment
  - Severe pruritus or thick skin areas: superpotent clobetasol (Temovate) or halobetasol (Ultravate) 0.05% ointment—limit use
- As steroid sparer, consider calcineurin inhibitors 1% pimecrolimus cream (Elidel) or 0.03%–1% tacrolimus ointment (Protopic)
- Manage anxiety and depression

**Specific for Pruritus Ani**

- Implement dietary changes
- Control fecal leakage and constipation
- Decrease sweating

**Specific for Pruritus Vulvae**

- Treat vaginitis
- Manage urinary incontinence and contributory menstrual flow

**For Neuropathic Pruritus**

- Amitriptyline (Elavil) 10–150 mg qhs
- Gabapentin (Neurontin) up to 3600 mg per day
- Pregabalin (Lyrica) 75 mg to 400 mg per day
- Mirtazapine (Remeron) 7.5 mg to 15 mg qhs

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1. Not FDA approved for this indication.

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should be sought. Dermatologic diseases, infections, and infestations need to be considered. Concurrent conditions can confuse the picture. Anxiety and depression can further cloud the diagnosis.

**Evaluation and Diagnosis**

A complete history and careful full-surface physical examination of the skin are needed. The examiner should adequately detail information about all hygiene practices and all topical products (prescribed and proprietary) used. For vulvar pruritus, a complete vulvar and vaginal examination is essential. Telephone diagnosis is unacceptable. For anal pruritus, a digital examination with anoscopy, proctoscopy, or colonoscopy may be indicated. Consider appropriate potassium hydroxide (KOH) preparations, cultures, skin biopsies, and patch testing as indicated (Box 2).

**Management**

Support and education of the patient are important (Box 3). All excess washing, irritants, and protease-containing laundry detergents must be eliminated. Unnecessary topical agents must be stopped. Infection control is important. Use oral antibiotics, and for women, add fluconazole (Diflucan) to prevent secondary yeast infection. Topical anesthetics such as lidocaine 5% ointment can help ease the need to scratch. Avoid benzocaine (Vagisil), because it can be a very strong irritant and allergen. Cooling the area is helpful, and this can be done with Sitz baths, gel packs (cold but not frozen), or compresses. Keep the gel packs or cool, moist
Diseases of the Skin

For anal pruritus, dietary factors may be important. Avoid foods, beverages, and medications that can exacerbate symptoms. Address dietary factors to improve bowel function. It is essential to control fecal leakage and constipation. Consider the possibility of rectal or prostatic pathology. Use bland emollients such as plain petrolatum or zinc oxide ointment to coat eroded, fissured skin after careful cleansing.

For genital pruritus, manage urinary incontinence and any contributing irritation from menstrual flow. Adjustments can be made to minimize flow with medications. Consider tampons rather than pads.

Gentle hygiene is important. The patient should use a hypoallergenic cleansing bar with hands only and avoid washcloths and wipes. Use a small amount of mineral oil or Albolene cleanser on a tissue to gently remove fecal material. Scratching must be controlled with nighttime sedation such as hydroxyzine (Vistaril) or doxepin (Sinequan). These patients have a tendency to scratch at night. They may be unaware of this. These medications assist with a deeper sleep to help stop the scratching. This is imperative at night. These medications assist with a deeper sleep to help stop the scratching.

Inflammation must be addressed. Classically, topical corticosteroid ointments are used. For mild disease, mild-potency hydrocortisone (Hyocort) 1% to 2.5% ointment may be all that is necessary. A 1% hydrocortisone/1% iodoquinol cream (Vytone) used topically as an antimicrobial with mild antiinflammatory action can be effective for perianal pruritus and skin fold areas such as labio-crural and inguinal folds and the gluteal cleft. For more severe pruritus, especially if the skin is thickened with lichen simplex chronicus or lichen sclerosus or is severely involved with lichen planus, a superpotent corticosteroid is needed. Vulvar lichen planus and lichen planus are treated with a superpotent steroid one or two times daily for 8 to 12 weeks and then three times per week, gradually decreasing to a maintenance regimen of one or two applications per week for the long term. Lichen simplex chronicus responds to superpotent steroid twice daily for 2 weeks, once daily for 2 weeks, and then three times per week. Consider switching to a calcineurin inhibitor such as pimecrolimus (Elidel) or tacrolimus (Protopic) twice daily as a steroid sparing. For perianal lichen sclerosus, lichen simplex chronicus, or lichen planus, superpotent topical steroid use should be limited to 2 to 3 weeks before reducing potency. Ointments are suggested because they are more effective and less allergenic than creams. Use as a thin, invisible film. There is controversy about the use of calcineurin inhibitors in the treatment of lichen sclerosus and lichen planus. Calcineurin inhibitors can cause a burning sensation.

For severe, intractable pruritus, a limited course of systemic corticosteroid may be indicated, using intramuscular triamcinolone acetonide (Kenalog 40), 1 mg/kg up to a maximum dose of 80 mg, or prednisone tapered over a three week course.

For perianal pruritus, a mild 1% to 2.5% hydrocortisone ointment may be all that is necessary. Because the skin is thin, strong corticosteroids should be used only for a limited time. The calcineurin inhibitors can be very helpful. For patients with intractable anal symptoms, cautious local injections of methylene blue have been beneficial.

For patients with neuropathy, management is like that for chronic pain conditions, with amitriptyline (Elavil), gabapentin (Neurontin), pregabalin (Lyrica), and mirtazapine (Remeron), or combinations of these drugs. Anxiety and depression need to be addressed in all of these patients.

Inching in these areas can be chronic and recurrent, and long-term follow-up will be needed. Treatment regimens must be used long enough to get adequate healing and completely break the itch, scratch, itch cycle. Otherwise, relapse is common.

References


PSYCHOCUTANEOUS MEDICINE

Method of

Ladan Mostaghimi, MD

CURRENT DIAGNOSIS

Delusions of Parasitosis

- The patient has false fixed beliefs about being infested.
- Look for the matchbox sign: Many samples of excoriated pieces of skin, scabs, clothing lint, or other debris are kept in plastic wrap, on adhesive tape, or in matchboxes by the patient and brought to the physician’s office for examination to detect suspected parasites.
- Determine the type of delusional disorder: primary or secondary, such as mood disorder with delusional features.
- Determine possible causes and contributing factors, such as substance abuse, organic brain pathology, pernicious anemia, hypothyroidism or hyperthyroidism, and systemic lupus erythematosus.
- Determine the extent of damage to the skin and history of skin infections.

Dermatitis Artefacta, Neurotic Excoriations, and Acne Excoriée

- Determine the type of problem: need to assume sick role (dermatitis artefacta), secondary gain (malingering), impulsive skin picking (neurotic excoriations and acne excoriée).
- Assess the degree of scarring, which may require intensive treatment.

Prurigo Nodularis and Lichen Simplex Chronicus

- Hard nodules that are 1 to 5 cm in diameter with hyperpigmentation and warty or excoriated surface in prurigo nodularis
- Lichenification (thickening) of the skin in lichen simplex chronicus
- Different histopathology for prurigo nodularis and lichen simplex chronicus
- Complete blood cell count to rule out lymphoma and polycythemia rubra vera
- Renal function tests (BUN, creatinine, and electrolytes) to rule out renal failure

1Not FDA approved for this indication.
- Liver function tests to rule out chronic obstructive biliary disease
- Serology for hepatitis
- Test for diabetes mellitus
- Levels of thyroid and parathyroid hormones
- Total serum IgE levels for atopy
- Patch test if allergies are suspected
- HIV test and PPD (if indicated)
- Skin biopsy and direct and indirect immunofluorescence assays to rule out immunobullous diseases
- Stool check for parasites
- Gastrointestinal testing to rule out malabsorption and gluten sensitivity
- Psychological evaluation

**Trichotillomania**
- Hair loss is caused by repeated hair pulling, producing oddly shaped patches of alopecia with broken hair and no signs of inflammation.
- Other areas beside the scalp may be affected.
- The age of onset and underlying psychopathology should be determined.
- If patients denies hair pulling, rule out other causes of alopecia.

**Cutaneous Sensory Disorders**
- Patients have a sensation of burning and itching in different areas of skin and mucous membranes, with no signs and symptoms of inflammation.

**CURRENT THERAPY**

**Delusions of Parasitosis**
- Treatment of main problem in cases of secondary delusional disorder helps to clear the delusions.
- Psychosocial intervention is warranted; work with families, and provide a good support system.
- Evaluate and monitor safety for the patient, family members, and health care providers.
- Some patients may try to get rid of parasites by burning their belongings or their body or by using toxic substances to treat parasites, thereby damaging their skin and causing serious toxicity, which must be treated.
- Treatment may include psychoeducation and cognitive-behavioral therapy (CBT).
- Neuroleptic and antipsychotic medications may be used; Pimozide (Orap) is a first-generation antipsychotic frequently used by dermatologists.
- There are case reports of second-generation antipsychotics working well in these situations.
- Treatment must be customized based on each patient’s profile and the medications’ side effects (Table 1).

**Dermatitis Arterfacta, Neurotic Excoriations, and Acne Excoriée**
- For dermatitis artefacta and malingering, the patient should be confronted in a nonjudgmental, empathetic way. Provide supportive dermatologic care for the skin and refer the patient for appropriate psychological interventions.
- For acne excoriée and neurotic dermatitis, rule out underlying psychopathology, and use a combination of therapy (cognitive-behavioral therapy or behavioral therapy) and medications that help impulsive behavior, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), buspirone (Buspar), anticonvulsants, naltrexone (ReVia), and neuroleptics, depending on the extent of the problem and scarring.

Psychocutaneous medicine explores the interactions between mind and skin. The spectrum of patients ranges from those who are delusional and refuse to see a psychiatrist to those who are depressed because of chronic disfiguring skin problems. The relationship between chronic skin diseases and psychological factors has been known for many years. In the first reference to it from 1200 bc, the physician to the Prince of Persia speculated that his patient’s skin disease (possibly psoriasis based on the description) was related to his anxiety about succeeding his father. Research in psychoneuroimmunology has better defined the relationship between skin and mind. This chapter discusses common psychodermatologic disorders and their treatment.

**Classification**

The five general categories of psychocutaneous medicine, as adapted from *Psychocutaneous Medicine* by Koo and Lee (see references), are as follows:
- Psychophysiologic disorders: Emotional factors can exacerbate a skin disorder, such as psoriasis.
- Primary psychiatric disorders: Patients have no primary skin disorder, and the cutaneous signs are self-induced, as with delusions of parasitosis.
Diseases of the Skin

(i.e., madness of two) or folie partage´ (i.e., shared delusions). Manual of Mental Disorders Delusions of Parasitosis also help with treatment choices and follow-up plans. the appointment with the physician. This classification system can questionnaires can be administered and rated by office staff before rating questionnaires are available for different conditions. These professional disorders, and impulse control disorders. Standardized self-rating questionnaires are available for different conditions. These questionnaires can be administered and rated by office staff before the appointment with the physician. This classification system can also help with treatment choices and follow-up plans.

Delusions of Parasitosis
Delusions of parasitosis falls under the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR), category of delusional disorder, somatic type. These patients have false fixed beliefs that they are infested by parasites. To meet the diagnostic criteria, the problem should last at least for a month, and it should not be part of schizophrenia manifestations. Apart from the impact of the delusions, the patient’s functioning is not markedly impaired, and behavior is not always odd or bizarre. Other delusional disorders for which a patient would seek dermatologic advice are delusion of bromhidrosis (i.e., patients are convinced they have a foul odor that no one else can perceive) and the delusion of dysmorphosis (i.e., patients are convinced that they have a defect in appearance that no one else can appreciate).

Another group of patients with delusions of parasitosis are those with psychotic mood disorders such as depression or bipolar disorder and false fixed somatic beliefs. If the patient has mood symptoms in addition to delusional symptoms, treatment of the mood problem may correct the delusional beliefs. For about 12% of patients, the delusion of parasitosis is shared by a family member or significant other. This condition is called folie à deux (i.e., madness of two) or folie partagé (i.e., shared delusions).

The patient with delusions of parasitosis usually has multiple superficial excoriations due to manipulating the skin to try to remove the parasites. Patients come to the clinic with many boxes and bags of skin samples, which is known as the matchbox sign. They can become very agitated when the physician denies presence of any infestation after physical examination or assessment of the samples collected and brought in.

Physicians should rule out substance abuse disorders. Some substances, especially amphetamines, cocaine, and phencyclidine (PCP), can cause formation and organic delusional syndrome in some patients. Organic reasons such as temporal lobe epilepsy or other brain pathology, neurosyphilis, pernicious anemia, hypothyroidism or hyperthyroidism, and systemic lupus erythematosus should be investigated, especially in older patients and if any neurolologic symptoms are identified during the physical examination.

Treatment consists of antipsychotic or neuroleptic medications. For patients with psychotic mood disorder, treatment of the mood disorder usually improves the delusional symptoms. Depending on the amount of distress that the delusions are causing, treatment may start with a combination of a neuroleptic medication and an antidepressant and later taper off the neuroleptic and continue only the antidepressant. To facilitate acceptance of the treatment, it is important for the physician to have a good rapport with patients and address their concerns; at the same time, the physician must not accept or feed into their delusions by giving the impression that the delusion is believed to be real. Statements such as the following may help to encourage patients to accept treatment: “I’ll be very honest with you; what you are telling me is very unusual. In most cases of infectious diseases, the doctors are able to easily identify the culprit. In your case, we have not found anything. Although we will keep looking to find the culprit, if any, I know it is difficult to live with this condition, and we have medications that can help to alleviate the symptoms you are experiencing.” If the patient refuses psychotropic medications, he or she should be monitored for safety. If, at any point, the safety of the patient, family, or physician is threatened due to dangerous behaviors related to delusional beliefs, local mental health providers should be consulted regarding institution of a court order for involuntary commitment for treatment.

Pimozide (Orap)1 is a first-generation antipsychotic that dermatologists have traditionally used for delusions of parasitosis. However, most antipsychotic medications can help this condition. Physicians should be familiar with the first- and second-generation antipsychotics (Table 2) and their side effect profile to select the treatment that is best tailored to each patient. Please notice the FDA warning about increased risk of stroke with the use of neuroleptics in elderly patients with Alzheimer’s disease. A detailed, step-by-step approach to treating patients with delusions of parasitosis is discussed in Cutis (see References).

Dermatitis Artefacta, Neurotic Excoriations, and Acne Excoriée
Dermatitis Artefacta or Factitious Dermatitis Dermatitis artefacta (i.e., factitious dermatitis) refers to intentional production of skin lesions to satisfy a psychological need. This may be achieved by different methods, such as excoriation, burning, or injection of toxic substances. Patients usually deny the self-induced nature of the problem. If the motivation for production of skin lesions is unconscious (e.g., assuming sick role), it falls under the category of factitious disorder. If the motivation is apparent and conscious (e.g., legal gain, disability), it falls under the category of malingering. Clinically, the lesions are located in reachable areas of the skin and can mimic any skin disease.

Factitious dermatitis usually occurs in patients with underlying psychopathology. After a diagnosis is made, the physician needs to discuss it with the patient in a nonjudgmental, empathetic way. Supportive dermatologic care should be provided for wounds, and the patient should be referred for psychological evaluation. Antidepressant and anxiolytic medications can help to treat underlying depression and anxiety. Supplementary therapies include biofeedback, relaxation, acupuncture, hypnosis, cognitive behavioral therapy, and behavioral therapy.

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1 Not FDA approved for this indication.
### TABLE 2  Medications Used in Psychocutaneous Disorders

<table>
<thead>
<tr>
<th>Neuroleptics</th>
<th>Drug Class</th>
<th>Drug Name</th>
<th>Adult Dosage Range</th>
<th>Side Effects to Monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-generation neuroleptics</td>
<td>Pimozide (Orap)</td>
<td>1 mg daily in divided doses, gradually increase up to maximum dose of 10 mg/d or 0.2 mg/kg/day; perform CYP2D6 genotyping when daily dose of pimozide is &gt;4 mg.</td>
<td>Multiple drug-drug interactions due to metabolism through CYP-450 1A2 and CYP 3A4; prolonged QT interval; torsades de pointes; GI, hemolytic, hepatic, and neurologic (tardive dyskinesia, neuroleptic malignant syndrome, extrapyramidal symptoms, akathisia) effects; drug-induced SLE and priapism</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.5–3 mg bid or tid</td>
<td>Neurologic side effects (tardive dyskinesia, NMS, etc.); QT prolongation; drug-drug interactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second-generation neuroleptics</td>
<td>Olanzapine (Zyprexa)</td>
<td>2.5–max 20 mg/d</td>
<td>QT prolongation; neurologic side effects (extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome) less with second-generation neuroleptics (least for quetiapine) but still exist; metabolic syndrome (needs regular monitoring; see Table 1); drug-drug interactions, blood dyscrasias; consider D/C if unexplained drop in WBC</td>
<td></td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>1–4 mg/d, max 8 mg/d; for age &gt;65 y, max 4 mg/d</td>
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<td></td>
</tr>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>2–max 30 mg/d</td>
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<tr>
<td>Quetiapine (Seroquel)</td>
<td>25–max 800 mg/d in divided doses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziprasidone (Geodon)</td>
<td>20–80 mg bid</td>
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</tbody>
</table>

### Antidepressants and Antianxiety Medications

<table>
<thead>
<tr>
<th>Antidepressants/antianxiety SSRIs</th>
<th>Sertraline (Zoloft)</th>
<th>50–200 mg/d</th>
<th>Each SSRI has own side effect profile (e.g., fluoxetine may prolong QT interval, Luvox may cause Stevens-Johnson syndrome); watch for sweating, GI symptoms, sexual side effects, myalgia, sleep problems, tremor, dizziness, bleeding tendencies, hypotension (rare), seizure (rare), manic episode, and suicidal ideation and suicide (rare); watch for drug-drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram (Celexa)</td>
<td>20–40 mg/d; max 20 mg/d over age 60 and in poor CYP2C19 metabolizers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram (Lexapro)</td>
<td>10–20 mg/d; max 10 mg/d in elderly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>20–60 mg/d</td>
<td></td>
<td></td>
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<tr>
<td>Paroxetine (Paxil)</td>
<td>20–50 mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine works best in OCD</td>
<td>50–300 mg/d in divided doses (bid)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antidepressants/antianxiety SNRs (help for peripheral neuropathies)</th>
<th>Venlafaxine, extended-release form available</th>
<th>37.5–225 mg/d</th>
<th>Hypertension, sweating, GI symptoms, blurred vision, sexual side effects, hypotension, hyponatremia (rare), serotonin syndrome, hepatitis (rare), drug-drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine (Cymbalta), also for treatment of fibromyalgia</td>
<td>30–60 mg/d; may increase to 120 mg/d, but doses &gt;60 mg/d are rarely more effective</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antidepressants/antianxiety others</th>
<th>Trazodone (Desyrel), helps insomnia and sometimes itching</th>
<th>50–400 mg/d</th>
<th>Sweating, weight change, GI symptoms, neurologic symptoms, blurred vision, hypertension, hypotension (rare), cardiac dysrhythmia (rare), priapism, seizure, drug-drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirtazapine (Remeron), helps insomnia and itching with higher affinity for histamine receptors than doxepin (Sinequan)</td>
<td>15–45 mg/d</td>
<td>Increased appetite, hyperlipidemia, somnolence, neurologic disorders, agranulocytosis and neutropenia (rare), seizure, drug-drug interactions</td>
<td></td>
</tr>
<tr>
<td>Bupropion (Wellbutrin), sustained-release and extended-release forms available</td>
<td>100–450 mg/d in divided doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buspirone (BuSpar), works for anxiety problems</td>
<td>5–60 mg/d in divided doses</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Tricyclic antidepressant for pruritus | Doxepin (Sinequan) | 10–300 mg/d single and divided doses for depression 10–25 mg/d for pruritus | Weight gain, GI symptoms, neurologic symptoms, blurred vision, urinary retention, arrhythmia (rare), blood pressure changes, bleeding tendencies, hematologic changes, drug-drug interactions |

| Tricyclic antidepressant for trichotillomania | Clomipramine (Anafranil) | 25–250 mg/d | Weight gain or loss, GI symptoms, blurred vision, neurologic symptoms, urinary retention, MI, orthostatic hypotension, hematologic side effects, hepatotoxicity |

<table>
<thead>
<tr>
<th>Neuropathic Pain Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic antidepressant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antiepileptic medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin (Neurontin), for postherpetic neuralgia</td>
</tr>
</tbody>
</table>
Because of a lack of clinical trials in psychocutaneous disorders, these medications do not have specific FDA approval for these disorders, and their use is based on case reports.

**Abbreviations:**
- AED: Antiepileptic drugs
- HLA-B: Human leukocyte antigen B
- MI: Myocardial infarction
- OCD: Obsessive-compulsive disorder
- OCD: Obsessive-compulsive disorder
- SLE: Systemic lupus erythematosus
- SNRI: Serotonin-norepinephrine reuptake inhibitor
- SSRI: Selective serotonin reuptake inhibitor
- TEG: Tegretol
- TEN: Toxic epidermal necrolysis
- TIA: Transient ischemic attack
- TLE: Temporal lobe epilepsy
- UDCA: Ursodeoxycholic acid

**Patients with acne excoriée create excoriations by repetitive scratching or picking. Women are affected more than men. Patients scratch and pick at their acne, an insect bite, or other bumps or rough spots on the skin, and any part of the skin that is not smooth can be a target. However, the patient may inflict neurotic excoriations without the trigger of any skin pathology because the condition is a psychological process with dermatologic manifestations. Patients usually have ritualistic picking habits and report building of tension before picking and release of tension afterward.**

**For any self-injurious behavior, patients must be screened for underlying psychopathologies such as personality disorders. However, in many patients, the behavior results from an impulse control problem.**

In addition to treating the underlying psychopathology, treatment includes a combination of behavioral therapy and medications that help with impulsive behavior. The success of treatment depends on patients' motivation to avoid scarring and to replace the self-injurious behavior with better behavior, including gentle skin care.

**Patients need to replace picking with other relaxing behaviors that are not harmful to skin, such as breathing relaxation or using a stress ball, Chinese exercise balls, Greek worry beads, stuffed animals, or Silly Putty. In finding appropriate replacement behavior, the physician should remember that tactile stimulation is important for these patients' anxiety relief.**

Another therapy model for skin pickers is to consider chronic picking as an addiction and apply the addiction therapy models to picking. Self-help groups and websites such as Pickers Anonymous could help with treatment.

There is no FDA-approved medication for this condition, and the use of different classes of medications is mostly based on case reports. The first step is to use an SSRI, such as fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), or citalopram (Celexa), or use an SNRI, such as venlafaxine (Effexor) or duloxetine (Cymbalta). Dosage and side effect profiles are provided in Table 2. If this is insufficient, the physician can add anti-anxiety medications, such as buspirone (Buspar), and

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**TABLE 2 Medications Used in Psychocutaneous Disorders—cont'd**

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>DRUG NAME</th>
<th>ADULT DOSAGE RANGE</th>
<th>SIDE EFFECTS TO MONITOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Various treatments for intractable pruritus</td>
<td>Thalidomide (Thalomid), also used in Behçet's syndrome</td>
<td>50–400 mg/d</td>
<td>Severe birth defects in pregnancy, edema, skin rash, GI symptoms, leukopenia, thrombotic disorder, peripheral neuropathy, Stevens-Johnson syndrome, TEN, seizure, pulmonary embolism, hypocalcemia, tremor, somnolence, drug-drug interactions</td>
</tr>
<tr>
<td></td>
<td>Naltrexone (ReVia)</td>
<td>50 mg/d</td>
<td>GI symptoms, headaches, anxiety, hepatic damage, opioid withdrawal (rare), drug-drug interactions</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine (Sandimmune)</td>
<td>4–5 mg/kg/d</td>
<td>Hirsutism, pruritus in some patients, GI symptoms, neuropathic pain, in Behçet's syndrome,1 also used</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Clonazepam (Klonopin)</td>
<td>0.25 mg at night, with gradual increase to 1 mg at night if needed</td>
<td>Salorrhhea, ataxia, dizziness, somnolence, impaired cognition, aggravation of seizure, depression, behavioral problems, respiratory depression</td>
</tr>
</tbody>
</table>

This table shows the more commonly used medications, not an exhaustive list of all medications for psychocutaneous disorders. There are newer antidepressant medications in addition to treating the underlying psychopathology, treatment includes a combination of behavioral therapy and medications that help with impulsive behavior. The success of treatment depends on patients' motivation to avoid scarring and to replace the self-injurious behavior with better behavior, including gentle skin care.
some of the newer anticonvulsant medications, such as lamotrigine (Lamictal). In the case of severe picking, multiple infections, and scarring, such as in patients with Prader-Willi syndrome, other medications such as the opioid antagonist naltraxone (ReVia) and sometimes the use of neuroleptics such as aripiprazole (Abilify) and quetiapine (Seroquel) can help to break the cycle of scratching and give time for behavioral treatments to take effect. After the patient has improved, medications can be tapered and discontinued, but he or she may need to stay on a maintenance dose of medications.

Prurigo Nodularis and Lichen Simplex Chronicus
Prurigo Nodularis
Clinically, prurigo nodularis (i.e., chronic circumscribed nodular lichenification or picker’s nodules) is a chronic, severe itch accompanied by 1- to 5-cm, hard nodules with smooth or warty surfaces surrounded by hyperpigmentation. The new lesions are usually red and inflamed, whereas old lesions are pigmented. The lesions may also be excoriated. The lesions are mostly located in extensor surfaces of limbs, but they can be located on the face and trunk. Histopathologic examination reveals lichenification, a dense infiltrate in dermis and neural hyperplasia, and proliferation of Schwann cells.

Computed tomography scans and chest radiographs are obtained if lymphoma is suspected.

Topical treatments with antipruritic creams are not very helpful. Potent topical steroids such as betamethasone dipropionate (Diprosone) ointment under occlusion or intralesional injection of steroids such as triamcinolone acetonide (Kenalog-10) may be successful, but they have the risk of skin atrophy. Topical capsaicin (0.025% to 0.1% Zostrix), a component of red pepper, can help in the early stages.

For diffuse and resistant forms of prurigo nodularis, broadband and narrowband ultraviolet B (UVB) and ultraviolet A (UVA) can be effective. Narrowband UVB is more effective and has fewer side effects than UVA.

For resistant forms, cyclosporine (Sandimmune) at the dosage of 4 mg/kg/day can help. It should be continued at least for 6 months (see Table 2).

Thalidomide (Thalomid) at the dose of 200 to 400 mg in different studies has been an effective treatment for prurigo nodularis. It is difficult to obtain because of its teratogenicity, and it has some serious side effects, such as irreversible peripheral neuropathies. Naltrexone (ReVia), an opioid antagonist, at the dosage of 50 mg/day is effective in some cases. Another treatment that had some success was the synthetic retinoid etretinate (Tegison), but it was removed from the U.S. market because of the high risk of birth defects.

Psychological intervention is important in breaking the itch/scratch cycle. Help can be obtained with techniques such as biofeedback, in which patients learn how to consciously control their autonomic responses; hypnosis; cognitive-behavioral therapy; and supportive counseling.

Some psychotropic medications can help with excessive itching and compulsive scratching, including doxepin (10 mg at bedtime, which can be increased up to 25 mg; the recommended dose for pruritus is lower than the dose for the treatment of depression, anxiety, or alcoholism, in which case it can be increased up to a maximum of 300 mg daily in divided doses); mirtazapine (Remeron) (15 to 45 mg at night); and trazodone (50 to 400 mg at night). Doxepin is a tricyclic medication, and because it has the potential to cause cardiac arrhythmias, it should not be used in patients with recent myocardial infarction. Patients need to have periodic cardiovascular evaluations if they use tricyclic medications long term. Antidepressants should not be used in patients with bipolar disorder without a mood stabilizer because of the risk of triggering a manic episode.

Lichen Simplex Chronicus
Lichen simplex chronicus (i.e., circumscribed neurodermatitis) is characterized by lichenification of skin due to chronic, excessive scratching. Clinically, it appears as plaques of thickened skin with hyperpigmentation and accentuated skin lines. The most commonly affected areas are the occipital scalp, sides of the neck, ankles, genital areas, and extensor forearms. Itching is the main symptom. The histopathologic pattern in lichen simplex chronicus is different from that of prurigo nodularis and does not show the neural hyperplasia.

The physician must rule out underlying diseases that may cause pruritus. The treatment for lichen simplex chronicus is similar to that for prurigo nodularis. In addition to other treatments, topical tacrolimus (Protopic) has been effective in some cases of lichen simplex chronicus.

Trichotillomania
Trichotillomania is partial hair loss caused by repeated hair pulling. Clinically, the patient has patches of alopecia with broken hair and different hair lengths without any inflammation of the scalp. The affected area has an unusual shape. A hair pull test result is negative. It can involve areas other than the scalp, and patients may pull hair in many sites. Trichotillomania occurs in any age group. In children, it is usually benign and self-limited, but in adults, it usually accompanies other psychopathologies and requires psychological intervention.

Trichotillomania is classified with impulse control disorders in the DSM-IV-TR. If a patient denies hair pulling, other causes of alopecia, especially alopecia areata, need to be ruled out.

In children, trichotillomania may occur during periods of increased stress, such as the arrival of a new sibling or parents’ divorce. It is usually self-limited, and parents should be reassured. In preadolescents and young adults, the diagnosis needs to be established first, followed by psychotherapeutic interventions; behavioral modification usually works well. Psychopharmacologic treatments should be reserved for last. Because of the FDA black box warning about the increased risk of suicide and suicidal behavior with use of antidepressants in children, adolescents, and young adults, these patients should be referred to a psychiatrist for medication, if needed.

In adults, trichotillomania often accompanies other psychopathology, and the treatment of the underlying illness helps to resolve the condition. Habit reversal therapy usually works better than negative feedback. Habit reversal therapy teaches the patient to monitor the behavior and the triggering factors and to replace the harmful habit with another habit. Working on increasing coping skills for stress is also helpful. Relaxation and other stress-relief techniques are helpful, especially in patients with underlying anxiety. The Trichotillomania Learning Center (www.trich.org) is a good source of information for patients.

Psychotropic medications can be used if psychotherapy alone is not enough. Most reports of effective medications are based on open-label studies. Clomipramine (Anafranil) at a dosage of 180 mg to 250 mg/day in a small, double-blind comparison with desipramine (Norpramin) showed greater efficacy with a significant decrease in symptoms. There have been some open-label studies showing efficacy of fluoxetine (Prozac), but this result was not reproduced in double-blind, placebo-controlled trials. Other SSRIs, such as sertraline (Zoloft), fluvoxamine (Luvox), and paroxetine (Paxil), have shown efficacy in case reports and open-label studies. In some augmentation trials, adding haloperidol (Haldol), pimozide (Orap), or olanzapine (Zyprexa) has been beneficial for patients taking fluoxetine or clomipramine. Small studies on using haloperidol or lithium (Eskalith) have shown some efficacy. Because of important side effects such as tardive dyskinesia with haloperidol and the narrow therapeutic window with lithium, it is best to leave these treatments to psychiatrists. Before these patients use antidepressants, it is important to screen them for bipolar disorder.

1Not FDA approved for this indication.

2Not FDA approved for this indication.
Cutaneous Sensory Disorders

Cutaneous sensory disorders are part of chronic pain syndromes, with pain occurring in different parts of the skin or mucous membranes. Disorders include burning mouth syndrome and vulvodynia (i.e., burning and itching of the vagina).

Burning mouth syndrome is a burning sensation that happens more frequently in middle-aged women. It affects the tongue more frequently, but other parts of the mouth also may be affected. It can be associated with dry mouth and a metallic taste in the mouth.

The physician should rule out local problems (e.g., dental disorders, allergic reactions, infection) and systemic problems (e.g., vitamin B, folate, iron, and zinc deficiencies; diabetes; autoimmune problems such as Sjögren’s syndrome; nerve injury; side effects of antivirals, antiretrovirals, antiseizure medications, hormones, and angiotensin-converting enzyme [ACE] inhibitors). The diagnosis needs a thorough physical examination and laboratory work-up, as well as screening for depression and anxiety. Mood problems may result from chronic pain issues.

The primary cause needs to be treated. In idiopathic cases, therapy to help relaxation, coping skills training, and biofeedback may help. There is no FDA-approved medication for this condition, but medications used to treat neuropathies may help. Gabapentin\(^1\) can result from chronic pain issues.

Medications used to treat neuropathies may help. Gabapentin\(^1\) can be started at 100 mg at night for 3 days and gradually increased to 100 mg three times a day. The dosage can be adjusted to 300 to 600 mg three times a day as tolerated, up to a maximum of 1800 mg.

Tricyclics such as amitriptyline (Elavil) (10 to 35 mg PO at bedtime\(^2\)) may increase every week to a maximum dosage of 150 mg/day. SNRIs such as venlafaxine (Effexor extended-release capsule)\(^1\) can be given at a dosage of 37.5 mg in the morning with a gradual weekly increase to the maximum of 225 mg daily, and duloxetine (Cymbalta)\(^3\) can be given as 60 mg daily. Clonazepam (Klonopin)\(^4\) given in small doses at night may help in some cases. Up to two thirds of patients report spontaneous partial recovery within 6 to 7 years of onset.

Vulvodynia is burning and pain in vulvar area. It should be evaluated by a gynecologist. Infectious, neoplastic, and inflammatory causes need to be ruled out. Depression and the impact on quality of life should be evaluated. Biofeedback and gabapentin\(^1\) or amitriptyline\(^3\) have been helpful in some cases. Depression and anxiety lower the pain threshold, and their treatment can help patients with chronic pain syndromes to better cope with their pain and have a higher pain threshold.

Medications for Pain and Itching

Some of the psychotropic medications can be used for various dermatologic conditions, such as urticaria or postherpetic neuralgia. The older tricyclic medications have specific effects on pain or itching.

When itching is the main symptom, doxepin\(^1\) has a much higher affinity for histamine receptors than do conventional antihistamines. It has a long half-life, and taking it once at night can control daytime itching. The effective antipruritic dosage is usually 10 to 25 mg at night, but it can be increased at weekly intervals as needed. Amitriptyline (Elavil)\(^1\) works best for disorders with pain as the main symptom, such as burning mouth syndrome or postherpetic neuralgia. The usual dosage is 10 to 35 mg taken orally at bedtime, but it may be increased every week to a maximum dosage of 150 mg/day. Because tricyclic medications can affect cardiac conduction, patients need to have stable cardiovascular status and a normal electrocardiogram. Periodic testing is required during long-term treatment. These drugs should not be used with other medications that prolong the QT interval, such as cisapride (Propulsid).\(^3\) They should not be prescribed during the immediate recovery period after myocardial infarction, and they should not be used at the same time as monoamine oxidase inhibitors. Patients need to be instructed to avoid driving due to drowsiness side effects of tricyclics.

Other medications can help with pain symptoms:

- Gabapentin is started at 100 mg at night, increased every 3 days to 300 mg at night, and then increased weekly to 900 to 1800 mg daily in three to four divided doses as tolerated.
- Pregabalin is started with 50 mg taken orally three times daily and increased to 100 mg three times daily within 1 week based on efficacy and tolerability. If patients with postherpetic neuralgia do not experience sufficient pain relief in 2 to 4 weeks and are tolerating the medication well, the dosage can be increased to 300 mg twice daily or 200 mg three times daily (600 mg/day).
- SNRIs such as duloxetine (60 mg daily) have FDA approval for diabetic neuropathy and fibromyalgia.\(^1\)
- Venlafaxine,\(^4\) which has a mechanism of action similar to that of duloxetine at the dosage of 37.5 mg in the morning, with a gradual weekly increase to the maximum of 225 mg daily, may help pain symptoms, but it is not FDA approved for pain treatment.
- There are some reports that SSRIs can help pain symptoms.

References


URTICARIA AND ANGIOEDEMA

Method of

Joyce M.C. Teng, MD, PhD

\(^1\)Not FDA approved for this indication.

\(^2\)Not available in the United States.
Urticaria, or hives, is a common cutaneous eruption that occurs in up to 25% of the general population sometime during their lives. It is characterized by transient, circumscribed, pruritic, erythematous papules or plaques, often with central pallor. Individual lesions often coalesce into large wheals on the trunk and extremities that may resolve over a few hours without leaving any residual skin changes. The process is mediated by mast cells in the superficial dermis.

Angioedema is a similar process occurring in deep dermis or subcutaneous tissue. Angioedema may occur independently, accompanied by urticaria, or as a component of anaphylaxis. It is characterized by localized swelling that develops over minutes to hours and resolves within 24 to 48 hours. Common locations of angioedema include the mucosa and areas with loose connective tissue, such as the face, eyes, lips, tongue, and genitalia. Patients usually do not have pruritus, but they may have pain and a sensation of warmth. Angioedema is usually a benign process that usually do not have pruritus, but they may have pain and a sensation of warmth. Angioedema is usually a benign process that usually do not have pruritus, but they may have pain and a sensation of warmth. Angioedema is usually a benign process that usually do not have pruritus, but they may have pain and a sensation of warmth. Angioedema is usually a benign process that usually do not have pruritus, but they may have pain and a sensation of warmth.

Angioedema must first be assessed for signs of airway compromise. More than two thirds of cases of urticaria are self-limited. Symptoms for more than 10 years. Approximately 40% of patients with chronic urticaria may have persistent symptoms for more than 10 years. Approximately 40% of patients with chronic urticaria have associated angioedema, although the incidence of laryngeal edema is low.

**Classification**

Urticaria can be classified as acute or chronic, depending on the duration. Acute urticaria usually lasts for less than 6 weeks and is commonly triggered by infection, medication, insect bite, and food (Table 1). The chronic form, lasting more than 6 weeks, accounts for approximately 30% of cases of urticaria, and no clear causes can be identified in more than 80% of these cases. A significant number of patients with chronic urticaria may have persistent symptoms for more than 10 years. Approximately 40% of patients with chronic urticaria may have associated angioedema, although the incidence of laryngeal edema is low.

**Diagnosis**

Urticaria is diagnosed clinically in most cases. A detailed history, physical examination, and complete review of systems are essential for diagnosing patients with urticaria and angioedema. The history should include the distribution and characteristics of lesions (e.g., pain, pruritus), duration of skin eruption, accompanying angioedema, airway involvement and other associated systemic symptoms (e.g., fever, arthralgia, swelling joints, refusal to walk by children). Patients should also be questioned about changes in dietary habits, recent exposures, infection, and newly administered medications, including antibiotics, over-the-counter analgesia, and hormones.

**Treatment**

More than two thirds of cases of urticaria are self-limiting. Spontaneous remission of chronic urticaria and angioedema is also common. The primary objective of management is to identify and discontinue the offending trigger. A patient presenting with angioedema must first be assessed for signs of airway compromise. Medical therapy is indicated for those who are symptomatic.

Antihistamines remain the first-line therapy for most patients with urticaria, because the primary complaint of pruritus is predominantly mediated by histamine released from mast cells. First-generation antihistamines such as hydroxyzine (Atarax or Vistaril 25 to 50 mg every 6 hours), diphenhydramine (Benadryl 25 to 50 mg every 6 hours), cyproheptadine (Periactin 4 mg three times daily), and chlorpheniramine (Chlor-Triment 4 mg every 6 hours) are potent and have the quickest onset of action. However, the treatments are often limited by their sedating and anticholinergic side effects. Many first-generation antihistamines are available over the counter, providing accessible first-line therapy for patients. Patients with urticaria that lasts for several days should be

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**Table 1** Mechanisms in Urticaria and Angioedema

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoglobulin-mediated urticaria</td>
<td>Ig-E mediated: food, medication, insect bites, contact allergen, aeroallergens, other causes</td>
</tr>
<tr>
<td>Urticaria associated with immunodeficiency</td>
<td>Antinuclear antibodies (ANAs), thyroid autoantibodies, other causes</td>
</tr>
<tr>
<td>Direct activation of mast cell degranulation</td>
<td>Physical stimuli: exercise, heat, cold, pressure, aquagenic, solar radiation, etc.</td>
</tr>
<tr>
<td>Other agents: opiates, antibiotics (e.g., vancomycin [Vancocin]), radiocontrast, ACTH (Cortrosyn), muscle relaxants</td>
<td></td>
</tr>
<tr>
<td>Complement-mediated</td>
<td>Viral infections, parasites, blood transfusion</td>
</tr>
<tr>
<td>C1 inhibitor deficiency</td>
<td>Genetic and acquired angioedema, paraproteinemia</td>
</tr>
<tr>
<td>Reduced kinin metabolism</td>
<td>Angiotensin-converting enzyme (ACE) inhibitors</td>
</tr>
<tr>
<td>Reduced arachidonic acid metabolism</td>
<td>Aspirin</td>
</tr>
</tbody>
</table>

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1Not FDA approved for this indication.
2Not available in the United States.
3Exceeds dosage recommended by the manufacturer.
4Investigational drug in the United States.
5May be compounded by pharmacists.
considered for treatment using second-generation antihistamines such as loratadine (Claritin® 10 mg twice daily), desloratadine (Clarinex 5 mg twice daily), cetirizine (Zyrtec 10 mg twice daily), levocetirizine (Xyzal 5 mg daily), and fexofenadine (Allegra 180 mg twice daily). Doxepin (Sinequan), an H1- and H2-receptor antagonist, is seven times more potent than hydroxyzine in suppression of wheal and flare responses. Because of its central nervous system side effects, combined use of doxepin with a first-generation antihistamine should be avoided. Topical 5% doxepin cream (Zonalon®) may help to suppress pruritus in patients with localized urticaria.

Systemic prednisone at 30 to 40 mg in a single morning dose is sufficient to suppress urticaria in adults. Tapering should be gradual over a 3- to 4-week period by decreasing the dosage 5 mg every 3 to 5 days to minimize rebound. Alternate-morning dosing when reaching 20 mg daily may help to minimize the steroid side effects. Methylprednisolone (Solu-Medrol 40 mg) should be given intravenously as initial therapy to patients with angioedema. This may be followed by a tapering oral course. Three months of treatment with cyclosporine (Neoral®) at 3 to 5 mg/kg can be given safely to patients who are refractory to corticosteroid therapy or have difficulty tapering their therapy. Close monitoring for hypertension and renal insufficiency is necessary during the treatment.

Leukotriene inhibitors such as zileuton (Zyflo® 600 mg four times daily), zafirlukast (Accolate® 20 mg twice daily), and montelukast (Singulair® 10 mg once daily) may be effective for patients with autoimmune urticaria. Successful treatment of chronic urticaria with anti-IgE (omalizumab [Xolair®]) has been reported but is not yet approved by the FDA.

Proper management of underlying autoimmune thyroid disease or autoimmune collagen vascular diseases has been beneficial for patients with associated urticaria. Life-threatening angioedema triggered by angiotensin-converting enzyme (ACE) inhibitors has been successfully treated with infusion of fresh-frozen plasma. Treatments with methotrexate, warfarin (Coumadin®), plasmapheresis, and intravenous immunoglobulin (Baygam®) have been reported for severe, refractory urticaria. These treatments are administered only by specialists on an individual basis.

References

VENOUS ULCERS
Method of
Zuleika L Bonilla-Martinez, MD, and Robert S. Kirsner, MD, PhD

CURRENT THERAPY
- Compression therapy is used to deliver a graded compression of 30 to 40 mm Hg at the ankle. Exclude arterial disease before using compression.
- Systemic medications as adjuvant therapy to compression bandages include aspirin, pentoxifylline (Trental), or micronized purified flavonoid fraction (Daflon 500).
- Other treatments, along with compression, include engineered skin, skin graft, electrical stimulation, locally derived growth factors, and venous surgery.
- The lifelong use of elastic compression stockings (30–40 mm Hg) is the mainstay of therapy.

CURRENT DIAGNOSIS
- Venous ulcers are the most common cause of lower-extremity ulceration, affecting up to 8% of the world’s population.
- Valvular incompetence, vein distention, muscular weakness, or a decrease in the range of motion of the ankle may lead to calf muscle pump failure.
- The mechanism of cutaneous ulceration resulting from venous insufficiency remains unknown.
- The typical location for a venous ulcer is around the medial malleolus.
- Complications of chronic venous ulcers are osteomyelitis and squamous cell carcinoma.
- Compression is the gold standard of treatment of venous disease.

Epidemiology
Venous disease affects approximately 5% of the world’s population and about 2% of the American population. It was once thought to be a disease affecting solely the elderly. The incidence increases from middle age onward. Seventy percent of all leg ulcers result solely from venous disease, and an additional 20% of patients have mixed arterial and venous disease. The other 10% of leg ulcers result from a variety of causes, including neuropathy, prolonged pressure, and infectious, malignant, and inflammatory causes.

The high prevalence of venous disease directly affects patients’ quality of life. Family history of venous disease, obesity, smoking, high cost of treatment, time off work, prolonged standing, and hypertension are among the factors that contribute to a strong socioeconomic impact of a country’s health care. A retrospective study from Cleveland Clinic Foundation showed the average cost per month of care was approximately $2,400, and the mean total cost per patient was between $9685 and $14,136 U.S. dollars.

Pathophysiology
In the lower extremities, the venous system comprises the deep and superficial veins, which are connected by the perforating venous system. Blood flows from the superficial to the deep veins through

Not FDA approved for this indication.
*Not available in the United States.
the communicating veins to ultimately reach the heart. Veins contain valves that prevent blood reflux and allow the unidirectional flow. When a healthy individual contracts the calf muscles, a high pressure develops in the deep vein system, allowing blood flow to go from the deep to the superficial veins. During calf muscle relaxation, the pressure difference (high pressure in the superficial veins) allows blood flow from the superficial to deep veins. Venous ulcers are associated with venous hypertension, which is defined as sustained elevated venous pressures during ambulation. Venous hypertension results from failure of the calf muscle pump, which normally assists in venous return. Blood reflux from the deep to superficial veins creates the sustained high pressure in the superficial vein system and therefore increased cutaneous blood flow. Vascular incompetence, vein distention, muscular weakness, and a decreased in the range of motion of the ankle may lead to calf muscle pump failure. Alterations in the microcirculation because of calf muscle pump failure ultimately lead to ulceration.

How does the skin ulcerate in patients with venous insufficiency? The mechanism of cutaneous ulceration as a consequence of venous insufficiency remains unknown. Several hypotheses have been reported since the beginning of the 20th century. In the early 1980s, Browse and Burnard suggested that venous hypertension could lead to endothelial distention, causing extravasation of fibrinogen into the interstitial fluid, which results in "pericapillary fibrin cuff" formation around the capillary vessels. Fibrin cuffs act as a barrier to diffusion of oxygen and nutrients, causing ischemia and ulcer formation. A few years later, Coleridge and colleagues suggested that venous hypertension could lead to decreased capillary perfusion, resulting in leukocyte trapping. The trapped leukocytes release proteolytic enzymes, which result in free radical formation and capillary damage. The increased capillary permeability causes extravasation of fibrinogen and other metabolites, which leads to formation of a fibrin cuff around the capillaries and ultimately ischemia.

Further studies supported the presence of increased levels of monocyte aggregation. Claudy and colleagues showed that leukocyte activation caused release of tumor necrosis factor alpha (TNF-α), ultimately leading to pericapillary fibrin cuff formation. In 1993, Falanga and Eaglstein observed that fibrin cuffs were discontinuous around capillaries and therefore did not form a barrier to oxygen and nutrients causing ischemia. They also postulated the "trap" hypothesis, which suggests that venous hypertension causes endothelial cell distention leading to extravasation of macromolecules (i.e., fibrinogen and 2-macroglobulin) into the dermis. Moreover, 2-macroglobulin can bind to growth factors, such as TNF-α and transforming growth factor beta (TGF-β), making them unavailable for wound repair. Patients with venous disease may have other factors that contribute to venous ulcer formation, such as systemic alteration in fibrinolysis and arteriovenous shunting. Despite all previously conducted studies and hypotheses, further research is needed to explain the mechanism of cutaneous ulceration resulting from venous insufficiency.

**Evaluation and Diagnosis**

The typical location for a venous ulcer is around the medial aspect of the lower extremity near the ankle (medial malleolus) or the gaiter area. The ulcer usually begins as a blister or erosion on the skin. Ulcer borders are irregular and usually smooth. The base of the ulcer may be covered with granulation tissue or yellow slough, or both.

Venous ulcers are associated with presence of pigmentation, erythema, dermatis, edema, and induration (i.e., lipodermatosclerosis) of the surrounding skin and with varicose veins in the lower leg. Hemosiderin deposition resulting from red blood cell extravasation causes the surrounding hyperpigmentation. Lipodermatosclerosis, commonly known as an inverted bottle shape, is caused by sclerosis of the dermis and subcutaneous tissue. The presence of lipodermatosclerosis has been associated with a greater impairment of fibrinolysis in patients with venous ulcers and may be a poor prognostic factor for restriction of leg movement. Other known prognostic factors are duration and size of the ulcer and history of venous surgery. Ulcers present for longer than 6 months and larger than 5 cm² in diameter tend to be more refractory to therapy. Duration (27 months) and size (15.9 cm²) were reported as poor prognostic factors.

A diagnosis of venous ulcers may be based on clinical presentation. The findings of a lower leg ulcer associated with lipodermatosclerosis or varicose veins, or both, suggest a venous ulcer. Other common findings include atrophy blanche (i.e., porcelain white scars with telangiectasia and dyspigmentation) and dermatis. Venous dermatitis is associated with erythema, eczema, pruritus, and scaling of the skin. Contact dermatitis surrounding the ulcer may result from the use of topical agents.

Venous disease can be confirmed by a variety of techniques, including duplex ultrasound or plethysmography. However, it is critical that arterial disease be excluded because treatment with compression bandages is the mainstay of therapy and should be used cautiously in patients with arterial disease. A simple, noninvasive measurement to assess peripheral vascular disease is the ankle brachial index (ABI). This value is calculated by dividing the systolic pressure in the ankle by the systolic pressure in the arm. An ABI of less than 0.9 indicates peripheral vascular disease and represents an independent risk factor for vascular disease in other vascular beds, such as the coronary arteries. Care must be taken with diabetic or elderly patients who may have a falsely negative ABI value. All patients with an abnormal ABI value should be further evaluated. Consider a vascular consultation, magnetic resonance angiography (MRA), angioplasty, and stent bypass.

To aid in the exclusion of any underlying disease (e.g., hematologic disease, diabetes), initial laboratory tests should include complete blood cell (CBC) count with a differential count, chemistry panel, hemoglobin A1C, prealbumin and albumin determinations, liver function tests, and levels of homocysteine, protein C and S, antithrombin III, and factor V Leiden.

Several vascular studies help in the diagnosis and severity of venous disease. Color duplex ultrasound is usually the initial study done to assess venous reflux in the lower extremities. Continuous-wave Doppler studies may yield false-negative results because it may be difficult to differentiate between the superficial and deep venous system. Air plethysmography and photoplethysmography are helpful in evaluating venous reflux and calf muscle dysfunction. Invasive venography is the gold standard to assess venous reflux, but it is used only as a last resort because of its invasive properties.

The CEAP classification was developed in 1994 by the American Venous Forum (AVF) to standardize the diagnosis and treatment of venous disease. It was based on clinical manifestations (C), etiologic factors (E), anatomic distribution of disease (A), and underlying pathophysiologic findings (P).

**Complications**

Main complications of long-term or chronic venous ulcers are osteomyelitis and squamous cell carcinoma. A finding of exposed tendon or bone, in addition to suggesting an underlying osteomyelitis, suggests an ulcer with a nonvenous cause.

Radiographs and biopsy for histology and culture are appropriate first steps in evaluation. Consult an orthopedic surgeon for further analysis and treatment, which may include a bone biopsy and bone débridement.

**Treatment**

Compression is the gold standard of treatment of venous disease. After arterial disease has been excluded, reversal of the effects of venous hypertension through compression bandages and leg elevation is the cornerstone of therapy.

The goal of compression therapy is to deliver sustained graded compression with 30 to 40 mm Hg at the ankle. These bandages are applied circumferentially from the toes to the knees (involving the heel) with the foot dorsiflexed. The optimal method to deliver this pressure is through multilayered elastic compression dressings. Elastic compression dressings deliver compression during ambulation (i.e., walking) and at rest, accommodate to reduction
in edema, and are superior to single-layered dressings. Inelastic compression (short-stretch compression) may deliver similar results but appear to require greater sophistication by those applying them to accomplish this. Inelastic bandages, which do not deliver compression at rest, may be advantageous in patients with arterial disease or patients who do not tolerate full compression (e.g., elderly). Patients with associated lymphatic damage may also benefit from pneumatic compression.

Systemic medication as adjuvant therapy to compression bandages, such as pentoxifylline (Trental 400 to 800 mg three times daily¹), aspirin, ² or micronized purified flavonoid fraction (MPFF, Dalfon 500² [diosmin 90% and hesperidin 10%]) may be superior to compression bandages alone with regard to the rate of healing. The use of pentoxifylline as adjuvant therapy to compression in venous ulcers has been shown to be very beneficial.

Wound bed preparation was proposed as a way to help the healing process. It is a multistep process that improves the wound bed by removing necrotic and fibrinous wound tissue, increasing the amount of granulation tissue, and decreasing edema, chronic wound fluid (i.e., exudate), and bacterial burden.

Local care is best accomplished with occlusive dressings. Occlusive dressings provide a moist environment for healing. A variety of types of occlusions may be used, and the choice depends on several factors, including the location of the wound and the amount of fibrinous slough and exudate present. A fear of excessive infection with the use of occlusive dressings is unfounded. Topical anesthetics and cleansing agents should be used with caution because they may increase the time required for healing. Topical agents such as cadexomer iodine (Iodosorb), silver-impregnated dressings, and topical antiseptics are alternatives that do not prolong healing, but they should be applied directly to the wound because they may lead to skin sensitization.

Up to 50% of venous ulcers may be refractory to compression therapy alone. This refractory subset may be predicted by baseline characteristics (size and duration) and by a decrease in size with 2 to 4 weeks of treatment (Figure 1). Other available treatments include tissue-engineered skin, autologous skin, electrical stimulation, treatment with locally delivered growth factors, and venous surgery. Three categories exist for skin grafts: autograft, allogeneic (cultured), and artificial (tissue-engineered skin). Two types of autografts are full-thickness (FTSG) and split-thickness (STSG) skin grafts. The latter is commonly used by expanding it with a meshing technique.

Apligraf, a bilayered engineered living skin composed of keratinocytes and fibroblasts from neonatal foreskin, is approved by the FDA for treatment of venous leg and diabetic neuropathic foot ulcers. Surgical treatment of incompetent superficial and perforator veins along with standard of care (i.e., compression) reduce the risk of recurrence.

After healing occurs, patients with venous insufficiency are at risk for recurrence. The lifelong use of elastic compression stockings (30–40 mm Hg) is the mainstay of therapy, but early intervention after recurrence is critical. Health professionals need to understand the importance of further research to ultimately minimize the psychological, physical, and socioeconomic impact that ulcers caused by venous insufficiency have on patients and society.

References


Figure 1. Simplified algorithm for the diagnosis and treatment of patients with venous ulcers. Abbreviations: ABI = ankle-brachial index; MPFF = micronized purified flavonoid fraction; SCC = squamous cell carcinoma.
Parovirus B19
- Clinical: “Slapped cheeks” reticular erythema on trunk or extremities following fever, constitutional symptoms; arthralgias, arthritides, purpuric eruptions; transient aplastic crisis, fetal hydrops
- Laboratory: B19 specific IgM serology, PCR

Molluscum Contagiosum
- Clinical: Few to multiple 1- to 4-mm umbilicated flesh-colored papules
- Laboratory: Histopathology if clinical appearance atypical

Orf
- Clinical: One to several solid to vesicular nodules on hands, forearms; history of exposure to sheep, goats, cattle
- Laboratory: Histopathology if clinical appearance atypical; PCR

Abbreviations: gG = glycoprotein G; HSV = herpes simplex virus; IVIg = intravenous immunoglobulin; PCR = polymerase chain reaction.

CURRENT THERAPY

Herpes Simplex Viruses 1 and 2
- Acyclovir (Zovirax), valacyclovir (Valtrex), famciclovir (Famvir)
- For acyclovir resistance: foscarnet (Foscavir),1 cidofovir (Vistide)1

Varicella-Zoster Virus
- Acyclovir, valacyclovir, famciclovir
- For acyclovir resistance: foscarnet,1 cidofovir (Vistide)1

Hand-Foot-and-Mouth Disease
- Supportive care

Parovirus B19
- Supportive care, IVIg (Gammagard)1

Molluscum Contagiosum
- Surgical or chemical methods of destruction
- Immunomodulators (imiquimod [Aldara],1 cimetidine [Tagamet]1)

Orf
- Self-limited

Abbreviations: HSV = herpes simplex virus; IVIg = intravenous immunoglobulin.

Herpes Simplex Viruses 1 and 2
Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) are the most closely related members of the human herpesvirus family, and the skin lesions they produce are clinically indistinguishable. Clusters of tense blisters on an erythematous base often quickly evolve into erosions or ulcerations with associated crustling. Lesions can develop at any mucocutaneous site but are typically found in the perioral or anogenital regions. Both HSV-1 and HSV-2 are transmitted by direct mucocutaneous contact with an infected host. Following viral replication in the skin or mucosa, intact viral nucleocapsids travel via sensory neurons to the corresponding dorsal root ganglia to establish latency. Later, a variety of stimuli can trigger reactivation. The virus travels back along the sensory neurons to the mucocutaneous surface to replicate and induce active or subclinical infection. In the case of subclinical infection, no active skin lesions are evident, but infectious particles are present, a state known as asymptomatic shedding. Although the viral titer is much lower than during clinically active disease, asymptomatic shedding of the virus in oral and genital secretions is thought to be responsible for the majority of cases of HSV transmission.

Primary, initial nonprimary (also known as first episode), and recurrent are terms used to further define the nature of the HSV infection. A primary infection refers to a patient’s first infection with either type of HSV at any site. These patients are seronegative initially but subsequently develop HSV type-specific antibodies. A patient who is already infected with one HSV type and then develops an infection with the alternate type experiences an initial nonprimary or first-episode infection (e.g., the first episode of genital herpes in a patient with a prior history of orofacial herpes). These patients are seropositive for one type-specific HSV antibody (e.g., HSV-1) and later develop antibodies specific for the alternate HSV type (e.g., HSV-2). A recurrent infection is one that occurs at a site of prior infection. These patients are seropositive for HSV-1 or HSV-2, or both. Because most primary infections, whether oral or genital, are asymptomatic, the first evidence of disease often represents a recurrent or initial nonprimary infection.

Orofacial Herpes Simplex Virus Infection
Orofacial HSV, also known as herpes labialis, fever blisters, or cold sores, is commonly acquired during childhood or adolescence. Symptomatic primary disease usually takes the form of gingivostomatitis with or without additional lesions on the cutaneous perioral surfaces. Fever, malaise, and tender lymphadenopathy may also be present. In recurrent episodes, clusters of blisters erupt along the vermilion border of the lips, and subsequent erosions and crusting persist for several days up to 2 weeks. Lesions can develop anywhere in the perioral area, especially on the cheeks. In men, a viral folliculitis of the beard area (herpetic sycosis) may be mistaken for a bacterial process because it is often pustular. The presence of a prodrome and recurrence in the same site are clues to the correct diagnosis. Although recurrent intraoral lesions of HSV can occur, they are uncommon in immunocompetent persons. Exposure to ultraviolet light is a common trigger factor for herpes labialis, as is fever or intercurrent infection.

Genital Herpes Simplex Virus Infection
When symptomatic, primary genital herpes often involves bilaterally distributed lesions in the anogenital area with associated fever, inguinal adenopathy, and dysuria or urinary retention. Aseptic meningitis can also occur. The lesions often persist for 2 to 3 weeks or longer. Nonprimary infections are usually less severe and have fewer constitutional symptoms. Recurrent episodes tend to be milder and shorter in duration. Often, there is a prodrome of tingling or burning followed by the development of localized vesicles that can quickly rupture, leaving nonspecific erosions or ulcerations. The lesions may be anywhere within the anogenital region but tend to recur close to the same area in subsequent episodes. The time between exposure and development of primary disease is estimated to be from 3 to 14 days. However, more often the first clinical indication of disease is a recurrence, which can occur weeks to years after the initial infection. Prior infection with HSV-1 provides some protection against acquisition of HSV-2.

Based on seroepidemiologic evidence, it is estimated that approximately 17% of the United States population aged 14 to 49 years is infected with HSV-2. In most of these persons, this disease has not been officially diagnosed and they are unaware that they are infected. Nevertheless, they experience asymptomatic shedding and unknowingly transmit the disease to sexual partners. Interrupting this cycle of transmission has become a major focus among health care providers who work with these patients. A combination of patient education and appropriate use of systemic antiviral agents may be gradually having some impact on this epidemic. Recommendations for patients with genital herpes include avoiding sex with uninfected partners when active lesions or prodromal symptoms are present and routinely using latex condoms to minimize transmission during periods of asymptomatic shedding. Chronic suppressive doses of oral antiviral agents (Table 1), including acyclovir (Zovirax), valacyclovir (Valtrex), and famciclovir (Famvir), significantly reduce the frequency of clinical recurrences as well as the rate of asymptomatic shedding and may be recommended together with these other practices to reduce the risk of transmission.

Although HSV-2 is the etiologic agent in a majority of cases of genital herpes infections, an increasing number of genital herpes
infections are caused by HSV-1. Symptomatic recurrences and asymptomatic shedding are less frequent with genital HSV-1 infection than with genital HSV-2 infection, and this distinction becomes important for patient counseling and prognosis.

Other Mucocutaneous Herpes Simplex Virus Infections

Eczema herpeticum, also known as Kaposi's varicelliform eruption, represents a cutaneous dissemination of HSV usually seen in patients with atopic dermatitis or other underlying skin disease. Herpetic vesicles develop over an extensive mucocutaneous surface, most often the face, neck, and upper trunk, presumably spreading from a recurrent oral HSV infection or asymptomatic shedding from the oral mucosa. Eczema herpeticum can also develop in the presence of genital HSV. As with other HSV infections, eczema herpeticum may be recurrent. In addition, patients can develop localized, recurrent HSV in previously involved areas. Because of the extensive and inflammatory nature of the process and the possible secondary bacterial infection, the underlying viral etiology may be obscured. A history of eczema and recurrent HSV in the patient and careful observation for the grouped vesicles or erosions can be key to the correct diagnosis.

Herpetic whitlow refers to HSV infection of the hand, usually one or more distal digits. Previously thought to be limited to health care professionals with exposure to oral secretions of their patients, it is now recognized that autoinoculation from orolabial or genital HSV contributes to a significant number of cases. Herpes gladiatorum is a problem seen most commonly in athletes who participate in close contact sports such as wrestling. Typically transmitted from active herpes labialis or asymptomatic shedding in oral secretions of an infected opponent, herpes gladiatorum often affects the head, neck, or shoulders and may be recurrent. In the wrestler with frequent outbreaks, chronic suppressive therapy may be recommended.

**Diagnosis**

Viral culture remains a common and acceptable method for diagnosing HSV infection. This method is sensitive when specimens are obtained from lesions that have not yet become too dry or crusted, usually during the first 2 to 3 days after onset. An adequate sample, obtained by unreroofing the blister and swabbing the base, increases the likelihood of an accurate result. Antigen detection tests can remain positive even after lesions have dried, as long as the specimen includes epithelial cells and not just debris. For this method, a scraping from the lesion is usually smeared on a glass slide to be sent to the laboratory. Not all antigen detection methods are designed to distinguish HSV-1 from HSV-2.

Polymerase chain reaction (PCR) is highly sensitive and has become routinely available for diagnosis of mucocutaneous HSV infections.

The Tzanck smear (cytologic detection) is both insensitive and nonspecific but may be of use in some clinical settings. It does not differentiate HSV types or HSV from varicella-zoster virus (VZV).

Serologic testing for HSV was previously of limited use because it could not reliably differentiate HSV-1 from HSV-2. Because they share significant genetic homology, HSV-1 and HSV-2 code for a number of common proteins that are not antigenically distinct. However, they also code for type-specific proteins that can be used to differentiate them. Current tests based on detecting type-specific viral glycoprotein G (gG-based, type-specific assays) are accurate and should be requested for this purpose. A positive HSV-2 serology may be useful in confirming the diagnosis of genital herpes in a patient with a negative viral culture or with unrecognized or asymptomatic disease. Alternatively, a negative serology can help exclude the diagnosis of HSV in a patient with chronic, nonspecific oral or genital symptoms.

**Varicella-Zoster Virus**

VZV, another member of the human herpesvirus family, produces two specific patterns of disease in the skin. The primary infection results in varicella, also known as chickenpox, a widespread vesicular eruption usually seen in the pediatric population. Following the primary infection, VZV establishes latency in the dorsal root ganglia until some later point, when reactivation can occur. The ensuing unilateral dermatomal distribution of blisters, often preceded by neuralgic pain, is known as herpes zoster or shingles. Herpes zoster is especially common in patients older than 50 years, but it may be seen at any age. It is also seen more commonly in immunocompromised patients, such as organ-transplant recipients or patients infected with HIV. Herpes zoster is no longer considered a marker for underlying cancer, and evaluation for occult malignancy in an otherwise asymptomatic patient is not indicated. A single recurrence of herpes zoster, usually in the same dermatome, occurs in up to 4% of zoster patients. Additional recurrences, however, suggest a dermatomal form of HSV, and laboratory assessment for this possibility may be indicated.

### TABLE 1
Recommendations for Systemic Antiviral Treatment of Mucocutaneous Herpes Simplex Virus Infection

<table>
<thead>
<tr>
<th>EPISODE</th>
<th>DRUG</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genital Herpes Simplex Virus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary or first episode</td>
<td>Acyclovir1</td>
<td>15 mg/kg PO tid × 7 d</td>
</tr>
<tr>
<td></td>
<td>Valacyclovir1</td>
<td>500 mg bid × 7 d</td>
</tr>
<tr>
<td>Recurrent episode (start at prodrome)</td>
<td>Acyclovir1</td>
<td>400 mg PO tid or 200 mg PO bid × 5 d</td>
</tr>
<tr>
<td></td>
<td>Valacyclovir</td>
<td>500 mg PO bid × 3 d</td>
</tr>
<tr>
<td>Chronic suppression</td>
<td>Acyclovir1</td>
<td>&gt;6 outbreaks per year: 400 mg PO bid or 200 mg PO tid</td>
</tr>
<tr>
<td></td>
<td>Valacyclovir</td>
<td>Adjust up or down according to response</td>
</tr>
<tr>
<td></td>
<td>Famiciclovir</td>
<td>1 g PO bid × 1 d or 125 mg PO bid × 5 d</td>
</tr>
<tr>
<td><strong>Orofacial Herpes Simplex Virus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary or first episode</td>
<td>Acyclovir1</td>
<td>15 mg/kg PO bid × 7 d</td>
</tr>
<tr>
<td></td>
<td>Valacyclovir1</td>
<td>500 mg PO bid × 7 d</td>
</tr>
<tr>
<td>Recurrent episode (start at prodrome)</td>
<td>Acyclovir1</td>
<td>400 mg PO bid × 3 d</td>
</tr>
<tr>
<td>Chronic suppression</td>
<td>Acyclovir1</td>
<td>400 mg PO bid-tid</td>
</tr>
<tr>
<td><strong>Orolabial or Genital Herpes Simplex Virus in Immunosuppressed Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent or suppressive</td>
<td>Acyclovir1</td>
<td>400 mg PO bid or 5–10 mg/kg IV q8h</td>
</tr>
<tr>
<td></td>
<td>Valacyclovir</td>
<td>500 mg PO bid</td>
</tr>
<tr>
<td></td>
<td>Famiciclovir</td>
<td>500 mg PO bid</td>
</tr>
</tbody>
</table>

1Not FDA approved for this indication.

3Exceeds dosage recommended by the manufacturer.
The most common dermatomes involved with herpes zoster are in the thoracolumbar (T3-L2) and trigeminal (V1) regions. Skin lesions typically evolve from papules to vesicles and pustules, and then to crusts and erosions, before healing approximately 2 to 4 weeks after onset. The associated neuropathic pain commonly persists after the lesions have healed. Pain that continues for more than 3 months after the skin lesions resolve is referred to as post-herpetic neuralgia, one of the most common and debilitating complications of this infection.

Several clinical presentations of herpes zoster deserve additional attention. Ophthalmic zoster, with lesions along the tip, side, or base of the nose indicating involvement of the nasociliary branch of the trigeminal nerve (Hutchinson’s sign), may be associated with increased risk for ocular complications. Prompt initiation of a systemic antiviral agent (Table 2) and evaluation by an ophthalmologist are recommended. Disseminated zoster, with more than a few lesions outside the primary and immediately adjacent dermatomes, can indicate visceral involvement and its associated complications. The term “zoster sine herpete” describes patients with neuropathic pain resembling zoster but without any skin lesions. The diagnosis can be supported by demonstration of increased IgG antibody titers between the acute and convalescent phases. Chronic zoster is seen predominantly in HIV-infected persons. Single or multiple warty growths can persist for weeks or months in areas of skin previously involved by typical lesions of varicella or herpes zoster. Chronic zoster is often resistant to acyclovir. Tissue biopsy and viral cultures, with further testing for antiviral resistance, may aid in assessment.

### TABLE 2 Recommendations for Systemic Antiviral Treatment of Herpes Zoster

<table>
<thead>
<tr>
<th>DRUG</th>
<th>IMMUNOCOMPETENT PATIENTS</th>
<th>IMMUNOSUPPRESSED PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>800 mg PO 5 × per d 7–10 d</td>
<td>800 mg PO 5 × per d 7–10 d*</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>1 g PO tid × 7 d</td>
<td>1 g PO tid × 10 d*</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>500 mg PO tid × 7 d</td>
<td>500 mg PO tid × 10 d*</td>
</tr>
</tbody>
</table>

*Continue until there are no new lesions for 48 h.

### TOPICAL TREATMENT OPTIONS FOR MUCOCUTANEOUS HERPES SIMPLEX VIRUS AND VARICELLA-ZOSTER VIRUS INFECTIONS

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cool, moist compresses using tap water or aluminum acetate 1:20 to 1:40 (Burow’s solution, Domeboro, Bluboro)</td>
<td>Good for moist, oozing lesions to accelerate drying. Apply wet dressing to involved skin and cover with a dry cloth to allow evaporation.</td>
</tr>
<tr>
<td>Calamine lotion or similar shake lotion containing alcohol, menthol, and/or phenol; Aveeno colloidal oatmeal</td>
<td>Useful as drying and antipruritic agent. May be applied after wet dressing.</td>
</tr>
<tr>
<td>Bacitracin, Polysporin, mupirocin (Bactroban)</td>
<td>Use if there is concern for localized secondary bacterial infection.</td>
</tr>
<tr>
<td>2% Viscous lidocaine, compounded suspensions (e.g., Kapectate or Maalox, diphenhydramine, lidocaine)</td>
<td>Useful for temporary pain relief of oral or genital mucosal involvement.</td>
</tr>
<tr>
<td>Acyclovir ointment</td>
<td>Used together with systemic antiviral agents, may be of benefit to immunocompromised individuals for localized HSV.</td>
</tr>
<tr>
<td>Penciclovir (Denavir) cream</td>
<td>Can decrease the duration of lesions in herpes labialis by half a day if applied every 2 h while awake for 4 days beginning at the first sign of disease.</td>
</tr>
</tbody>
</table>

1Not FDA approved for this indication.

6May be compounded by pharmacists.

Abbreviation: HSV = herpes simplex virus.

### Herpes Zoster

**Diagnosis**

Diagnosis of herpes zoster is often made on clinical grounds alone. A Tzanck smear can provide additional support of the viral etiology. With atypical presentations, however, the diagnosis is best confirmed by either an antigen detection method or viral culture. Both differentiate VZV from HSV. Samples submitted for viral culture should be obtained from vesicular fluid because dried or crusted lesions are unlikely to yield positive results. Viral cultures are required if there is a need to assess possible antiviral resistance. PCR can be useful for detecting VZV in bodily fluids such as cerebrospinal fluid. Basic VZV serology is rarely useful for diagnosis, because a majority of the population is seropositive.

### Treatment

There are three systemic antiviral agents routinely used for the treatment of HSV and VZV infections: acyclovir, valacyclovir, and famciclovir. All three are highly effective and generally well tolerated. Because they inhibit only actively replicating viral DNA, they have no impact on latent infection. Recommendations for antiviral treatment of mucocutaneous HSV infections and herpes zoster, localized topical measures, and available formulations are outlined in Tables 1 to 5. Optimal antiviral dosage schedules for less-common HSV infections, such as herpetic whitlow, have not been determined. The doses outlined in Table 1 for either episodic or chronic suppressive therapy can be used as a guideline in these cases.

Acyclovir became available more than 25 years ago and continues to be widely used. Inside an infected host cell, acyclovir must be phosphorylated—first by a virally encoded enzyme (thymidine kinase) and then by host-cell enzymes—to the active form of the drug, acyclovir triphosphate. As a nucleotide analogue, acyclovir triphosphate is incorporated into replicating viral DNA, abruptly terminating further synthesis of that viral DNA chain. Acyclovir triphosphate also interferes with viral DNA replication by directly inhibiting viral DNA polymerase. Valacyclovir is an oral prodrug of acyclovir and has a much higher bioavailability. After ingestion, valacyclovir is rapidly metabolized to acyclovir, and the subsequent mechanism of action is as just described. Famciclovir is an oral prodrug of penciclovir (Denavir), designed for greater bioavailability. Similar to acyclovir, penciclovir must first be phosphorylated by viral thymidine kinase and then by cellular enzymes to penciclovir triphosphate. In this active form, penciclovir triphosphate interferes with viral DNA synthesis and...
replication by inhibiting viral DNA polymerase. Famciclovir has greater bioavailability and a longer intracellular half-life than acyclovir. For all three agents, the required activation by viral thymidine kinase and the preferential inhibition of viral DNA synthesis contribute to the highly specific antiviral activity.

If taken as recommended, acyclovir, valacyclovir, and famciclovir are generally comparable in their safety and effectiveness. Valacyclovir and famciclovir offer the convenience of less-frequent dosing. Dosing for all three should be adjusted in the presence of renal insufficiency (see Table 5).

Although antiviral therapy does not decrease the incidence of postherpetic neuralgia, all three agents decrease the time for lesion healing and shorten the overall duration of pain if initiated within 48 to 72 hours after the onset of herpes zoster. Valacyclovir and famciclovir appear to be more effective than acyclovir for this purpose, presumably because of easier dosing. An otherwise healthy person younger than 50 years who has discrete involvement on the trunk and mild to moderate pain might benefit minimally or not at all from this intervention, especially if it is initiated after 72 hours of lesion onset. However, patients who are older than 50 years, are immunosuppressed, have involvement in the ophthalmic distribution, or have more-extensive lesions or severe pain should receive systemic antiviral therapy, even if the 72-hour dead- line has expired. Adequate pain control, often requiring opiates, is also important.

The addition of systemic corticosteroids to the antiviral regimen remains controversial. There is evidence to suggest this can lessen the severity of the acute episode but does not decrease the incidence or duration of postherpetic neuralgia. Corticosteroids may be of benefit in herpes zoster complicated by facial paralysis or cranial polyneuropathy. Corticosteroids should not be used without concomitant systemic antiviral therapy.

In patients 60 years of age or older, the live-attenuated herpes zoster vaccine (Zostavax) was shown to substantially reduce the incidence of both herpes zoster and postherpetic neuralgia. It is recommended that this option be discussed with immunocompetent patients in this older age group.

Despite widespread use of these antiviral agents, antiviral resistance is rarely a problem in the immunocompetent population. However, it does arise in the setting of immunosuppression. The basis for the resistance is most commonly a mutation in the gene coding for thymidine kinase. Less often there is a mutation in the viral DNA polymerase. In either case, all three standard drugs become ineffective. Alternative antiviral agents available for

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Formulations of Acyclovir, Valacyclovir, and Famciclovir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRUG</strong></td>
<td><strong>ORAL</strong></td>
</tr>
<tr>
<td>Acyclovir</td>
<td>200, 400, 800 mg</td>
</tr>
<tr>
<td></td>
<td>200 mg/5 mL suspension</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>500 mg, 1 g</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>125, 250, 500 mg</td>
</tr>
<tr>
<td>Penciclovir (Denavir)</td>
<td>No</td>
</tr>
</tbody>
</table>

| TABLE 5 | Recommended Antiviral Dose Modification in Patients with Impaired Renal Function |
|----------------------|---------------------------------|--------------------------------|
| **CREATININE CLEARANCE (ml/min)** | **GENITAL HERPES SIMPLEX VIRUS** | **HERPES ZOSTER** | **HERPES LABIALIS** |
| Acyclovir (Zovirax)  | **INITIAL**                     | **RECURRENT**                  | **SUPPRESSION**  | **1 G Q12H**          |
| >25                  | 200 mg 5 ×/d                    | 200 mg 5 ×/d                   | 400 mg q12h     | 800 mg 5 ×/d          |
| 10–24                | 200 mg 5 ×/d                    | 200 mg 5 ×/d                   | 400 mg q12h     | 800 mg q8h            |
| <10                  | 200 mg q12h                     | 200 mg q12h                    | 200 mg q12h     | 800 mg q12h           |
| Valacyclovir (Valtrex)| 1 g q12h                       | 500 mg q12h                    | 500 mg-1 g q24h | 1 g q8h               |
| >50                  | 1 g q12h                       | 500 mg q12h                    | 500 mg-1 g q24h | 1 g q12h              |
| 30–49                | 1 g q12h                       | 500 mg q12h                    | 500 mg q24-48h  | 1 g q24h              |
| 10–29                | 1 g q24h                       | 500 mg q24h                    | 500 mg q24-48h  | 500 mg bid for 1 d    |
| <10                  | 500 mg q24h                     | 500 mg q24h                    | 500 mg q24-48h  | 500 mg q24h           |
| Famciclovir (Famvir)| >60                            | 125 mg q12h                    | 250 mg q12h     | 500 mg q8h            |
| 40–59                | 125 mg q12h                    | 250 mg q12h                    | 500 mg q12h     | 500 mg q12h           |
| 20–39                | 125 mg q24h                    | 125 mg q12h                    | 500 mg q24h     | 500 mg q24h           |
| <20                  | 125 mg q24h                    | 125 mg q24h                    | 250 mg q24h     | 500 mg q24h           |
| >60                  | 1 g bid × 1 d                  | 1500 mg single dose            |                |
| 40–59                | 500 mg bid × 1 d               | 750 mg single dose             |                |
| 20–39                | 500 mg single dose             | 500 mg single dose             |                |
| <20                  | 250 mg single dose             | 250 mg single dose             |                |
Hand-Foot-and-Mouth Disease
Hand-foot-and-mouth disease is typically a disease of childhood. The most common etiologic agent is a nonpolio enterovirus, Coxsackie A16, and transmission is via the oral–oral or fecal–oral route. It is highly contagious. Several days after exposure, a prodrome of low-grade fever, malaise, abdominal pain, or respiratory symptoms can develop, followed by the appearance of papulovesicles on the palate, tongue, or buccal mucosa. Similar lesions can subsequently develop on the feet and hands. The eruption persists for 7 to 10 days and then resolves. Treatment is symptomatic.

Since 1997, outbreaks of hand-foot-and-mouth disease caused by enterovirus 71 have been reported in Asia and Australia. Although hand-foot-and-mouth disease associated with Coxsackie A16 infection is typically a mild illness, hand-foot-and-mouth disease caused by enterovirus 71 has shown a higher incidence of neurologic involvement, including fatal cases of encephalitis.

Parvovirus B19
Cutaneous manifestations of parvovirus B19 infection include the childhood exanthem known as erythema infectiosum (fifth disease) and, less commonly, petechial or purpuric eruptions. The virus is transmitted primarily via respiratory secretions and, to a much lesser extent, through blood or blood products. The host cells for viral replication are erythroid progenitor cells, which subsequently undergo cell lysis.

A child with erythema infectiosum typically develops a low-grade fever and nonspecific upper respiratory symptoms approximately 2 days before the onset of rash. The rash has been described as having a slapped-cheeks appearance, with prominent redness over the malar eminences. This is followed by a pink-to-red lacy or reticular eruption over the trunk and extensor surfaces of the arms and legs. The rash usually lasts a week to 10 days but can transiently recur over months in response to precipitating factors such as sunlight, exercise, and bathing. Diagnosis of erythema infectiosum is usually made on clinical grounds, and treatment is symptomatic. By the time the rash appears and the diagnosis has been made, the child is no longer infectious. Much less commonly parvovirus B19 infection may manifest as a papular-purpuric eruption with edema, erythema, and patechiae in a “gloves and socks” distribution on the hands and feet.

Infection with parvovirus B19 in older adolescents and adults often manifests with arthralgias or arthritis rather than a rash. In certain patient populations, parvovirus B19 infections may be associated with complications including transient aplastic crisis, chronic anemia, and hydrops fetalis. In these less-typical presentations, serology (anti-B19 IgM or documented seroconversion) may be indicated for diagnosis.

Viral Diseases of the Skin

Molluscum Contagiosum
Molluscum contagiosum are benign umbilicated papules caused by infection with the *Molluscipoxvirus*, a member of the poxvirus family. Lesions are limited to the mucocutaneous surface and typically appear in clusters on the face, trunk, and skin fold areas in children and on thighs, lower abdomen, and suprapubic areas in sexually active adults. Large numbers of lesions in an extensive distribution may be seen in the immunosuppressed population.

Transmission routinely occurs by skin-to-skin contact with an infected host, but transmission from contaminated fomites has been reported. Autoinoculation commonly occurs. Diagnosis is usually based on clinical examination, but histopathology of atypical lesions may be used for confirmation.

Because molluscum contagiosum tends to be self-limited, treatment is not always required, but it can reduce the risk of autoinoculation and transmission to others. Treatment modalities are primarily aimed at destroying the lesions, similar to those used for verruca vulgaris (Table 6). In the case of sexual transmission, evaluation for other sexually transmitted diseases may be indicated.

Orf and Milker’s Nodules
Orf (also known as echthema contagiosum) and milker’s nodules are caused by the closely related *Parapoxvirus*, a member of the poxvirus family. The virus responsible for orf is widespread in sheep and goats, whereas the virus causing milker’s nodules is found in cattle. Transmission to humans is by direct contact with infected animals or recently vaccinated animals and is usually seen several days and up to 2 weeks after exposure. Preexisting skin trauma or other disruption of the normal cutaneous barrier enhances the risk of transmission. Barrier precautions and proper hand hygiene are important preventive measures.

Orf and milker’s nodules most commonly appear as one to several nodules on the dorsal aspect of the hands or forearms. Lesions evolve through several clinical stages over a period of 3 to 5 weeks, ranging from solid red nodules to vesicular, exudative, or wartlike tumors. As with other poxvirus infections, lesions of orf often demonstrate central umbilication. Regional lymphadenopathy and lymphangitis are commonly seen.

Diagnosis is based on a history of exposure and clinical examination. Tissue biopsy for histopathology or electron microscopy

<table>
<thead>
<tr>
<th>TABLE 6 Treatment Options for Molluscum Contagiosum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TREATMENT</strong></td>
</tr>
<tr>
<td>Cryotherapy (liquid nitrogen)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Curettage</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Cantharidin (Cantharone)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Podophyllin (25% in tincture of benzoin)</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Podofilox (Condylox 0.5% gel or solution)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Salicylic acid/lactic acid (Occlusal, Duofilm)</td>
</tr>
</tbody>
</table>
|                                             | Podofilox (Occlusal, Duofilm)                 | 1
| Imiquimod (Aldara) 5% cream                  | Done by patient: Apply daily 5 consecutive d/wk |
|                                             | Leave on overnight                           |
|                                             | Continue for 8–12 wk                          |
|                                             | Cimetidine (Tagamet)                         | 1
|                                             | 30 mg/kg/d PO × 6–12 wk                      |
|                                            | Can boost cell-mediated immunity              |
| *Candida* antigen (Candin)                  | Intranasal injection 0.3 mL                   |

1Not FDA approved for this indication.

2Exceeds dosage recommended by the manufacturer.
may also be used. Orf virus infection can resemble skin lesions associated with potentially life-threatening zoonotic infections such as tularemia, cutaneous anthrax, and erysipeloid. Should this be a concern, definitive diagnostic testing using PCR is available through the Centers for Disease Control and Prevention (CDC).

In general, the lesions of orf are self-limited, resolving within 4 to 6 weeks, and treatment is not routinely required. However, immunocompromised persons can develop more progressive and destructive lesions requiring therapeutic intervention such as topical cidofovir\(^1\)\(^2\) or imiquimod (Aldara).\(^1\)

\(^1\)Not FDA approved for this indication.
\(^2\)May be compounded by pharmacists.

### References


### WARTS (VERRUCA)

**Method of**

Anne E. Rosin, MD

### CURRENT DIAGNOSIS

- Common warts: rough, hyperkeratotic, firm papules on the hands, legs, or feet
- Flat warts: small, flat-topped, pink or flesh-colored papules on the face, arms, or legs
- Plantar and palmar warts: hard, thickened, callus-like lesions that disrupt skin lines
- Mosaic warts: large clusters of warts
- Filiform warts: small, finger-like lesions on the face
- Differential diagnoses: seborrheic keratoses, keratoacanthoma, squamous cell carcinoma, callus, and corns

### CURRENT THERAPY

- Keratolytics such as salicylic acid
- Cantharidin (Cantharone)\(^1\)\(^6\)\(^8\)
- Cryotherapy

Warts are a nuisance. For the most part, they are benign and harmless skin growths caused by one of the more than 80 saprophytic human papillomaviruses (HPVs). These viruses are ubiquitous and spread by contact with an infected person or indirectly through fomites such as wet towels, swimming pools, and locker room floors. The conventional thinking is that the epidermis must be defective at the site of inoculation.

### Clinical Features

Nongenital warts affect 10% of the population and are among the three most common reasons for dermatologic visits. Warts are more common in adolescents and in immunosuppressed persons because of immature or compromised immune systems.

Several types of warts occur with variations in appearance, the site affected, and the virus involved. Common warts (i.e., verruca vulgaris) are rough, hyperkeratotic, firm papules that most often occur on the hands and legs and that are caused by HPV types 1, 2, or 4. Flat warts (i.e., verruca planae), caused by HPV 3 or 10, are small, flat-topped, and flesh-colored growths that occur in large numbers on the face, arms, or legs. Plantar and palmar warts (i.e., verruca plantares et palmares) are hard, thickened, callus-like lesions that disrupt skin lines on the soles or palms. Mosaic warts are larger clusters of these warts. Filiform warts are small, digitate or finger-like lesions most commonly seen on the face, especially around the eyelids, nose, and mouth. Periungual warts are common warts impinging on and growing under fingernails or toenails. Genital warts are discussed in a separate chapter.

Differential diagnoses include seborrheic keratoses, keratoacanthoma, squamous cell carcinoma, callus, and corns. Paring the stratum corneum (outer layer of the skin) may reveal thrombosed or bleeding capillaries seen as black dots.

The manifestation of viral warts and various modes of therapy have been referenced throughout history. The word *condyoma* is of Greek origin and means “knuckle or knob”; *verruca* is Latin for “little hill.” Warts are mentioned in early Hippocratic writings and in the Old and New Testaments of the Bible. In Arthurian legend, King Arthur was known by the diminutive nickname wart until he proved his royalty by pulling Excalibur from a stone. Chaucer described a distinctive wart on the Miller’s nose in his *Canterbury Tales*. Shakespeare invokes warts as the result of a curse in *Hamlet*. The phrase “warts and all” is attributed to Oliver Cromwell, who gave specific instructions to his portraitist. Tom Sawyer was afflicted with common warts from “playing with frogs” (obviously not possible because HPV is species specific). Even “The King,” Elvis Presley, had a wart removed from his right hand. It now resides in a velvet-lined box in a museum in Hawaii.

### Treatment

**Alternative and Standard Approaches**

Because 40% of warts will spontaneously disappear within 2 years in healthy individuals, treatment is not always necessary. As a corollary, treatment of warts does not guarantee their complete resolution. Many patients are compelled to seek treatment of their warts because of the social embarrassment or physical discomfort that warts can cause. Patients with compromised immune systems due to immunodeficiency or immunosuppression are at higher risk for numerous warts, and treatment to prevent their progression to squamous cell carcinoma is important.

Popular reports and the medical literature are replete with descriptions of successful methods for treating warts. Whether
Warts (Verruca)

anecdotal or evidence based, reports are largely without the support of randomized, controlled trials. No one therapy is always effective, and warts resolve, recur, shrink, or grow despite therapy. It is likely that all wart therapies work by triggering an immune response to the presence of papillomavirus in the skin.

Treatment methods fall into several broad categories, which include folk remedies, over-the-counter (OTC) treatments, and office-based therapies. Office-based treatments include destructive methods, surgical or laser procedures, immunologic intervention, and combination therapy.

Folk remedies for curing warts are espoused by Tom Sawyer and Huck Finn more than once in Mark Twain’s classics. Tom recommended rubbing the warts with a split potato and then burying the potato, whereas Huck was certain that swinging a dead cat over his head and then burying it trumped the potato. They recited the wart chant:

*Barley-corn, barley-corn, injun meal shorts,*

*Spunk-water, spunk-water, swallow these warts.*

Both agreed that the wart chant spoken at midnight in the middle of the woods was the superior method, although neither was brave enough to prove the hypothesis.

The many alternative folk cures include transference, various prayers and incantations, hypnosis, and applications of garlic extract, tea tree oil, bacon fat, blood or entrails of various animals, and saliva of a loved one. Duct tape application has received much attention. One study comparing cryotherapy with duct tape occlusion of common warts showed resolution in 85% of the children treated by occlusion, compared with 60% in the liquid nitrogen group. Another study found no statistically significant difference between duct tape and moleskin for the treatment of warts in an adult population.

Treatment of warts is often initiated by the patient, who most often uses one of the OTC salicyclic acid products available. These keratolytic products, when used consistently and as directed, can be quite successful. Unfortunately, salicylic acid treatment, which destroys the infected epidermis and causes an immune reaction, can be irritating and tedious, prompting many patients to seek medical care.

Office-based treatments are largely destructive or immunomodulating, or both. The first line of therapy in the physician’s office is usually cryotherapy. Liquid nitrogen is −196°C in the canister, and when applied by cotton-tipped application or cryospray, it effects a freeze that far surpasses a Wisconsin winter’s frostbite. It is painful, unfortunately. Another destructive physician-applied treatment is cantharidin (Cantharone), a chemical derived from blister beetles. It is painless on application and well tolerated by children. Acids, including bichloroacetic and trichloroacetic (Tri-Chlor), have risks, including pain on application, ulceration, and scarring.

Other destructive methods of wart removal usually are reserved for resistant or multiple lesions. Surgical removal followed by electrodessication and curettage is effective for large, solitary common warts but requires local anesthesia and results in scarring. Laser therapy, most often with pulsed-dye (PDL) or carbon dioxide (CO₂) lasers, has its place for selected patients. The PDL method is less aggressive and less painful than CO₂ vaporization, which is reserved for resistant common or plantar warts, multiple warts in immunosuppressed patients, or genital warts.

Immune modulation alone or in combination with destructive methods is helpful in treating resistant warts. The newest immunomodulator in the wart warrior’s armamentarium is imiquimod (Aldara), which was initially approved for treatment of genital warts but has since received FDA approval for treatment of non-melanoma skin cancers. It is also frequently used to treat flat warts, acting through immune system modulation by inducing cytokines, including interferon-α. Other topical immunomodulators, such as squaric acid dibutylester (SADBE) and diphenycyprone, are contact sensitizers that induce an allergic dermatitis through type IV hypersensitivity reactions. Treatment with SADBE is well tolerated and a good choice for recalcitrant warts in children, although it is time consuming.

Intralesional immunotherapy by *Candida* antigen injection (Candin) is effective in improving or clearing warts in up to 74% of patients. It is considered a first-line therapy in children with large or multiple warts and second-line therapy for warts resistant to standard therapies. It is well tolerated. Intralesional interferon alfa-2b (Intron A) has been used successfully to treat genital warts and warts that have not responded to conventional therapies.

Oral immunomodulation with high-dose cimetidine (Tagamet) has been proposed as a helpful adjunctive therapy in the treatment of multiple warts in children and adults. It is postulated to enhance cell-mediated immune response. Studies comparing cimetidine with placebo have not been convincing, but cimetidine is well tolerated, and anecdotal reports of its usefulness abound.

Other topical products available for off-label treatment of warts include retinoids, formaldehyde compounds, and 5-fluorouracil (Efudex). These agents interfere with epidermal proliferation, effect a nonspecific antiviral action, or inhibit mitosis, leading to keratinocyte and therefore viral death.

Because photodynamic therapy (PDT), with 20% 5-aminolevulinic acid (ALA [Levulan Kerastick]), is all the rage in dermatologic practice for the treatment of actinic keratoses, acne, nonmelanoma skin cancers, and aging, why not add warts to the list? Studies have shown various success rates, but most demonstrated improvement or resolution of recalcitrant warts treated by ALA-PDT.

Family medicine physicians, internists, and dermatologists are asked to treat warts on a regular basis. Almost 50% of visits to a dermatologist are for wart treatment. The choice of therapeutic modality depends on the wart, the patient, and the practitioner. As Lennepierre stated in his treatise on the treatment of warts: “Of all the futile disorders of the skin, it would be hard to find any that are regarded with greater contempt by the lay public and yet capable of resisting a greater variety of treatment than the group of papillary lesions commonly known as warts.”

The American Academy of Dermatology has established guidelines for the treatment of warts:

- **Desire of the patient for therapy**
- **Symptoms of pain, bleeding, itching, or burning**
- **Disabling or disfiguring lesions**
- **Large numbers or large size of lesions**
- **Desire to prevent spread to unblemished skin of the patient or others**
- **Immunocompromised condition**

The goal of all therapy, including treatment of the pesky wart, should be “First, do no harm.” To ensure resolution and nonrecurrence of warts, however, the patient and practitioner must often make compromises that include inconvenience, discomfort, and scarring. Treatment choices depend on the patient’s age and level of pain tolerance; the location, type, and size of the warts; and the comfort level of the practitioner with the specific treatment.

Selected Treatment Methods

Over the years, I have used most of the office methods mentioned previously, often asking the patient to incorporate OTC methods as well. Simple methods are appropriate for warts that are small and few. In children, painless methods are preferred and usually successful. I tend to combine modalities of destruction and immune stimulation, such as cantharidin, and cimetidine in children or use liquid nitrogen and *Candida* antigen injection in more mature patients.

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1. Not FDA approved for this indication.
2. May be compounded by pharmacists.
3. Available as a dietary supplement.
Diseases of the Skin

Keratolytics, which are 40% salicylic acid plaster pads (OTC Mediplast), are an excellent first-line therapy for common hand warts and plantar warts in motivated patients. Repeated application, with pumice stone or callus file use, results in cure rates of up to 80%. This method can cause irritation if the pad slips out of place (patients should try duct tape over the plaster) and can take several weeks to work.

Cantharidin 1,6 in a 0.7% colloidal solution can induce a painless blister after application and occlusion for 8 hours. It is applied in the office and repeated every 4 weeks. It is useful for treatment of common, periungual, and plantar warts in children, and the cure rate approaches 80%. Unfortunately, an occasional “donut wart,” a ring of new warts surrounding the cleared original, occurs.

Cryotherapy uses liquid nitrogen applied by cotton applicator or, better, by a cryospray gun, and it is the most commonly used office-based treatment. The wart and a 1- to 2-mm margin around it should be frozen for 10 to 20 seconds. The freeze should be repeated once after a thaw of 20 seconds. If the warts are thick, they can be pared first. The patient is told that a blister (sometimes hemorrhagic) will result and should be left intact if possible. Treatment should be repeated every 3 to 4 weeks until normal skin markings return. If warts persist beyond 3 months of therapy, another method of treatment should be selected.

Surgery is used for large warts. Large common warts of the hands or extremities are more easily treated if they are debulked. If the wart is solitary, this method is more direct and often more successful than others. The wart should be anesthetized, removed at its base using a blade, and then curetted and cauterized. This method is not recommended for plantar warts because of scarring.

Pulsed-dye lasers (585- to 595-nm wavelength) can provide selective photothermalysis of blood vessels within the wart, which compromises blood supply and results in necrosis. This technique results in destruction of blood vessels within the wart but minimal damage to normal skin. It is generally well tolerated, but local anesthesia can be used if necessary. I use the following parameters: 7-mm spot size, pulse duration of 1.5 msec, and fluence of 10 to 12 J/cm², with double pulses applied to achieve purpura. This method is useful for recalcitrant flat, periungual, common, and plantar warts and has a success rate of 50% to 90%.

Immunotherapy is an effective method of treating some patients. I often add oral cimetidine 1 at daily doses of 30 to 40 mg/kg to other painless therapies for wart treatment in children. If the patient tolerates injections, I am a fan of Candida antigen 1 as monotherapy in patients with multiple warts or in combination with a destructive method such as cryotherapy or PDL. I choose the largest wart and inject 0.2 to 0.3 mL of a commercially available 1:1000 dilution of Candida antigen directly into the wart using a 30-gauge needle and tuberculin syringe. Pretesting is unnecessary, side effects are minimal, and more than 75% of patients treated with a series of three injections have clearing of the injected and distant warts. Imiquimod 2 is effective as monotherapy for genital warts, and I agree with anecdotal reports of its efficacy in flat warts. However, it is expensive (gram for gram it costs as much as platinum), and I have not found it useful except as adjunctive therapy for common warts. Treatment protocol is a thin coat of imiquimod cream applied three times weekly and combined with cryotherapy or salicylic acid.

Photodynamic therapy is useful for patients with multiple recalcitrant warts, especially patients who are immunosuppressed due to organ transplantation and anti-rejection therapy or human immunodeficiency virus (HIV) disease. PDT, which involves a topically applied photosensitizer that is activated by visible light, results in tissue destruction, and studies of this method for treatment of warts have been promising. My protocol includes a 60-minute incubation of affected lesions with topically applied ALA 1 followed by a 15-minute exposure to blue light, repeated every 4 weeks as needed. Transplant recipients I have treated, who typically present with many warts and early squamous cell cancers, have shown remarkable improvement in their skin lesions.

Warts are a bane and frustration to the patient and the physician who treats them. The myriad treatments available are for the most part supported by anecdotal evidence rather than randomized control trials. There are few inclusive reviews of successful treatment methods, and until an effective HPV vaccine is developed for all strains that cause warts, we will have to limp along using methods that are comfortable and have produced results. Each treatment should be tailored to fit the wart, the patient, and the practitioner.

1Not FDA approved for this indication.
2May be compounded by pharmacists.

References

SUNBURN
Method of
Warwick L. Morison, MD

CURRENT DIAGNOSIS
- Sunburn appears 3 to 4 hours after exposure to sunlight or an artificial source of UV radiation such as a sunlamp.
- The redness of skin is diffuse and continuous, unlike rashes, which are often discontinuous.
- Sunburns are graded as pink, red, and blistering.

CURRENT THERAPY
- Prevention is the best approach to management and consists of a package of measures: avoiding over-exposure, using sunscreens, and wearing protective clothing.
- Treatment of a sunburn consists of cool baths and use of moisturizing creams.
- Topical and systemic corticosteroids do not alter the course of a sunburn.

Sunburn is a common problem, particularly in fair-skinned white persons, caused by excessive exposure to ultraviolet (UV) radiation from sunlight or artificial sources such as sunlamps. When induced by sunlight, it is mainly due to UVB (280–320 nm) radiation plus a smaller contribution from UVA (320–400 nm) radiation. Sunburn is also described as erythema, and it appears 3 to 4 hours after exposure, reaches a maximum at 12 to 18 hours, and usually settles after 72 to 96 hours. In severe reactions with blistering, complete resolution can take a week or more.

Sunburns are graded as pink, red, and blistering. In contrast, thermal burns are graded by degree (first, second, and third), but this classification should not be applied to sunburns because thermal burns have quite different sequelae, such as scarring and death, which are extremely rare consequences of a sunburn. Keratoconjunctivitis, or ocular sunburn, can also be caused by UV radiation and it follows a similar time course.

There are two facets to management of sunburn: prevention and treatment. Because there is no effective treatment for an established sunburn, most emphasis should be placed on prevention.

Prevention
Skin color and the capacity of a person to tan will determine how important it is for an individual person to take preventive measures. However, even dark-skinned people can sunburn provided the exposure dose is sufficiently high. Skin color, past history of sunburn, and likely exposure should therefore be used as a guide in advising people about protection. Protection from sunlight is often equated with use of sunscreens, but this approach is too narrow, and protection should consist of a package of measures: avoiding overexposure to sunlight, using sunscreens, and wearing protective clothing.

Avoidance of Exposure
Simple avoidance of excessive exposure to a threshold dose of UV radiation is often the best advice for fair-skinned people. Scheduling outdoor activities for before 10 am and after 4 pm will avoid the peak UV irradiance period and still permit enjoyment of the outdoors. This advice should be accompanied by several warnings. Sitting in the shade or under a beach umbrella only reduces exposure by about 70%. A cloudy day is often the setting for the worst sunburns because even complete white cloud cover reduces UV exposure by only about 30%.

Clothing is not always an effective protector. If it is possible to see through a fabric, UV radiation can also penetrate to a significant extent. The geographic location of exposure must also be considered because UV radiation may be twice as intense at the equator as compared with much of continental North America.

Sunscreens
There are now a great number of sunscreens on the market, and they contain numerous active ingredients. If this is not enough to cause confusion, some are not even labeled as sunscreens: sunblocks and tanning lotions are other terms. However, the informed physician need only know four properties of a sunscreen: the sun protection factor (SPF), the spectrum of protection, the base, and whether or not it is water resistant.

The SPF is a index of the amount of protection provided by the sunscreen. For example, a fair-skinned person who normally begins to sunburn after a 10-minute exposure to sunlight should be able to tolerate up to 150 minutes of exposure after application of an SPF 15 sunscreen.

There are several provisos for this statement. To provide the stated protection, a sunscreen must be applied 10 minutes before exposure to allow binding to skin proteins to occur, and it must be applied in an adequate amount. Several studies have shown that under ideal circumstances in which sunscreen is supplied freely and the subject is observed while making the application, most people only use one half the required amount. Ordinary use probably provides much less protection. As a rough guide, one ounce of sunscreen is necessary to cover a 70-kg adult in a bathing suit; in other words, a four ounce bottle of sunscreen only provides four applications.

Sunscreens vary in the amount of the solar spectrum for which they provide protection. All sunscreens provide protection against UVB radiation and the shorter end of UVA radiation. Some sunscreens claim to provide broad-spectrum protection against UVB and UVA radiation and contain avobenzone or titanium dioxide to protect against the longer wavelengths in the UVA spectrum. Ecamsule (Mexoryl SX), a recently approved sunscreen active, provides good absorption in the middle of the UVA spectrum; a sunscreen containing this, avobenzone, and octocrylene—an absorber of UVB radiation—provides very good broad-spectrum protection.

The base of a sunscreen is also important because it often determines whether or not a sunscreen will be used. Men usually prefer alcohol-based lotions because they dry quickly and leave a dry and nongreasy film. Women usually prefer lotions or creams because they give a moisturizing feel to the skin.

Finally, a sunscreen may be labeled water resistant or very water resistant. Because almost all outdoor pastimes involve perspiring or contact with water, a very water-resistant sunscreen should be selected.

A fair-skinned person should always use a sunscreen with an SPF 15 or higher. People who tan well and never burn are probably adequately protected with an SPF of 8 to 10. People with black or brown skin probably do not need sunscreens except for extreme occupational or social exposure.

A few myths should be dismissed. There is no effective oral sunscreen. Many have been tested and all have failed. Self-tanning preparations are not sunscreens. They do provide the appearance of a tan and are safe to use but they provide no significant protection against UV radiation.

Protective Clothing
There has been significant progress in recent years in the development, testing, and classification of UV-protective clothing. Akin to the SPF for sunscreens, such clothing is labeled with an ultraviolet protective factor (UPF), and a fabric with a UPF of 50 blocks
transmission of 98% of UV radiation. A hat with a 3-inch brim all around completes the package of protection.

Protective Tanning
The proliferation of suntan parlors has generated a lot of interest in protective tanning, with much misinformation provided by the commercial interests involved. Little scientific information is available to provide a guide as to whether protective tanning is of any value in preventing the long-term hazards of excessive exposure to sunlight, namely skin cancer and premature aging of the skin. Certainly, preventive tanning using multiple suberythemal doses of UV radiation can prevent sunburn, but the cost in terms of chronic damage is unknown.

Most tanning salons claim to use only UVA radiation in their tanning beds, but this claim is false. All so-called UVA tanning beds emit some UVB radiation, the most damaging wavelengths, and in addition, UVA radiation, especially in large doses, can produce the same damaging effect as UVB radiation. Furthermore, a UVA-induced tan is not very protective and at most has an SPF of 6 to 8.

A person who tans well and never burns might gain some protection from sunlight by preventive tanning without incurring too much damage. However, the risk-to-benefit ratio for people who do sunburn is probably very unfavorable.

Treatment
When a person has a sunburn, general supportive measures are the only approach to treatment. Cold compresses and cool baths with bath oil provide some relief. Frequent application of moisturizing creams help alleviate dryness. Blistering of the skin can lead to secondary infection and require use of an antibiotic cream. Rarely, an extremely severe sunburn necessitates hospitalization and management as a thermal burn.

Topical corticosteroids reduce erythema by causing vasoconstriction, but this effect is temporary and does not reduce epidermal damage. Systemic corticosteroids, even in very large doses, do not alter the course of a sunburn. Nonsteroidal antiinflammatory drugs, if given at the time of exposure or beforehand, reduce the degree of erythema over the first 24 hours but do not change epidermal damage. Of course, few people lying on the beach anticipate an excessive exposure, so they are unlikely to embark on such preventive measures.