Dermatology for the Allergist

Dennis Kim, MD, and Richard Lockey, MD

Abstract: Allergists/immunologists see patients with a variety of skin disorders. Some, such as atopic and allergic contact dermatitis, are caused by abnormal immunologic reactions, whereas others, such as seborrheic dermatitis or rosacea, lack an immunologic basis. This review summarizes a select group of dermatologic problems commonly encountered by an allergist/immunologist.

Key Words: dermatology, dermatitis, allergy, allergic, allergist, skin, disease

(*WAO Journal* 2010; 3:202–215)

INTRODUCTION

Allergists/immunologists see patients with a variety of skin disorders. Some, such as atopic and allergic contact dermatitis, are caused by abnormal immunologic reactions, whereas others, such as seborrhoic dermatitis or rosacea, lack an immunologic basis. This review summarizes a select group of dermatologic problems commonly encountered by an allergist/immunologist.

ATOPIC DERMATITIS

Atopic dermatitis (AD) is a chronic inflammatory skin disease that is often associated with asthma and rhinoconjunctivitis. Prevalence in the United States among school-age children 5 to 9 years old is estimated to be 17%, the incidence of which has increased over the past 30 years.[1] Sixty percent of affected individuals present with the disease in the first year of life and 90% before 5 years of age.[2] There is a strong genetic predisposition, with a prevalence of 80% if both parents have this disease.[3]

Clinical features of AD include pruritus, both localized and generalized, a chronic and relapsing course, typical morphology and distribution of the skin lesions (Fig. 1), and a family history of atopy. The diagnosis is clinical because specific laboratory tests and pathognomonic skin findings do not exist (Table 1).

There are 3 forms of AD: acute, subacute, and chronic. Acute AD is characterized by intensely pruritic, erythematous papules associated with excoriations, vesiculations, and serous exudates. Subacute AD is associated with erythematous, excoriated, scaling papules. Chronic AD is associated with thickened lichenified skin and fibrotic papules. There is considerable overlap of these 3 forms, especially with chronic AD, which can manifest in all 3 ways in the same patient.

The relationship between AD and causative allergens is difficult to establish. However, clinical studies suggest that extrinsic factors can impact the course of disease. Therefore, in some cases, it is helpful to perform skin testing on foods that are commonly associated with food allergy (wheat, milk, soy, egg, peanut, tree nuts, molluscan, and crustaceous shellfish) and aeroallergens to rule out allergic triggers that can sometimes exacerbate this disease. Many patients are also infected or colonized with *Staphylococcus aureus* and are susceptible to contract herpes simplex, *Molluscum contagiosum*, or *Trichophyton rubrum*.

Genetic associations contributing to skin barrier breakdown include a loss-of-function mutation in the filaggrin gene, which encodes a protein that is essential to maintain the formation of the stratum corneum barrier.[4] Polymorphisms in the SPINK5 gene, which encodes a protein that inhibits serine protease, and malfunctioning stratum corneum chymotryptic enzymes, also contribute to impaired stratum corneum integrity and function.[5,6] AD has also been associated with toll-like receptor (TLR)-2 gene polymorphisms and reduced production of skin defensin and cathelicidins.[7,8]

Once an antigen, such as house dust mite allergen, passes through the epidermal skin barrier, a number of immunoregulatory abnormalities involving both innate and adaptive immunity occur. Antigen presenting cells in the epidermis, such as Langerhan's cells and dendritic cells, are present in higher numbers compared with skin from normal subjects. B lymphocytes from patients with AD also make increased amounts of IgE. This cascade of events results in excessive stimulation of T lymphocytes that, in turn, increase the production of proinflammatory cytokines interleukin (IL)-4, IL-5, and IL-13. There has also been a suggested role of $CD4^+CD25^+FOXP3^+$ regulatory T cells to promote a T_H2 immune response in the skin.[9]

Treating AD is comprehensive and begins with avoidance of triggers such as irritating fabrics, soaps, and chemicals. Exacerbating factors include excessive humidity, tight-fitting clothing, and excessive hand washing and sweating. Oral antihistamines, particularly first-generation antihistamines, can help

From the Division of Allergy and Immunology, Department of Internal Medicine, University of South Florida College of Medicine and James A. Haley Veterans' Administration Hospital, Tampa, Florida.

The authors state that they have no conflicts of interest to declare.

Correspondence to: Dennis Kim, MD, Division of Allergy and Immunology, Department of Internal Medicine, University of South Florida College of Medicine and, James A. Haley Veterans' Administration Hospital, 13000 Bruce B. Downs Boulevard (VAR 111D), Tampa, FL 33612.
Phone: (813) 972-7631. Fax: (813) 910-4041. E-mail: Dkim2@health.usf.edu.

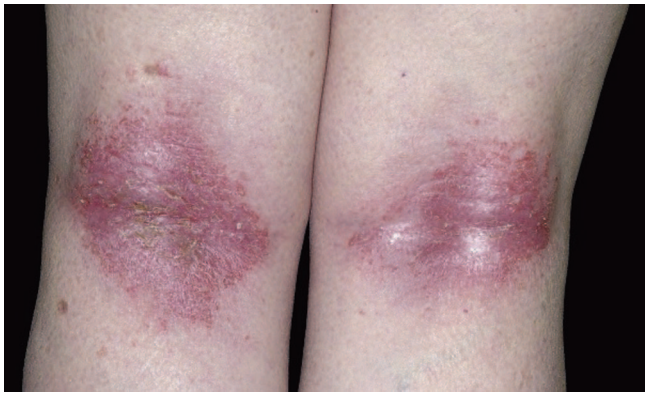

FIGURE 1. Atopic dermatitis. Note erythema and scaling of flexural areas. Reprinted with permission from Habif, *Clinical Dermatology*, 5th ed. Elsevier, 2009.

TABLE 1. Criteria for the Diagnosis of Atopic Dermatitis

Pruritus (or parental report of skin rubbing or scratching) plus 3 of the following:

- Involvement of skin creases (antecubital, popliteal fossa, eyelid, neck)
- History of asthma or hay fever (or history of atopic disease in a first-degree relative if the child is <4 years old)
- Generally dry skin in the past year
- Onset when child was ≤2 years old (only applies if child is ≥4 years old)
- Visual flexural dermatitis

Table reprinted with permission from reference.[4]

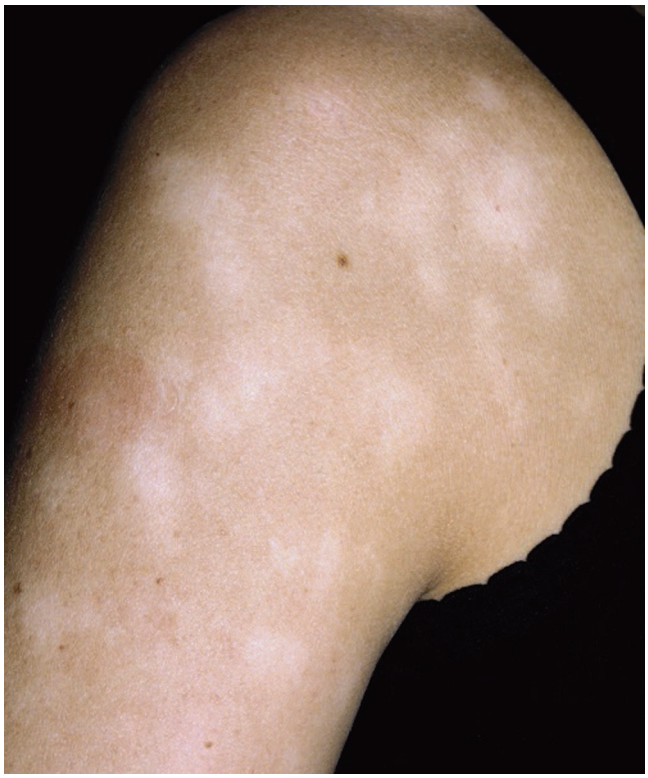

FIGURE 2. Pityriasis alba hypopigmentation. Reprinted with permission from Habif, *Clinical Dermatology*, 5th ed. Elsevier, 2009.

control pruritus and assist with sleep because of their sedative effects. Liberal use of moisturizers and emollients with oral vitamin D supplementation can help restore and preserve the stratum corneum barrier. Topical corticosteroids reduce inflammation, pruritus, and *S. aureus* colonization. Topical calcineurin inhibitors also reduce inflammation by blocking T-cell activation in the skin without the potential side effects of moderate- to high-potency corticosteroids. They also can be used on the eyelids and face. Treatment with systemic antimicrobials is sometimes necessary to control bacterial or fungal superinfections. Severe or recalcitrant disease can be treated with systemic corticosteroids and occlusive wet dressings to hydrate the most severely affected areas.

PITYRIASIS ALBA

Pityriasis alba is often considered to be a mild form of atopic dermatitis.[10] The disease affects 5% of children aged 3 to 16 years with improvement after puberty. The lesions mostly affect the face, neck, and upper extremities but can also occur on the trunk and lower extremities. The rash initially appears as mildly erythematous and scaly circular plaques, 0.5 to 2 cm in diameter, followed by hypopigmentation (Fig. 2). The hypopigmentation may be more conspicuous in dark-skinned individuals and typically lasts several months, but can remain for more than 1 year. The lesions are usually asymptomatic, but patients may complain of local itching or burning.

Etiology is unknown, but a connection with atopy has been suggested, thus making it important to inquire about personal or family history of atopic diseases such as asthma, allergic rhinitis, or eczema. The condition can be exacerbated by excessive, unprotected sun exposure and environmental factors such as temperature and humidity.[11] Differential diagnosis includes other disorders that cause hypopigmentation such as vitiligo, tinea versicolor, halo nevus, and nevus depigmentosus. Although unnecessary for diagnosis, histology will show nonspecific acanthosis and mild spongiosis with moderate hyperkeratosis and patchy parakeratosis.[12]

Pityriasis alba responds very well to topical moisturizers and emollients. The lesions typically resolve spontaneously without further treatment, but topical hydrocortisone (1% or 2.5%) or tacrolimus can be used to relieve symptoms such as itching caused by inflammation.

ALLERGIC CONTACT DERMATITIS

The skin is the first organ to encounter environmental irritants and allergens. Allergic contact dermatitis (ACD) is caused by a type IV or delayed-type hypersensitivity reaction. The T lymphocytes are sensitized by a contact allergen on the skin, such as oil from poison ivy, and upon re-exposure, these sensitized T cells trigger an inflammatory response at the site of skin contact, producing an extremely pruritic, erythematous, papulovesicular rash with scaling and dryness of the skin.

Haptens are low molecular weight compounds, not inherently immunogenic, and most are highly lipophilic and readily pass through the epidermis, binding covalently to epidermal proteins, which act as carrier proteins. This antigen hapten-carrier protein complex is taken up by cutaneous dendritic cells and presented to T lymphocytes in the context of the major histocompatibility complex classes I and II. These cells then migrate from the skin to the regional lymph nodes where the hapten-protein complex is presented to both $CD4^+$ and $CD8^+$ T lymphocytes, which are then primed and able to specifically recognize the hapten-protein complex. The T cells enter the circulation, ending the sensitization phase, 10 to 15 days after the initial contact with the hapten.

Upon future cutaneous exposure to the same hapten, sensitized T cells in the dermis and epidermis undergo recruitment and recognize the hapten-protein complex in the context of major histocompatibility complex classes I and II, become activated, and produce interferon-γ and other cytotoxic molecules that stimulate resident inflammatory skin cells to produce additional inflammatory mediators. Lastly, polymorphonuclear cells, monocytes, and additional T cells are recruited to the inflamed skin which undergoes morphologic changes.

The most common histologic feature of acute ACD is spongiosis of the lower epidermis as a result of intercellular edema characterized by lymphocytic infiltration of the perivascular tissues and epidermis. In chronic stages, the edema and spongiosis is replaced by hyperplasia and parakeratosis of cells in the epidermis.

Clinically, the elicitation phase appears approximately 24 to 96 hours after exposure to the antigen to which the susceptible individual is sensitized. In the acute phase, the skin is erythematous, edematous, and very pruritic, but soon, papules and vesicles appear, which can blister, ooze serum, and eventually crust over (Fig. 3). In the chronic stage, exacerbated by scratching, the skin becomes lichenified, cracked, and hyperpigmented.

Some of the most common sources of allergens to cause ACD are metals, skin care products, clothing, medications, and plants. Nickel is the most common metal sensitizer, particularly among women who become allergic to nickel-containing jewelry. Chromate is a common cause of ACD among men, usually related to occupational exposures from cement, chrome-tanned leather, paint, bleaches, and printing solutions. Cosmetics and other skin care products can cause ACD from a variety of chemicals, including preservatives, excipients, perfumes, active or inactive ingredients, emulsifiers, and sunscreens. Many skin care products now provide ingredient labels in an effort to reduce the risk of allergic reaction among sensitized individuals. Common clothing sensitizers include dyes, adhesive resins, and chemicals or antioxidants used in manufacturing synthetic fabrics. The axilla is particularly prone because it is an area of high moisture and friction associated with wearing clothing. Topical medications such as antimicrobials, anesthetics, and antiseptics can cause ACD through active ingredients and preservatives. Reactions are usually localized to the area of application, but systemic reactions also can occur if a sensitized patient is given a medication orally or parenterally that contains the antigen or cross-reacts with any agent to which the patient is sensitized. An example of this is systemic corticosteroid administration in a patient who has been sensitized and develops ACD after using topical corticosteroids. Plants are one of the most common causes of ACD in the United States, with 50% of adults being sensitive to urushiol, the hapten found in poison ivy, poison oak, and poison sumac.[13]

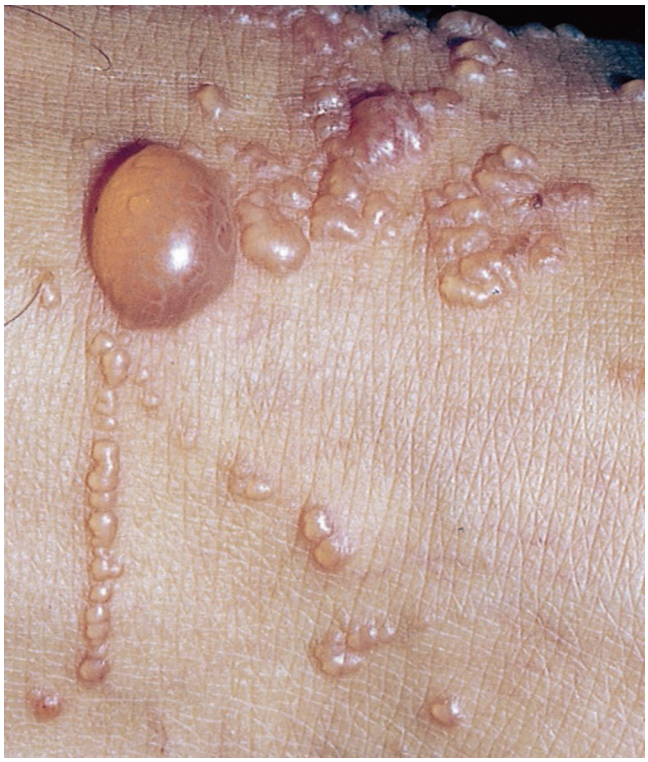

FIGURE 3. Poison ivy rash with vesicles, blisters, and linear lesions. Reprinted with permission from Habif, *Clinical Dermatology*, 5th ed. Elsevier, 2009.

A detailed and methodically obtained history with questions focusing on occupations, hobbies, home environment, clothing, and personal objects in contact with the skin is necessary to make this clinical diagnosis. The appearance and distribution of the affected skin often provide clues to the agent causing the disease; for example, nickel dermatitis affects areas of skin that are in contact with jewelry, blue jeans buttons, wrist watches, and other metallic objects. Ingredients of nail polish can sometimes cause periorbital skin itching and lichenification.

If a history and physical examination does not reveal a causative agent, patch testing can be used to attempt to detect the contact allergen. The most common contact allergens have been identified and grouped into a series of patch tests and are available in products such as T.R.U.E.TEST (Allerderm, Phoenix, AZ). Individual tests can also be selected and applied by the allergist using Finn Chambers (Epitest, Finland) in either aqueous or petrolatum base. This latter method also allows testing to the patient's own products. Patch tests are applied to the upper back for 48 hours. Reading is done the day the patches are removed, at 48 hours, and again in 72

TABLE 2. Grading Scale for Recording Results of Cutaneous Patch Test[13]

NR	Negative reaction
?	Doubtful reaction (weak erythema only)
+	Weak positive reaction: erythema, induration, possibly papules
++	Strong positive reaction: erythema, induration, papules, vesicles
+++	Extreme positive reaction: intense erythema and induration, coalescing vesicles, bullous reaction
IR	Irritant reaction

Adapted with permission from reference.[13]

hours. Results of patch tests must be carefully correlated with the clinical history. A grading scale for reading patch tests is summarized in Table 2.

Treatment of ACD is based on identification and elimination or avoidance of the offending contact allergen. Patients should be educated on allergen identification, its known or potential sources, and cross-reacting substances (ie, skin of mango fruit protein cross-reacting with urushiol of poison ivy). Pruritus can be relieved with cold compresses, topical calamine or oatmeal, aluminum acetate, and moisturizers. Topical steroids can be used in the acute phase to control inflammation and inhibit pruritus. Short bursts of systemic corticosteroids can be used in severe, extensive dermatitis.

SEBORRHOIC DERMATITIS

Seborrhoic dermatitis is a skin disorder affecting areas rich in sebaceous glands. The inflammation is chronic and relapsing in nature and primarily affects the scalp, face, chest, and intertriginous areas (Fig. 4). People of all ages can be affected, but clinically significant disease usually affects persons aged 35 to 44 years and less commonly among those younger than 12 years.[14] The disease is also more severe in patients infected with human immunodeficiency virus, especially if the $CD4^+$ T-cell count is <400 cells per milliliter.[15,16] There is no sex predilection, but the disease rarely affects African Americans.

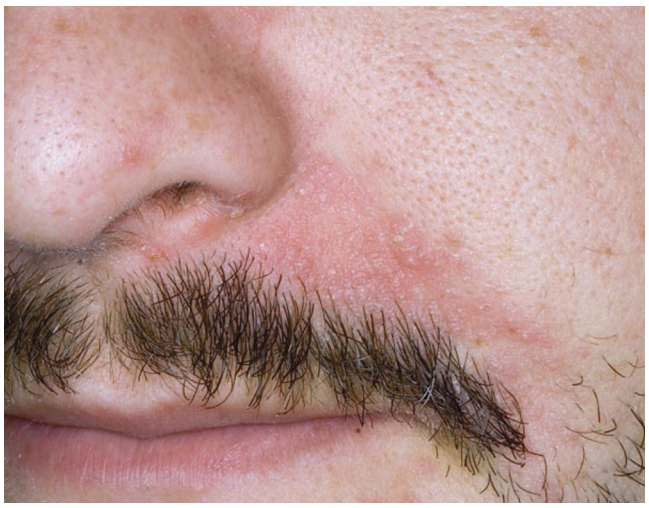

FIGURE 4. Seborrhoic dermatitis affecting nasolabial folds. Reprinted with permission from Habif, *Clinical Dermatology*, 5th ed. Elsevier, 2009.

Multiple causes of seborrhoic dermatitis have been postulated. Malassezia fungus species is considered the most likely pathogenic cause. The fungus has been shown to be present on affected skin and the dermatitis responds to antifungal treatment. Malassezia fungus sp. is also present on the skin of individuals unaffected by seborrhoic dermatitis, which suggests a possible predilection for the disease as a result of a dysfunctional immune response.[17] Other proposed causes include stress, exposure to solar ultraviolet radiation, hormone levels causing hyperfunctioning of sebaceous glands, and nutritional deficiencies; however, these are unproven.[18]

Tissue histology of affected skin shows epidermal cell proliferation with focal parakeratosis. More severely affected areas can show spongiosis caused by dermal edema and neutrophil infiltration at the lesion margins. Parakeratosis is more widespread in chronic lesions and in patients with advanced human immunodeficiency virus.[17,19]

Topical antifungal preparations are the most effective and safest method for treating seborrhoic dermatitis. Ketoconazole 2% (shampoo, gel, foam, and cream), bifonazole 1% (shampoo and cream), and ciclopirox olamine 1% to 1.5% (shampoo and cream) should be applied to the scalp 2 to 3 times a week for initial clearance and then once a week to maintain remission. Treating nonscalp skin requires daily or twice daily application for clearance and daily use for maintenance.

Other treatment options include topical calcineurin inhibitors, selenium sulfide shampoos (scalp only), topical corticosteroids, topical lithium gluconate or succinate (nonscalp only), coal-tar shampoos (scalp only), and ultraviolet B light phototherapy. However, they are less effective than topical antifungal treatment. There are sparse clinical data on efficacy of systemic antifungal agents, with trials showing either no benefit compared to placebo[20] or only improving skin that is usually covered, such as the scalp or torso.[21] Hepatotoxicity and the required laboratory monitoring should be weighed carefully when considering this class of medication.[18]

ROSACEA

Rosacea is a chronic inflammatory skin disorder affecting 14 million people in the United States, most commonly women aged 30 to 50 years.[22–24] Disease in males can be more severe with a higher incidence of complications.[25–28] Risk factors include chronic actinic damage, use of topical corticosteroids, a spontaneous tendency for flushing, genetic factors, and northern or eastern European descent.[25,28]

The face is the most commonly affected part of the body with erythema, flushing, telangiectasias, papules, pustules, and edema of the nose, cheeks, chin, forehead, and glabela (Fig. 5).[25,26,29] Lesions are symmetrical and spare the periocular region and the papules do not form comedones, distinguishing them from acne.

There are 4 phenotypes of rosacea as proposed by the National Rosacea Society Expert Committee in 2002.[30] Pap-

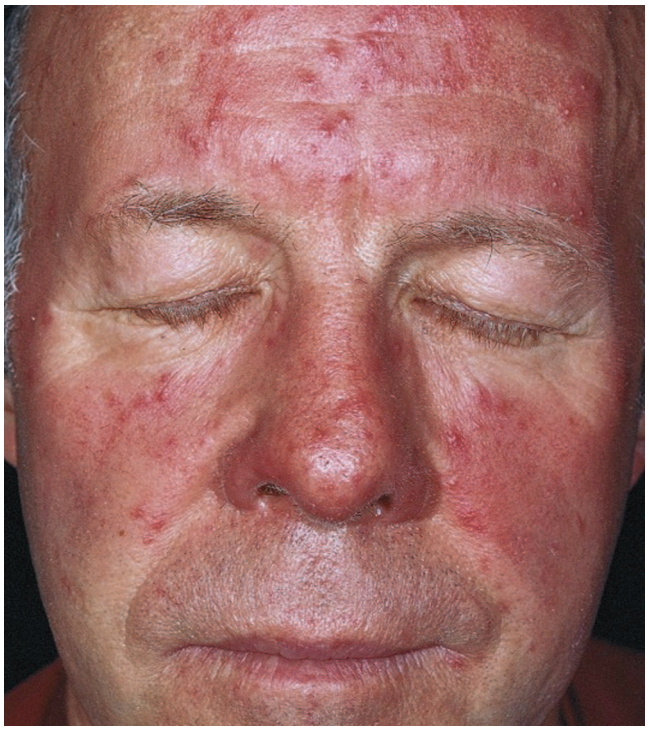

FIGURE 5. Rosacea erythema and few pustules affecting the face. Reprinted with permission from Habif, *Clinical Dermatology*, 5th ed. Elsevier, 2009.

ulopustular, or classic rosacea, is characterized by central facial papules and pustules. Chronic erythema with intermittent flushing can lead to edema of the forehead, glabela, nose, and cheeks. In erythematotelangiectatic rosacea, a history of flushing is the most important clinical feature. Flushing can be triggered by skin care products or topical medications, often lasts beyond 10 minutes, and can result in chronic edema, telangiectasia, and edema of the central face. Phymatous rosacea more commonly affects men and is characterized by pustules, papules, thickened skin, enlarged follicular orifices, and telangiectasias. This subtype most commonly affects the nose, but the forehead, chin, ears, and eyelids can also be involved. Lastly, ocular rosacea affects the eyelid, conjunctiva, and cornea. Patients can present with symptoms including blepharitis, conjunctivitis, and corneal lesions, which can lead to opacification, scarring, or vision loss.

The pathophysiology of rosacea is not well understood but several mechanisms have been suggested. Vascular disease may contribute to rosacea by predisposing individuals to vasodilation via an abnormal response to thermoregulation. This postulate is supported by the finding that certain triggers for flushing, such as alcohol, spicy food, exercise, menopause in women, emotional stress, and warm environmental temperatures, can worsen rosacea.[26] Repeated flushing eventually leads to permanent dilation of blood and lymph vessels in the skin.[31–33]

The innate immune system may also be dysregulated, specifically, cytokine signaling and upregulation of proinflammatory molecules such as cathelicidin, as a result of toll-like receptor signaling in the skin. Other pathogenic mechanisms include overproduction of reactive oxygen species from neutrophils, exposure from ultraviolet light, cutaneous proteases, such as kallikrein-5, and microbial involvement from organisms *Demodex folliculorum* and *Helicobacter pylori*. Each of these causes share a common feature of promoting direct damage and inflammation to skin, sebaceous glands, or hair follicles.[34]

Diagnosis is clinically based on a patient's history and presence of characteristic skin findings. History should focus on precipitating or alleviating factors, duration and frequency of episodes, and lesion morphology and time course. On physical examination, patients should have at least one of the following features affecting the convex areas of the face: transient flushing, papules, pustules, persistent erythema, and telangiectasia. Burning, pruritus, plaques, edema, and dryness of skin can also be present. There are no diagnostic tests to confirm rosacea. If skin biopsy is done during the acute phase, histology will show perivascular lymphocytic infiltrate, telangiectasias, and neutrophil and lymphocyte infiltration around follicular infundibula. Chronic lesions will demonstrate more neutrophils within the follicles and infiltration of lymphocytes, epitheliod cells, and histiocytes around follicles. Noncaseating epitheliod granulomas can also be seen and will be surrounded by lymphocytes and plasma cells. The upper dermis will contain marked telangiectasias and actinic elastosis.[26]

Treatment of rosacea is targeted toward the specific symptoms and phenotype classification. There are 5 general categories of treatment options: topical metronidazole, topical azelaic acid, topical benzoyl peroxide combined with topical antimicrobials, oral antimicrobials, and a miscellaneous group. Topical metronidazole (0.75%, 1%) or azelaic acid (15% gel, 20% cream) are both equally effective for pustular/papular disease[35,36] and superior to placebo.[37–39] Pustular/papular disease can also be treated with clindamycin lotion, permethrin 5% cream, tretinoin cream, or sulfacetamide 10%/sulfur 5%.

Oral antibiotics can be used for more extensive pustules/papules. Oral metronidazole and tetracycline have equal clinical efficacy[40] with one trial showing oral tetracycline to be superior to placebo according to physician assessment.[41,42] Oral erythromycin and ampicillin can also be considered, but these and other oral antimicrobials should be switched to topical agents once clinical improvement is achieved.

Oral isoretinoin can be used for severe or refractory rosacea but should be used with caution in women of reproductive age and laboratory monitoring for hepatotoxicity and dyslipidemia is suggested. Ocular treatment options include topical metronidazole or oral tetracycline, and laser phototherapy can alleviate symptoms of rhinophyma.[43]

PITYRIASIS ROSEA

Pityriasis rosea is a common, benign skin condition that accounts for 3% of visits to dermatologists in North America. Most cases occur among older children and young adults between the ages of 10 and 35 years; it is rare in infants and the elderly. The disease affects both sexes and all ethnic groups equally and may occur at any time of year but is most common during colder months.[44] The etiology of pityriasis

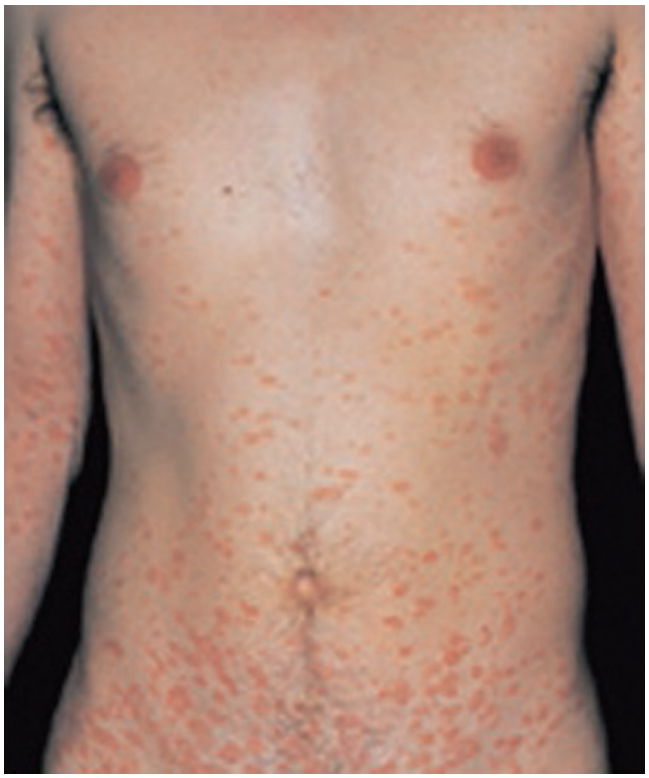

FIGURE 6. Pityriasis rosea fully evolved two weeks after onset. Reprinted with permission from Habif, *Clinical Dermatology*, 4th ed. Elsevier, 2004.

rosea is unknown, but researchers have been investigating viruses such as human herpes virus 6 and 7 as possible causes.[45–47] The rash does not spread by casual contact.

Clinically, this disease begins in about 50% of patients as a viral prodrome with headache, malaise, and pharyngitis. The skin then develops a single "herald" patch, pink or salmon in color and round or oval in shape with a diameter of 2 to 10 cm that typically appears on the neck, chest, or back. The herald patch then scales at the margins, imitating eczema and tinea corporis.[48]

Several days or weeks after the herald patch appears, new crops of smaller lesions 5 to 10 mm in diameter appear on the torso or, less commonly, the extremities (Fig. 6). These secondary lesions follow the contours of the cleavage lines of the skin (also called Langer lines). This is where the characteristic "Christmas tree" pattern can be visualized when lesions align along the oblique contours of the back.[48]

The rash tends to spread in a centrifugal pattern into the extremities and usually clears within 4 to 6 weeks but can occasionally persist for several months. The erythema, desquamation, and scaling resolves completely, but postinflammatory hyperpigmentation may persist for several months.

Pityriasis rosea is a clinical diagnosis based on the presence of a herald patch by history or examination, time, appearance and distribution of secondary lesions, and the lack of other symptoms such as pruritus. The differential diagnosis includes tinea corporis, secondary syphilis (if the palms and soles are affected and the patient is sexually active), nummular eczema, guttate psoriasis, viral exanthema, lichen planus, and drug rash. Skin biopsy is not necessary to make the diagnosis, but if done, it will show focal parakeratosis with or without acanthosis, spongiosis, perivascular lymphocyte, or histiocyte infiltrates and red blood cell extravasation.

Most cases do not require treatment and resolve within 5 to 8 weeks. Pruritus may be a significant symptom in 25% of patients,[49] which can be treated with topical agents such as Sarna or calamine lotion, zinc oxide, low- to moderate-potency topical corticosteroids, and oral antihistamines.[50] Clinical studies using oral antimicrobial medications erythromycin[51–53] and azithromycin[54] and antiviral treatment using acyclovir[55] have not demonstrated clear benefit and are not recommended. Referral to a dermatologist should be considered in patients whose rash lasts beyond 3 months or if phototherapy with ultraviolet light is being considered for extensive disease.

ACNE

In Western cultures, acne affects up to 95% of adolescents and persists into middle age in 12% of women and 3% of men. It can vary in severity, from a few pustules and comedones to highly inflamed, cystic lesions that leave scars on both skin and psyche. Severe disease is more common among males, but the disease is more persistent in females, with exacerbations related to menstrual periods and pregnancy.[44]

Acne is the result of a combination of several pathogenic factors that involve the pilosebaceous unit of the skin and is most frequent and intense in areas where sebaceous glands are largest and most numerous (face, chest, back, and upper outer arms). Overproduction of sebum from sebaceous glands is considered to be the most important pathogenic factor in the formation of acne. Increased amounts of sebum lead to follicular hyperkeratosis and plugging of the pilosebaceous duct. The result is a follicular plug and formation of a closed comedone (firm, white papule) or open comedone (blackhead) if the follicle orifice reopens.[56]

Another important cause of acne is bacterial overgrowth of *Propionibacterium acnes*, a normal skin flora that is not normally pathogenic. *P. acnes* produces proinflammatory products such as lipases, superoxide radicals,[57] proteases, and hyaluronidase, which are primary irritants and comedogenic, and chemotactic factors that attract neutrophils to potentiate the inflammatory response.[58] Inflammatory cytokines such as interleukin-1 and leukotriene B4 and androgen hormones have also been identified as key components of acne pathophysiology.[59] *P. acnes* also interacts with cells via membrane toll-like receptors 2 and 4.[60]

Acne is diagnosed based on an evaluation of lesions and their complications, which include drainage and hemorrhage from lesions and pain that can be associated. Acne lesions are categorized as either noninflammatory (open or closed comedones) or inflammatory (papules, pustules, and nodules). Inflammatory nodules are further graded in severity based on number of pustules/papules/nodules, occupational disability, psychosocial impact, and the failure of response to previous treatment. Grading classification is summarized in Figure 7.

Current acne treatments include oral and topical antibiotics, topical retinoids, benzoyl peroxide, azelaic acid, oral

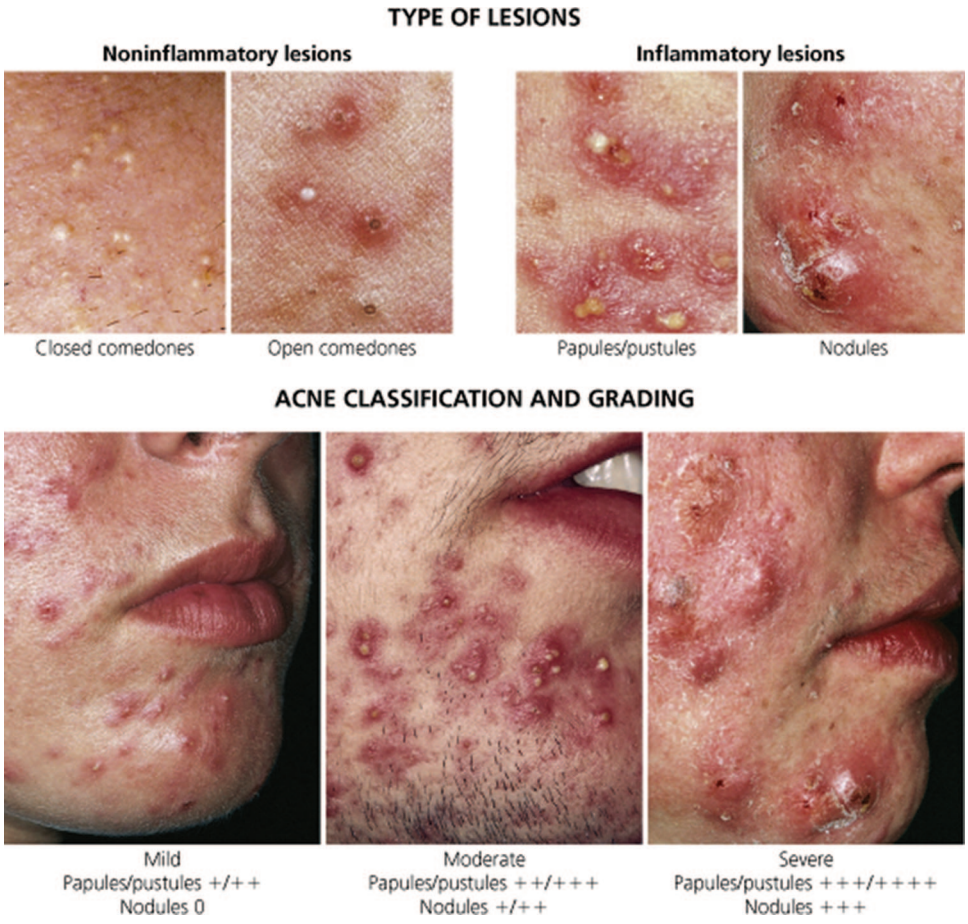

FIGURE 7. Acne classification and grading. Habif, *Clinical Dermatology*, 5th ed. Elsevier, 2009.

isoretinoin, and hormonal therapy only in women. Mild-moderate acne can be treated with benzoyl peroxide, a topical antibiotic, and a retinoid. Options for topical antibiotics include erythromycin and clindamycin gels, picolinic acid gel (10%), and dapsone gel (5%). Additional efficacy and compliance can also be attained with combination topical medications such as clindamycin/zinc acetate, clindamycin/benzoyl peroxide, or clindamycin/tretinoin gels. These should be applied at the lowest dose and frequency that controls disease.

If acne lesions do not improve after several weeks or for patients with moderate-severe disease, topical medications should be applied twice daily with addition of oral antibiotics if there are extensive pustules and/or nodules. Antibiotics such as tetracyclines, trimethoprim, and macrolides are the mainstay of treatment for moderate-severe acne, beneficial for both their antimicrobial and anti-inflammatory properties.[61–63] Resistance of *P. acnes* to antibiotics is a growing problem, mostly with erythromycin, less so with trimethoprim, doxycycline, and tetracycline, and rarely with minocycline.[64,65] Acne can also be treated with oral lymecycline[66] (a second-generation tetracycline) and subantimicrobial doses of doxycycline[67] (20 mg twice daily), and azithromycin is an option for use in pregnant women.[68,69] Oral antibiotics should be tapered and discontinued if lesions are improving and patients can be maintained on topical therapies.

Oral isoretinoin (13-*cis*-retinoic acid) is approved for treatment of severe nodular acne or for acne that is resistant to treatment or causing physical or psychological scarring.[61] This medication should be prescribed under the direction of a dermatologist and with female patients required to use some form of contraception or abstinence because of potential fetal abnormalities that can occur in pregnant women who take this medication. Photodynamic light can also be used to induce formation of porphyrins on the skin that can be activated by visible light, enabling them to destroy bacteria-causing acne.[70]

TINEA

Tinea are aerobic fungi that can be hosted on humans (anthropophilic), and animals (zoophilic) and in the soil (geophilic). There are 3 genera of dermatophytes: Trichophyton, Epidermophyton, and Microsporum. Direct contact with any of these organisms can lead to infection of the stratum corneum skin layer. Some individuals, however, will be asymptomatic carriers and may spread the organism to perpetuate infections.[71,72]

Tinea refers to dermatophyte infection of the skin and is grouped according to lesion location: tinea capitis (scalp), tinea cruris (Fig. 8a; groin), tinea pedis (Fig. 8b; feet), tinea

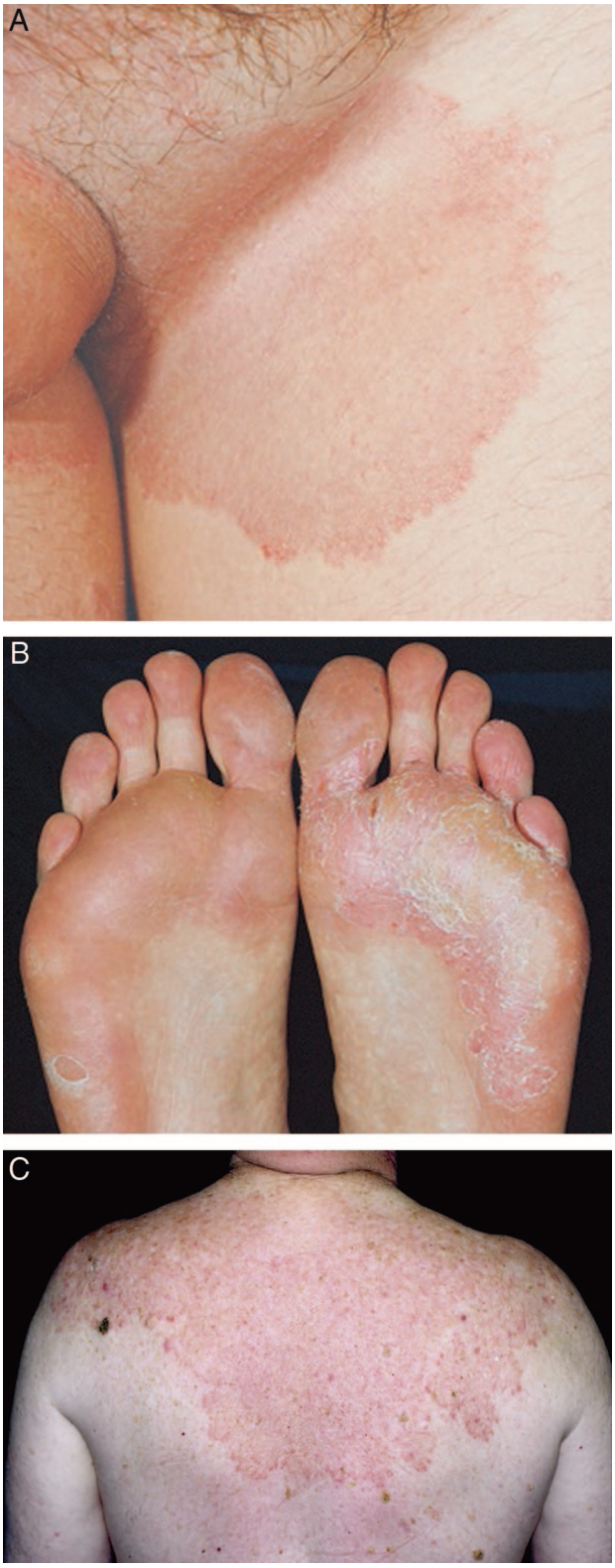

FIGURE 8. A, Tinea cruris; B, tinea pedis; C, tinea corporis. Reprinted with permission from Habif, *Clinical Dermatology*. 4th ed. Elsevier, 2004; 5th ed, Elsevier, 2009.

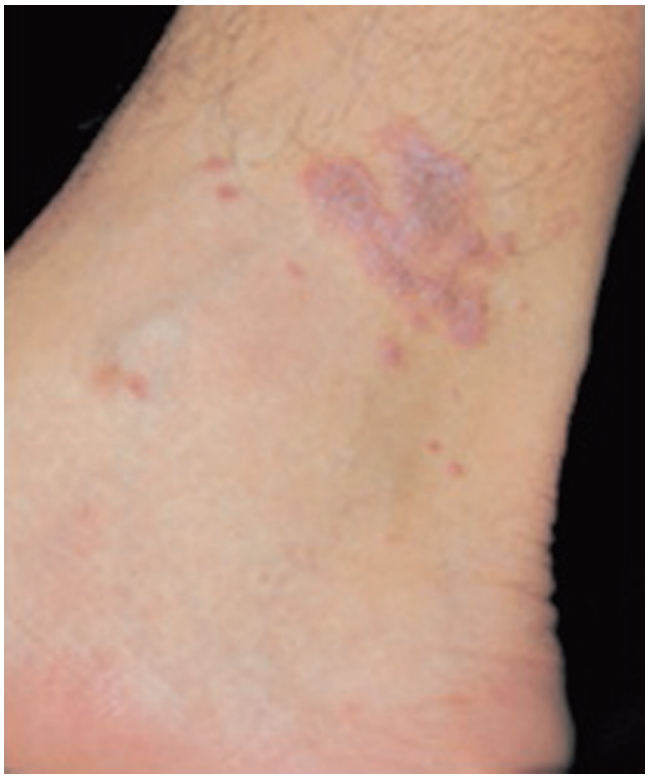

FIGURE 9. Lichen planus with characteristic purple papules and Wickham's striae. Habif, *Clinical Dermatology*, 4th ed. Elsevier, 2004.

corporis (Fig. 8c; body), tinea unguium (nails, also known as onychomycosis), tinea faciale (face), tinea barbae (beard), and tinea manuum (hands/palms).

Infection is caused by dermatophyte invasion of the stratum corneum and keratinized layer of the outer skin. Dermatophytes produce enzymes such as keratinase, which helps them penetrate tissue and enables their hyphae to invade and spread outward. Dermatophytes can also invade hair shafts, as in tinea capitis. Host defenses against dermatophytes include increasing the rate of epidermal turnover, increasing fatty acid content of sebum, and cell-mediated adaptive immune defense with T lymphocytes.[72]

Tinea capitis is the most common fungal infection in children, with >90% of cases in the United States caused by *Trichophyton tonsurans*. Infection is limited to the scalp and typically presents with scaling, patchy alopecia with local erythema, pruritus, pustules and black dots (hair shafts broken off at follicular orifice). Suboccipital or posterior cervical lymphadenopathy can also be present.[72]

Tinea corporis, also known as ringworm, is most commonly caused by the Trichophyton species in the United States. Only glabrous (smooth and bare) skin is affected. Early lesions appear as red, scaly papules that spread outward and coalesce into annular patches or plaques. These patches or plaques then develop a raised outer edge with central clearing caused by increased epidermal cell turnover.

Tinea cruris is a dermatophyte infection of the groin most commonly caused by *T. rubrum*, *Trichophyton menta-*

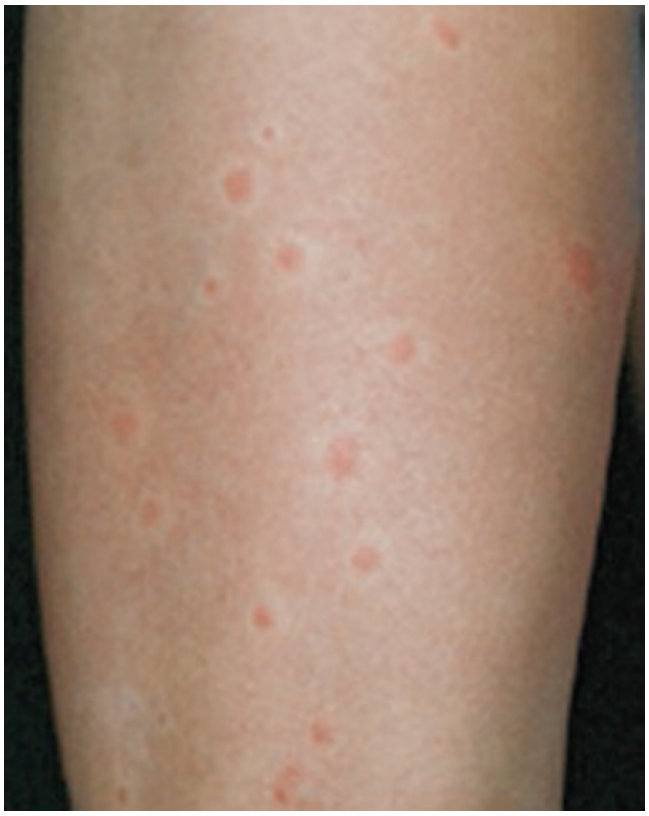

FIGURE 10. Ictus reaction from insect bites. Habif, *Clinical Dermatology*, 4th ed. Elsevier, 2004.

grophytes, and *Epidermophyton floccosum*. Also known as "jock itch," this infection occurs more frequently in adolescent and adult males.[72] Infection is favorable in warm, humid environments and can be enhanced by wearing wet or tight-fitting clothing.[73] The rash primarily affects the proximal medial thighs, but can also extend onto the buttocks and lower abdominal wall. The scrotum is usually not affected. Intense pruritus and burning are the main symptoms of this rash, which appears as multiple pustules and vesicles with a raised, leading edge surrounded by skin that is erythematous and scaling.[73]

Tinea pedis, or athlete's foot, can be caused by the same organisms that cause tinea cruris, and as such, the feet should also be examined as a possible source for groin involvement. There are 3 presentations for tinea pedis. The most common form, called intertriginous or interdigital, is characterized by erythema, scaling, foul odor, fissuring, and cracking of the toe web spaces. A second form, moccasin type, demonstrates erythema, scaling, fissuring, dryness, and hyperkeratosis on the plantar and lateral margins of the foot. Finally, the vesiculobullous form presents with vesicles and large bullae, usually affecting the soles.[72,73]

Most tinea infections can be diagnosed on the basis of history, physical examination, and direct microscopic examination of affected tissue scrapings stained with potassium hydroxide. Fungal culture can be useful when long-term treatment is anticipated, if infections are resistant to standard therapy, or if the diagnosis is uncertain.[71]

Treatment options for tinea infections include both topical and oral antifungal medications. Tinea cruris and corporis can usually be treated with topical agents such as terbinafine or butenafine cream. Topical agents should be applied once to twice daily at least 2 cm beyond the margins of the rash for 2 to 4 weeks and continued for 1 week after the rash resolves. Low-potency topical corticosteroids can also be used for short periods to reduce acute inflammation. Oral antifungal agents are rarely needed to treat tinea cruris and corporis, except for severe or refractory infections.

Infection of the hair or nails as seen in tinea capitis, tinea barbae, and tinea unguium, however, requires systemic antifungal therapy because topical agents do not sufficiently penetrate the hair root or nail bed. Oral griseofulvin (20 mg/kg per day for 8 weeks) is often the first choice because of its proven efficacy and safety profile. Laboratory monitoring for hepatic toxicity is not required. Oral terbinafine (62.5 to 250 mg/kg per day based on weight) is an appealing option because of its ability to clear infection in 4 weeks, but laboratory monitoring for hepatic toxicity is necessary. Adjunctive use of antifungal shampoos is also recommended when treating patients with tinea capitis as well as close contacts in an effort to reduce spore counts and inhibit transmission. Selenium sulfide 2.5% and ketoconazole shampoos are the most commonly recommended. Children should continue to attend school because spore shedding can continue for months and asymptomatic carriers are common in the general population.[72]

LICHEN PLANUS

Lichen planus is an inflammatory reaction involving the skin and mucous membranes. The disease mostly affects middle-aged adults; children are rarely affected. Etiology is not known, but 10% of patients have a positive family history, suggesting a possible genetic link,[74] particularly with human leukocyte antigen (HLA)-DR1.[75] Liver disease may also be a risk factor, especially in patients with hepatitis C.[76,77] Medications have also been implicated in inducing lichen planus, including beta blockers, methyldopa, penicillamine, quinidine, nonsteroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, sulfonylureas, carbamazepine, gold, lithium, and quinine.[78]

There are several clinical forms of lichen planus, each sharing a common lesion morphology and distribution. The rash appears as a flat-topped, polyangular, violaceous papule. Patients will experience pruritus, pain if the papules ulcerate, and postinflammatory hyperpigmentation of affected areas. Closer examination of the surface reveals a lacy, reticular pattern of criss-crossed white lines called Wickham striae (Fig. 9).[44]

The lesions typically affect the skin, nails, mucous membranes, vulva, and penis.[79] In the most common localized papular form, the papules usually affect the flexor surfaces of the extremities, especially the wrists and forearms, lower legs, and back. Some will undergo spontaneous remission within a few months, but most lesions become chronic and last an average of 4 years.[44]

Hypertrophic lichen planus, the second most common form, can affect any part of the body, but has a predilection for the pretibial areas and ankles. The rash is characterized by pruritus and appears as a thick, hyperkeratotic plaque with a rough or verrucose surface. This form lingers for an average of 8 years, often perpetuated by scratching.[44]

Lichen planus affecting the scalp is called follicular lichen planus or lichen planopilaris. Patients present with patchy alopecia and pinpoint, hyperkeratotic follicular papules that can lead to scarring if left untreated.[44]

Oral lichen planus most commonly affects the buccal mucosa, but the tongue and lips can also be affected. Mucous membrane involvement occurs more in women (2:1) and slightly later than cutaneous disease, usually in the sixth decade of life. Examination of the oral cavity will reveal mucous membranes covered in a lacy, white reticular pattern; these lesions are usually asymptomatic. The mucous membranes, however, may ulcerate either locally or extensively, which is called erosive mucosal lichen planus. These are very painful lesions and may become superinfected with fungus or bacteria.[44]

Genital lichen planus appears as violaceous papules on the vulva or glans penis. In women, the vaginal mucosa can become friable and erythematous with the potential to form vaginal or labial adhesions. A variant of mucosal lichen planus, called vulvovaginal-gingival syndrome, is characterized by erosion and desquamation involving the vulva, vagina, and gingiva. This variant is particularly resistant to treatment.[44]

Lichen planus is a clinical diagnosis based on characteristic appearance and distribution of the rash. Buccal involvement should prompt an evaluation for white Wickham striae. A patient's medications should also be reviewed to rule out drug-induced rash. Skin biopsy can confirm the diagnosis using direct immunofluorescence, which shows globular deposits of IgG, IgM, IgA, and complement and linear basement membrane deposits of fibrin and fibrinogen.[44]

Most cases of lichen planus spontaneously resolve in 1 to 2 years, though oral lesions tend to be more chronic and can last for several years. Cutaneous lichen planus can be treated with moderate- to high-potency topical corticosteroids twice daily for 2 to 3 weeks. Oral corticosteroids can be used for more severe, generalized disease, using 30 to 60 mg of prednisone once daily for 4 to 6 weeks and tapered for an equal length of time. The oral retinoid acitretin (30 mg/d) is an effective steroid-sparing agent with proven efficacy.[80,81] Oral antihistamines can be used to help soothe pruritus. Other treatment options for cutaneous disease include intralesional steroids, phototherapy,[82] azathioprine,[83] and cyclosporine.[84] Genital lesions should be treated with topical corticosteroids whereas scalp and hypertrophic lesions can be treated with either topical or intralesional corticosteroids.

Oral lesions are usually best treated with high-potency topical corticosteroids,[85,86] but other preparations such as fluticasone propionate spray or betamethasone sodium phosphate mouth rinse can also be used.[87] Systemic corticosteroids can be used for refractory or ulcerative oral lichen planus.[88] Other therapeutic options for treating oral lichen planus include topical calcineurin inhibitors,[89] intralesional corticosteroids,[90] dapsone (50 to 150 mg/d),[91,92] hydroxychloroquine sulfate (200 to 400 mg/d),[93] azathioprine,[83,94] topical cyclosporine (100 mg/5 mL),[95] methotrexate,[96,97] and mycophenylate mofetil.[98,99]

TABLE 3. Stage Classifications of Prurigo Simplex

Stage 1	Introduction period with no observable skin reaction
Stage 2	Delayed skin reaction
Stage 3	Immediate skin reaction followed by a delayed reaction
Stage 4	Immediate skin reaction only
Stage 5	No reaction

PRURIGO SIMPLEX

Prurigo simplex most commonly affects children and some adults during the spring or summer months. Biting arthropods of the order Diptera (black flies, house flies, sand flies, gnats, mosquitos, and midges), Siphonaptera (fleas), and Acari (ticks) are the most common culprits.

Children are bitten by these insects, become sensitized, and develop a progression of reactions on repeated bites. Table 3 describes the stage classifications of prurigo simplex.[100]

Reactions typically appear within 10 to 15 minutes and range in size from <1 mm to the size of a half-dollar or larger (Fig. 10). Lesion morphology and symptoms can also vary, ranging from erythema, whealing, induration, pruritus, vesiculation, hemorrhage, and pain.[101] Lesions usually disappear within 1 hour but can last for weeks. Skin can develop areas of excoriation or ulceration from habitual scratching, resulting in crusts and secondary pyoderma or impetigo. Chronic lesions, especially when continuously irritated by scratching, can last for months and eventually leave a scar.

The histopathology of prurigo simplex demonstrates mild acanthosis, spongiosis, subepidermal edema, erythrocyte extravasation, moderate inflammatory cell infiltrate, and interstitial eosinophilia. A cellular infiltrate comprised of T cells, macrophages, and eosinophils suggests the pathophysiology of papular urticaria is immunologically mediated. It should be noted, however, that there is no significant evidence in the literature to suggest that these local reactions are IgE-mediated.

The disease can usually be successfully managed by avoidance, that is, wearing protective clothing and using appropriate insect repellents when outdoors. Insect repellents containing *N*,*N*-diethyl-*meta*-toluamide offer superior, longer lasting protection compared with non–*N*,*N*-diethyl-*meta*-toluamide repellents (soy based, botanicals, and wrist bands).[102] Pets should be treated for fleas and ticks because they are a common reservoir for biting insects. Once lesions have appeared, low- to moderate-potency topical corticosteroids such as triamcinolone 0.025% to 0.1% cream and systemic antihistamines usually relieve the pruritus. Secondary impetigo or pyoderma should be treated with topical or systemic antibiotics. Parents need to be reassured that the condition is benign and self-limited, and with time, children usually "outgrow" these reactions.

TINEA VERSICOLOR

Tinea versicolor is a superficial skin infection caused by yeasts of the genus Malassazia (also known as Pityrosporum). Malassazia yeast is a normal human cutaneous flora found especially in areas of the skin with many sebaceous glands such as the scalp, forehead, shoulders, and trunk. This organism thrives on lipids and triglycerides; therefore, the disease is more common in adolescents and young adults who have oily skin and higher amounts of sebum. It is also a common problem in tropical regions of the world.[44]

Lesions can take on a variety of appearances, ranging from hypopigmented patches, red or salmon-colored macules, papules, and patches, or tan and dark brown macules or patches. A fine scale with surrounding erythema is also commonly present. Lesions usually begin on the upper trunk and shoulders but can spread to the upper and lower extremities, head, and neck (Fig. 11). Affected individuals commonly present with this disease during the warmer months, indicating that this rash reappears during the same time each year. The lesions are usually asymptomatic, but some patients can complain of pruritus, especially if inflammation is severe.[103]

Diagnosis is usually made solely on the basis of the appearance and distribution of the lesions. If additional testing is necessary, glass slide scrapings of the lesions can be obtained and stained with potassium hydroxide. Microscopic morphology reveals yeast present as both spores and hyphae, giving a "spaghetti and meatballs" appearance. Culturing the scrapings is rarely necessary, but when performed, it should be done on a lipid-containing medium to ensure proper growth.[103]

Treatment options include topical agents for limited disease and oral medications for extensive, refractory, or recurrent disease. Topical antifungal creams, such as ketoconazole 2%, miconazole 2%, terbinafine 1%, or clotrimazole 1%, should be applied to affected areas once or twice daily for 2 to 4 weeks. Shampoos, such as ketoconazole 2% and selenium sulfide 2.5%, can be applied for several days to treat both scalp and body lesions. Oral antifungal options include ketoconazole, 400 mg once weekly for 2 weeks, fluconazole, 300 mg once weekly for 2 weeks, and itraconazole, 200 mg daily for 7 days.

Once disease remission is achieved, symptomatic relief is often temporary for tinea versicolor and can recur in 40% to 60% of cases.[44] For such subjects, topical agents can be used weekly or oral medications monthly for maintenance therapy.[103] Patients should also be informed that skin healing will continue long after treatment ends and depigmented areas may require several months to regain natural color.

LICHEN SIMPLEX CHRONICUS

Chronic pruritus, whether from a primary skin disorder (eczema) or underlying systemic disease (xerosis from hypothyroidism), and repetitive rubbing or scratching eventually causes the irritated skin to lichenify. Also known as neurodermatitis, lichen simplex chronicus affects areas of the skin within easy reach, including the following areas in decreasing order of frequency: lateral leg, scrotum, vulva, anal or pubic areas, wrists and ankles, upper eyelids, upper back, neck, external ear canal, extensor forearms near the elbow, posterior auricular area, and the scalp.[44] Pruritus may begin from a nonspecific insult to the skin. Insect bites, minor trauma, burns, eczema, and contact dermatitis are common instigators. Pruritus can be intermittent, but scratching or rubbing provides temporary relief and leads to local erythema. With continued scratching, the skin then forms thickened plaques and/or nodules that are hyperpigmented, firm, well demarcated, scaly, and erythematous (Fig. 12). If scratching becomes too abrasive, linear excoriations or ulcers often develop and increase the risk of superinfection.

The differential diagnosis for lichen simplex chronicus is extensive, including chronically pruritic conditions such as

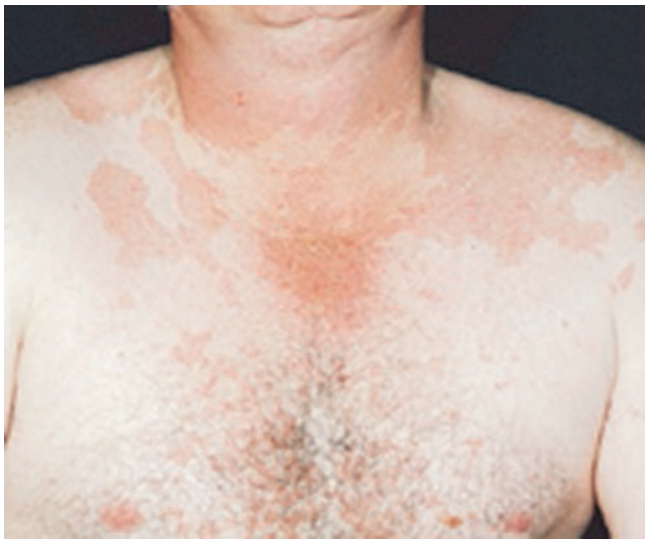

FIGURE 11. Tinea versicolor of neck and trunk appears as confluent, fawn-colored patches. Habif, *Clinical Dermatology*, 4th ed. Elsevier, 2004.

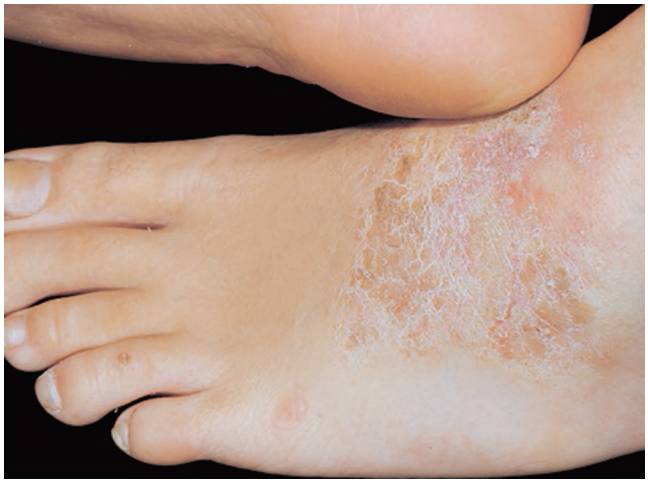

FIGURE 12. Lichen simplex chronicus (neurodermatitis) caused by chronic scratching by the opposite heel. Habif, *Clinical Dermatology*, 4th ed. Elsevier, 2004.

TABLE 4. Summary of Skin Disorders and First-Line Treatment Options

Skin Disease	Characteristic Lesion	First-Line Treatment Options
Atopic dermatitis	Erythematous, scaling papules involving flexural areas	• Moisturizer • Low- to moderate-potency topical corticosteroid • Oral antihistamine
Pityriasis alba	Erythematous, scaly, circular plaques on head and neck; may leave areas of hypopigmentation	• Moisturizer and emollient • Low-potency topical corticosteroid
Allergic contact dermatitis	Pruritic, erythematous, papulovesicular rash with scaling and dry skin	• Identify/avoid trigger • Low- to moderate-potency topical corticosteroid
Seborrhoic dermatitis	Erythematous papules in areas with abundant sebaceous glands	• Topical antifungal
Rosacea	Erythema, flushing, papules, telangiectasias, pustules, and edema on face	• Topical metronidazole • Topical azelaic acid
Pityriasis rosea	"Herald" patch followed by crops of smaller lesions along Langer's lines on torso and extremities	• Topical antipruritic • Low- to moderate-potency topical corticosteroid • Oral antihistamine
Acne	Open or closed comedones, inflammatory papules, pustules, and nodules	• Topical antibiotic • Topical retinoid • Topical benzoyl peroxide
Tinea	Erythematous, pruritic, scaling plaques on scalp, groin, toes, or body	• Topical antifungal for tinea cruris and corporis • Oral antifungal for tinea capitis, barbae, unguium
Lichen planus	Violaceous and pruritic papules with Wickham's striae on skin or mucous membranes	• Moderate- to high-potency topical corticosteroids
Prurigo simplex	Erythematous, indurated, pruritic hives or vesicles following insect bite	• Avoidance measures • Low- to moderate-potency topical corticosteroids
Tinea versicolor	Multicolored patches, papules, and macules with a fine scale and surrounding erytema	• Topical antifungal
Lichen simplex chronicus	Thick plaques and erythematous, hyperpigmented, scaly nodules	• Moisturizer • Low-to moderate-potency topical corticosteroid • Oral antihistamine

atopic dermatitis, lichen planus, contact dermatitis, or systemic diseases such as uremic pruritus or hyperbilirubinemia secondary to hepatic or cholestatic disease. A history and physical examination with focused laboratory testing when necessary will help direct the differential diagnosis. Histologic examination demonstrates hyperkeratosis, acanthosis, spongiosis, and patches of parakeratosis in the epidermis. Epidermal thickening occurs in all skin layers with elongation of rete ridges and pseudoepitheliomatous hyperplasia. Papillary dermal fibrosis with vertical streaking of collagen bundles also occurs.

If chronic pruritus is caused by an underlying disease, then treatment should target the disease to achieve long-term relief. In the meantime, the itch-scratch cycle should be interrupted using topical moisturizers and corticosteroids. Topical immune modulators, such as tacrolimus or pimecrolimus, are also effective antipruritic medications and can be used on steroid-sensitive areas such as the face or antecubital skin. Oral antihistamines also are indicated to relieve pruritus and can help patients who suffer from insomnia from their pruritus.

CONCLUSIONS

A practicing allergist will commonly encounter patients with skin diseases. Atopic dermatitis is seen most frequently because it often relates closely to extrinsic factors such as environmental or food allergies, but the physician should be familiar with each of the discussed conditions (Table 4). A thorough history and physical examination is often all that is required for an accurate diagnosis. Confirmatory testing options are limited and treatment with medications using the most effective dose with the least toxicity should be the goal to provide relief.

REFERENCES

1. Laughter D, Istvan JA, Tofte SJ, Hanifin JM. The prevalence of atopic dermatitis in Oregon schoolchildren. *J Am Acad Dermatol.* 2000;43: 649–655.
2. Georg R. *Atopic Dermatitis*. London: Saunders; 1975.
3. Uehara M, Kimura C. Descendant family history of atopic dermatitis. *Acta Derm Venereol.* 1993;73:62–63.
4. McGrath JA, Uitto J. The filaggrin story: novel insights into skin-barrier function and disease. *Trends Mol Med.* 2008;14:20–27.
5. Vasilopoulos Y, Cork MJ, Murphy R, Williams HC, Robinson DA, et al. Genetic association between an AACC insertion in the 3′UTR of the stratum corneum chymotryptic enzyme gene and atopic dermatitis. *J Invest Dermatol.* 2004;123:62–66.
6. Walley AJ, Chavanas S, Moffatt MF, Esnouf RM, Ubhi B, et al. Gene polymorphism in Netherton and common atopic disease. *Nat Genet.* 2001;29:175–178.
7. Schauber J, Gallo RL. Antimicrobial peptides and the skin immune defense system. *J Allergy Clin Immunol.* 2008;122:261–266.
8. Mrabet-Dahbi S, Dalpke AH, Niebuhr M, Frey M, Draing C, et al. The toll-like receptor 2 R753Q mutation modifies cytokine production and Toll-like receptor expression in atopic dermatitis. *J Allergy Clin Immunol.* 2008;121:1013–1019.

9. Fonacier LS, Dreskin SC, Leung DY. Allergic skin diseases. *J Allergy Clin Immunol.* 125:S138–S149.
10. Watkins DB. Pityriasis alba: a form of atopic dermatitis. A preliminary report. *Arch Dermatol.* 1961;83:915–919.
11. Blessmann Weber M, Sponchiado de Avila LG, Albaneze R, Magalhães de Oliveira OL, Sudhaus BD, Cestari TF. Pityriasis alba: a study of pathogenic factors. *J Eur Acad Dermatol Venereol.* 2002;16:463–468.
12. Vargas-Ocampo F. Pityriasis alba: a histologic study. *Int J Dermatol.* 1993;32:870–873.
13. Saint-Mezard P, Rosieres A, Krasteva M, Berard F, Dubois B, Kaiserlian D, Nicolas JF. Allergic contact dermatitis. *Eur J Dermatol.* 2004;14:284–295.
14. Johnson MT, Roberts J. Skin conditions and related need for medical care among persons 1–74 years. United States, 1971–1974. *Vital Health Stat.* 11 1978:i–v, 1–72.
15. Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous disease and drug reactions in HIV infection. *N Engl J Med.* 1993;328:1670–1674.
16. Mallal SA. The Western Australian HIV Cohort Study, Perth, Australia. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1998;17 Suppl 1:S23–S27.
17. Gupta AK, Bluhm R, Cooper EA, Summerbell RC, Batra R. Seborrheic dermatitis. *Dermatol Clin.* 2003;21:401–412.
18. Naldi L, Rebora A. Clinical practice. *Seborrheic dermatitis. N Engl J Med.* 2009;360:387–396.
19. Schwartz RA, Janusz CA, Janniger CK. Seborrheic dermatitis: an overview. *Am Fam Physician.* 2006;74:125–130.
20. Cömert A, Bekiroglu N, Gürbüz O, Ergun T. Efficacy of oral fluconazole in the treatment of seborrheic dermatitis: a placebo-controlled study. *Am J Clin Dermatol.* 2007;8:235–238.
21. Vena GA, Micali G, Santoianni P, Cassano N, Peruzzi E. Oral terbinafine in the treatment of multi-site seborrhoic dermatitis: a multicenter, double-blind placebo-controlled study. *Int J Immunopathol Pharmacol.* 2005;18:745–753.
22. Baldwin HE. Oral therapy for rosacea. *J Drugs Dermatol.* 2006;5:16–21.
23. Berman B, Zell D. Subantimicrobial dose doxycycline: a unique treatment for rosacea. *Cutis.* 2005;75:19–24.
24. Del Rosso JQ. Update on rosacea pathogenesis and correlation with medical therapeutic agents. *Cutis.* 2006;78:97–100.
25. Ceilley RI. Advances in the topical treatment of acne and rosacea. *J Drugs Dermatol.* 2004;3:S12–S22.
26. Buechner SA. Rosacea: an update. *Dermatology.* 2005;210:100–108.
27. Laube S, Lanigan SW. Laser treatment of rosacea. *J Cosmet Dermatol.* 2002;1:188–195.
28. Gupta AK, Chaudhry MM. Rosacea and its management: an overview. *J Eur Acad Dermatol Venereol.* 2005;19:273–285.
29. Diamantis S, Waldorf HA. Rosacea: clinical presentation and pathophysiology. *J Drugs Dermatol.* 2006;5:8–12.
30. Wilkin J, Dahl M, Detmar M, Drake L, Feinstein A, Odom R, Powell F. Standard classification of rosacea: Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol.* 2002;46:584–587.
31. Dorschner RA, Pestonjamasp VK, Tamakuwala S, Ohtake T, Rudisill J et al. Cutaneous injury induces the release of cathelicidin antimicrobial peptides active against group A Streptococcus. *J Invest Dermatol.* 2001;117:91–97.
32. Yamasaki K, Di Nardo A, Bardan A, Murakami M, Ohtake T, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med.* 2007;13:975–980.
33. Gallo RL, Ono M, Povsic T, Page C, Eriksson E, Klagsbrun M, Bernfield M. Syndecans, cell surface heparan sulfate proteoglycans, are induced by a proline-rich antimicrobial peptide from wounds. *Proc Natl Acad Sci U S A.* 1994;91:11035–11039.
34. Yamasaki K, Gallo RL. The molecular pathology of rosacea. *J Dermatol Sci.* 2009.
35. Maddin S. A comparison of topical azelaic acid 20% cream and topical metronidazole 0.75% cream in the treatment of patients with papulopustular rosacea. *J Am Acad Dermatol.* 1999;40:961–965.
36. Elewski BE, Fleischer AB Jr, Pariser DM. A comparison of 15% azelaic acid gel and 0.75% metronidazole gel in the topical treatment of papulopustular rosacea: results of a randomized trial. *Arch Dermatol.* 2003;139:1444–1450.
37. Bjerke R, Fyrand O, Graupe K. Double-blind comparison of azelaic acid 20% cream and its vehicle in treatment of papulo-pustular rosacea. *Acta Derm Venereol.* 1999;79:456–459.
38. Nielsen PG. A double-blind study of I% metronidazole cream versus systemic oxytetracycline therapy for rosacea. *Br J Dermatol.* 1983;109:63–65.
39. Thiboutot D, Thieroff-Ekerdt R, Graupe K. Efficacy and safety of azelaic acid (15%) gel as a new treatment for papulopustular rosacea: results from two vehicle-controlled, randomized phase III studies. *J Am Acad Dermatol.* 2003;48:836–845.
40. Saihan EM, Burton JL. A double-blind trial of metronidazole versus oxytetracycline therapy for rosacea. *Br J Dermatol.* 1980;102:443–445.
41. Marks R, Ellis J. Comparative effectiveness of tetracycline and ampicillin in rosacea. A controlled trial. *Lancet.* 1971;2:1049–1052.
42. Sneddon IB. A clinical trial of tetracycline in rosacea. *Br J Dermatol.* 1966;78:649–652.
43. van Zuuren EJ, Gupta AK, Gover MD, Graber M, Hollis S. Systematic review of rosacea treatments. *J Am Acad Dermatol.* 2007;56:107–115.
44. Thomas P, Habif M. *Clinical Dermatology: A Color Guide to Diagnosis and Therapy*. 4th ed. Philadelphia: Mosby; 2004.
45. Drago F, Ranieri E, Malaguti F, Battifoglio ML, Losi E, Rebora A. Human herpesvirus 7 in patients with pityriasis rosea. Electron microscopy investigations and polymerase chain reaction in mononuclear cells, plasma and skin. *Dermatology.* 1997;195:374–378.
46. Watanabe T, Kawamura T, Jacob SE, Aquilino EA, Orenstein JM, Black JB, Blauvelt A. Pityriasis rosea is associated with systemic active infection with both human herpesvirus-7 and human herpesvirus-6. *J Invest Dermatol.* 2002;119:793–797.
47. Broccolo F, Drago F, Careddu AM, Foglieni C, Turbino L, et al. Additional evidence that pityriasis rosea is associated with reactivation of human herpesvirus-6 and -7. *J Invest Dermatol.* 2005;124:1234–1240.
48. Stulberg DL, Wolfrey J. Pityriasis rosea. *Am Fam Physician.* 2004;69:87–91.
49. Bjornberg ATE. *Dermatology in general medicine*. 5th ed. New York: McGraw-Hill; 1999.
50. *Dermatology in General Medicine*. 4th ed. New York: Mcgraw-Hill; 1993.
51. Sharma PK, Yadav TP, Gautam RK, Taneja N, Satyanarayana L. Erythromycin in pityriasis rosea: A double-blind, placebo-controlled clinical trial. *J Am Acad Dermatol.* 2000;42:241–244.
52. Chuh AA, Dofitas BL, Comisel GG, Reveiz L, Sharma V, Garner SE, et al. Interventions for pityriasis rosea. *Cochrane Database Syst Rev.* 2007:CD005068.
53. Rasi A, Tajziehchi L, Savabi-Nasab S. Oral erythromycin is ineffective in the treatment of pityriasis rosea. *J Drugs Dermatol.* 2008;7:35–38.
54. Amer A, Fischer H. Azithromycin does not cure pityriasis rosea. *Pediatrics.* 2006;117:1702–1705.
55. Drago F, Vecchio F, Rebora A. Use of high-dose acyclovir in pityriasis rosea. *J Am Acad Dermatol.* 2006;54:82–85.
56. Degitz K, Placzek M, Borelli C, Plewig G. Pathophysiology of acne. *J Dtsch Dermatol Ges.* 2007;5:316–323.
57. Grange PA, Chereau C, Raingeaud J, Nicco C, Weill B, Dupin N, Batteux F. Production of superoxide anions by keratinocytes initiates P. acnes-induced inflammation of the skin. *PLoS Pathog.* 2009;5:e1000527.
58. Graham GM, Farrar MD, Cruse-Sawyer JE, Holland KT, Ingham E. Proinflammatory cytokine production by human keratinocytes stimulated with Propionibacterium acnes and P. acnes GroEL. *Br J Dermatol.* 2004;150:421–428.
59. Bhambri S, Del Rosso JQ, Bhambri A. Pathogenesis of acne vulgaris: recent advances. *J Drugs Dermatol.* 2009;8:615–618.
60. Jugeau S, Tenaud I, Knol AC, Jarrousse V, Quereux G, Khammari A, Dreno B. Induction of toll-like receptors by Propionibacterium acnes. *Br J Dermatol.* 2005;153:1105–1113.
61. Strauss JS, Krowchuk DP, Leyden JJ, Lucky AW, Shalita AR, et al. Guidelines of care for acne vulgaris management. *J Am Acad Dermatol.* 2007;56:651–663.

62. Webster G, Del Rosso JQ. Anti-inflammatory activity of tetracyclines. *Dermatol Clin.* 2007;25:133–135, v.
63. Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. *J Am Acad Dermatol.* 2006;54:258–265.
64. Ross JI, Snelling AM, Carnegie E, Coates P, Cunliffe WJ, et al. Antibiotic-resistant acne: lessons from Europe. *Br J Dermatol.* 2003; 148:467–78.
65. Eady EA, Jones CE, Tipper JL, Cove JH, Cunliffe WJ, Layton AM. Antibiotic resistant propionibacteria in acne: need for policies to modify antibiotic usage. *BMJ.* 1993;306:555–556.
66. Bossuyt L, Bosschaert J, Richert B, Cromphaut P, Mitchell T, et al. Lymecycline in the treatment of acne: an efficacious, safe and cost-effective alternative to minocycline. *Eur J Dermatol.* 2003;13:130–135.
67. Skidmore R, Kovach R, Walker C, Thomas J, Bradshaw M, et al. Effects of subantimicrobial-dose doxycycline in the treatment of moderate acne. *Arch Dermatol.* 2003;139:459–464.
68. Fernandez-Obregon AC. Azithromycin for the treatment of acne. *Int J Dermatol.* 2000;39:45–50.
69. Kapadia N, Talib A. Acne treated successfully with azithromycin. *Int J Dermatol.* 2004;43:766–767.
70. Katsambas A, Dessinioti C. New and emerging treatments in dermatology: acne. *Dermatol Ther.* 2008;21:86–95.
71. Andrews MD, Burns M. Common tinea infections in children. *Am Fam Physician.* 2008;77:1415–1420.
72. Shy R. Tinea corporis and tinea capitis. *Pediatr Rev.* 2007;28:164–174.
73. Hainer BL. Dermatophyte infections. *Am Fam Physician.* 2003;67: 101–108.
74. Kofoed ML, Wantzin GL. Familial lichen planus. More frequent than previously suggested? *J Am Acad Dermatol.* 1985;13:50–54.
75. Powell FC, Rogers RS, Dickson ER, Moore SB. An association between HLA DRI and lichen planus. *Br J Dermatol.* 1986;114:473–478.
76. Gumber SC, Chopra S. Hepatitis C: a multifaceted disease. Review of extrahepatic manifestations. *Ann Intern Med.* 1995;123:615–620.
77. Campisi G, Di Fede O, Craxi A, Di Stefano R, Margiotta V. Oral lichen planus, hepatitis C virus, and HIV: no association in a cohort study from an area of high hepatitis C virus endemicity. *J Am Acad Dermatol.* 2004;51:364–370.
78. Ball SB, Wojnarowska F. Vulvar dermatoses: lichen sclerosus, lichen planus, and vulval dermatitis/lichen simplex chronicus. *Semin Cutan Med Surg.* 1998;17:182–188.
79. Scully C, el-Kom M. Lichen planus: review and update on pathogenesis. *J Oral Pathol.* 1985;14:431–458.
80. Lebwohl M. Strategies to optimize efficacy, duration of remission, and safety in the treatment of plaque psoriasis by using tazarotene in combination with a corticosteroid. *J Am Acad Dermatol.* 2000;43:S43–S46.
81. Laurberg G, Geiger JM, Hjorth N, Holm P, Hou-Jensen K, et al. Treatment of lichen planus with acitretin. A double-blind, placebo-controlled study in 65 patients. *J Am Acad Dermatol.* 1991;24:434–437.
82. Gonzalez E, Momtaz TK, Freedman S. Bilateral comparison of generalized lichen planus treated with psoralens and ultraviolet A. *J Am Acad Dermatol.* 1984;10:958–961.
83. Lear JT, English JS. Erosive and generalized lichen planus responsive to azathioprine. *Clin Exp Dermatol.* 1996;21:56–57.
84. Ho VC, Gupta AK, Ellis CN, Nickoloff BJ, Voorhees JJ. Treatment of severe lichen planus with cyclosporine. *J Am Acad Dermatol.* 1990; 22:64–68.
85. Carbone M, Conrotto D, Carrozzo M, Broccoletti R, Gandolfo S, Scully C. Topical corticosteroids in association with miconazole and chlorhexidine in the long-term management of atrophic-erosive oral lichen planus: a placebo-controlled and comparative study between clobetasol and fluocinonide. *Oral Dis.* 1999;5:44–49.
86. Voûte AB, Schulten EA, Langendijk PN, Kostense PJ, van der Waal I. Fluocinonide in an adhesive base for treatment of oral lichen planus. A double-blind, placebo-controlled clinical study. *Oral Surg Oral Med Oral Pathol.* 1993;75:181–185.
87. Hegarty AM, Hodgson TA, Lewsey JD, Porter SR. Fluticasone propionate spray and betamethasone sodium phosphate mouthrinse: a randomized crossover study for the treatment of symptomatic oral lichen planus. *J Am Acad Dermatol.* 2002;47:271–279.
88. Carrozzo M, Gandolfo S. The management of oral lichen planus. *Oral Dis.* 1999;5:196–205.
89. Bergman J, Rico MJ. Tacrolimus clinical studies for atopic dermatitis and other conditions. *Semin Cutan Med Surg.* 2001;20:250–259.
90. Ferguson MM. Treatment of erosive lichen planus of the oral mucosa with depot steroids. *Lancet.* 1977;2:771–772.
91. Beck HI, Brandrup F. Treatment of erosive lichen planus with dapsone. *Acta Derm Venereol.* 1986;66:366–367.
92. Falk DK, Latour DL, King LE Jr. Dapsone in the treatment of erosive lichen planus. *J Am Acad Dermatol.* 1985;12:567–570.
93. Eisen D. Hydroxychloroquine sulfate (Plaquenil) improves oral lichen planus: an open trial. *J Am Acad Dermatol.* 1993;28:609–612.
94. Silverman S Jr, Gorsky M, Lozada-Nur F, Giannotti K. A prospective study of findings and management in 214 patients with oral lichen planus. *Oral Surg Oral Med Oral Pathol.* 1991;72:665–670.
95. Sieg P, Von Domarus H, Von Zitzewitz V, Iven H, Färber L. Topical cyclosporin in oral lichen planus: a controlled, randomized, prospective trial. *Br J Dermatol.* 1995;132:790–794.
96. Boyd AS. New and emerging therapies for lichenoid dermatoses. *Dermatol Clin.* 2000;18:21–29, vii.
97. Torti DC, Jorizzo JL, McCarty MA. Oral lichen planus: a case series with emphasis on therapy. *Arch Dermatol.* 2007;143:511–515.
98. Dalmau J, Puig L, Roé E, Peramiquel L, Campos M, Alomar A. Successful treatment of oral erosive lichen planus with mycophenolate mofetil. *J Eur Acad Dermatol Venereol.* 2007;21:259–260.
99. Frieling U, Bonsmann G, Schwarz T, Luger TA, Beissert S. Treatment of severe lichen planus with mycophenolate mofetil. *J Am Acad Dermatol.* 2003;49:1063–1066.
100. Feingold BF BE, Michaeli D. The allergic response to biting insects. *Ann Rev Entomol.* 1968;13:137–158.
101. J F. Simuliosis. Analysis of dermatological manifestations following blackfly (Simuliidae) bites as observed in the years 1981–1983 in Bratislava (Czechoslovakia). *Derm Beruf Umwelt. 1984.* 1984;32:171–173.
102. Fradin MS, Day JF. Comparative efficacy of insect repellents against mosquito bites. *N Engl J Med.* 2002;347:13–18.
103. Levin NA. Beyond spaghetti and meatballs: skin diseases associated with the Malassezia yeasts. *Dermatol Nurs.* 2009;21:7–13, 51; quiz 14.

