3 Eczematous Eruptions in Childhood

CHAPTER OUTLINE

Eczematous eruptions are characterized as inflamed papules and plaques, often in association with pruritus and serous discharge. The specific subtype of eczematous dermatitis is based on the clinical morphology, distribution of lesions, and, in many cases, history of exposure. Biopsy of the skin in these conditions is usually not helpful, except to consider alternative diagnoses with distinct histopathologic features.

Atopic Dermatitis

Atopic dermatitis (AD) is one of the most common skin disorders seen in infants and children, and the most common eczematous disorder. Although the term *eczema* is commonly used, *atopic dermatitis* (or, less commonly, atopic eczema) is a more precise term to describe this subset of dermatitis or inflammation of skin.[1] AD begins during the first 6 months of life in 45% of children, the first year of life in 60% of affected individuals, and before 5 years of age in at least 85% of affected individuals.[2,3] The prevalence of AD in American children is 10% to 13%,[4,5] which is consistent with the prevalence in Scandinavia[6,7] and Japan[8] and represents a marked increase during the past several decades.[9] Of these, 67% have mild disease, 26% have moderate disease, and 7% have severe AD.[5] AD severity is increased in older children, in the eldest child in a family, and in Black and Hispanic children.[5] AD occurs more often in urban areas than in rural areas, in smaller families, and in higher socioeconomic classes, which may suggest that exposure to antigenic pollutants and lack of exposure to infectious agents or other antigenic triggers early in life may play a role in the development of the dermatitis.

The 1-year prevalence of AD in adults is up to 10.2%.[10] Despite its early onset for most patients, a meta-analysis of 7 birth cohort studies with follow-up of up to 26 years revealed no difference in AD prevalence before and after childhood (up to 14.6%),[11] suggesting that the percentage of patients with persistence of AD into adulthood or with relapse after an interval without manifestation is relatively high, although the numbers from studies are variable. In one study, more than 80% of children with mild to moderate AD had recurrent symptoms or required medication use at least into the second decade of life.[12] In another meta-analysis of 45 studies, children with AD of greater severity and that had been persistent already for more than 10 years had the lowest chance for clearance.[13]

PATHOGENESIS OF ATOPIC DERMATITIS

Our improved understanding of the basis for AD has led to new therapeutic interventions (see the Management section). AD involves genetic factors dictating immune response and skin barrier integrity, as well as environmental influences, including one's microbiome.[14] The "inside-out" concept of AD pathogenesis focuses on immune abnormalities as being primary, and the "outside-in" theory considers the epidermal barrier dysfunction (a form of innate immunity) as primary, but it is the interplay of these factors that leads to disease.[14–17]

A role for genetic alterations is suggested by the concordance of 77% in monozygotic twins[18] and the greater probability of having AD if one or, even more so, both parents have AD.[19] By far the most common and influential genetic change is having uniallelic or biallelic loss-of-function mutations in profilaggrin *(FLG)*. *FLG* mutations occur overall in approximately 10% of the population and are the cause of ichthyosis vulgaris, a genetic disorder characterized by climate-dependent dry, scaling skin and hyperlinear palms (see Chapter 5). Mutations in *FLG* occur in 10% to 30% of AD patients.[20–24] In addition to the tight linkage of AD with genes of the epidermal differentiation complex (particularly encoding profilaggrin),[25] genome-wide association (GWA) studies have shown numerous other associated loci, primarily related to epidermal barrier function and innate-adaptive immunity.[26]

Heterozygous loss-of-function mutations in *CARD11* (encoding caspase recruitment domain-containing protein 11) have also been associated[27,28] with moderate to severe AD. Many but not all patients have concurrently been affected by other forms of atopy, pneumonia, bronchiectasis, cutaneous viral infections, oral ulcerations, autoimmunity, neutropenia, hypogammaglobulinemia, or lymphoma. Affected individuals may have reduced T-cell responsiveness *in vitro* with increases in B lymphocytes and abnormal B-cell differentiation.[29] Interestingly, homozygous null mutations in *CARD11* cause a form of severe combined immunodeficiency (SCID), whereas heterozygous gain-of-function mutations lead to a form of B-cell lymphoproliferative disease. Loss-of-function mutations in *CARD14* (vs. the gain-of-function mutations associated with the psoriasis–pityriasis rubra pilaris spectrum) may also underlie a severe variant of AD.[30] Heterozygous gain-of-function mutations in *JAK1* have recently been associated with severe AD with hypereosinophilia but not high levels of immunoglobulin E (IgE).[31] Eosinophilic infiltration of the liver and gastrointestinal tract with hepatosplenomegaly, autoimmune disease, and failure to thrive or short stature are other features, and patients respond to Janus kinase (JAK) inhibition.

In the acute phase of AD, environmental triggers such as irritants, allergens, and microbes and mechanical injury (scratching or rubbing) activate the skin's innate immune system, which includes epidermal Langerhans cells and keratinocytes.[32,33] Expression of cytokines, particularly alarmins interleukin-25 (IL-25), IL-33, and

thymic stromal lymphopoietin (TSLP) activate group 2 innate lymphoid cells (ILC2s), leading to T helper 2 (Th2) cell activation.[34] Th2 cells express IL-4, -5, and -13, which promote eosinophilia and IgE production but suppress the expression of epidermal barrier proteins as well as antimicrobial peptides such as β-defensins and cathelicidin. This reduction in antimicrobial peptide production may contribute to the propensity toward development of skin infection in AD patients.[35] TSLP, IL-4/-13, and IL-31 are thought to mediate AD pruritus.[36,37]

Recent studies show that AD T cells also differentiate into Th22 cells, which produce IL-22 and thereby stimulate expression of keratinocyte S100As.[38,39] IL-22 has been implicated in the thickening of skin with lichenification. The role of Th17 cells in AD is not well understood, but increased levels of IL-17 are found in some patients (although not to the extent of Th2 cytokines and IL-22), particularly in young children with recent onset, patients with intrinsic (vs. extrinsic) AD, and people of Asian descent.[40] Although adults with chronic AD also may have increases in Th1 cytokines, Th1 immunity and the Th1/Th2 ratio are very low in children with AD.[41D45] The immune profile of AD is age dependent, with older children and adolescents having an intermediate profile between those of recent-onset AD in young children and in adults.

The intact epidermis itself also plays a role in the skin's innate immune system because it functions as a barrier against water loss (preventing dry skin) and activation of the innate immune system by high-molecular-weight allergens such as dust mite antigens, foods, and microbes. This barrier primarily is composed of tight junction proteins (particularly claudins, middle of the stratum granulosum) and stratum corneum structural proteins and lipids. Filaggrin is the major component of the stratum granulosum of epidermis and binds to keratin.[46,47] Its precursor, profilaggrin, contains 10 to 12 monomers of filaggrin, and fewer monomers within the profilaggrin gene (e.g., 10 vs. 12) have been linked to an increased risk of developing AD,[48] which complements the known increased risk of developing AD with filaggrin insufficiency.[49,50] Filaggrin is also broken down into natural moisturizing factor (NMF), particularly urocanic acid, which promotes skin hydration, providing another explanation for the dry skin of AD and ichthyosis vulgaris. NMF has been shown to be low during the first year of life, especially on the cheeks.[51] AD in association with mutations in *FLG* has been shown to be more severe and more persistent.[12,52]

The stratum corneum lipid matrix predominantly is composed of cholesterol, free fatty acids, and ceramides, densely stacked into a highly ordered, three-dimensional structure of lipid lamellae, which depends on lipid composition. These lipids are secreted by the lamellar bodies into the intercellular space of the stratum corneum. AD skin has a decreased content of very long chain ceramides[53,54] and free fatty acids, related to a deficiency of elongases that synthesize very long-chain fatty acids. The barrier can also be altered by the increased activity of proteases (especially kallikreins 5 and 7), which degrade barrier proteins and are more active at increased pH, as occurs in association with deficiency of filaggrin products (e.g., urocanic acid).

The skin (and perhaps gut) microbiome is another environmental influence on both the barrier and skin immunity.[14] A meta-analysis of 95 studies showed that *Staphylococcus aureus* is found on lesional skin of 70% and nonlesional skin of 39% of patients with AD.[55] Most of the *S. aureus* is methicillin-sensitive *S. aureus* (MSSA), although 7% of patients have methicillin-resistant *S. aureus* (MRSA). Flares of AD are associated with a shift in the microbiome toward a greater percentage of *S. aureus* (and *S. epidermidis*) and reduced bacterial diversity,[56] and the shift is greater in patients with MRSA than MSSA.[57] Commensal organisms are recognized to play a key role in killing *S. aureus* and modulating immune responses. A recent birth cohort suggested that having commensal *Staphylococcus* spp. at day 2 could protect infants against the development of AD.[58] Patients with AD not only have fewer commensals with active disease but also have fewer commensals that are able to kill *S. aureus*.[59] Topical application of commensal organisms (e.g., *Staphylococcus hominis* or *Roseomonas mucosa*)[60] as treatment for AD is a new direction that in early studies appears to reduce AD severity and the use of topical corticosteroid.

Box 3.1 American Academy of Dermatology Clinical Criteria for Atopic Dermatitis

Essential Features

Pruritus (or parental reporting of itching or rubbing) in past 12 months
Eczena (acute, subacute, chronic)
- Typical morphology and age-specific patterns (infants and young children: face, neck, extensors; spares diaper area; any age group: flexural lesions
- Chronic or relapsing history

Important Features (seen in most cases and support diagnosis)

Early age of onset
Personal and/or family history of atopy
IgE reactivity
Xerosis

Associated Features (can help with diagnosis but too nonspecific for diagnosis)

Atypical vascular responses (e.g., delayed blanch response, facial pallor, white dermographism)
Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
Ocular/periorbital changes
Other regional changes (perioral, periauricular)
Perifollicular accentuation/lichenification/prurigo lesions

Exclusionary Conditions in Children

Contact dermatitis (irritant or allergic; can be concurrent)
Immunodeficiency (and other causes of erythroderma)
Psoriasis
Seborrheic dermatitis
Ichthyoses
Scabies
Cutaneous T-cell lymphoma
Photosensitivity disorders

IgE, Immunoglobulin E.

CLINICAL FEATURES

The cardinal features of AD are pruritus, chronicity, and the age-specific morphology and distribution of lesions (Box 3.1).[61] Extent of involvement may range from mild and limited—for example, to "flexural areas"—to generalized and severe. The tremendous itch of AD can translate into issues with sleep, especially with wake after sleep onset, but also difficulty in falling asleep, because the pruritus tends to be worst at bedtime. Skin pain[62] can also be a feature.

The morphology of AD and distribution of lesions is often age dependent, although there is considerable overlap (e.g., infants may show the typical distribution of adult AD). Infants with AD typically have intense itching, erythema, papules, vesicles, oozing, and crusting. In infants, AD often begins on the cheeks, forehead, or scalp (Figs. 3.1, 3.2, and 3.3) and then may extend to the trunk (Fig. 3.4) or particularly the extensor aspects of the extremities in scattered, ill-defined, often symmetric patches. Generalized xerosis is common. Exacerbation of facial dermatitis on the medial cheeks and chin is often seen concomitant with teething and initiating foods. This localization likely reflects exposure to irritating saliva and foods, although contact dermatitis or urticaria may contribute. By 8 to 10 months of age the extensor surfaces of the arms and legs often show dermatitis (Fig. 3.5), perhaps because of the role of friction associated with crawling and the exposure of these sites to irritant and allergenic triggers such as those found in carpets. Although dermatitis of the antecubital and popliteal fossae, periorbital areas, and neck are more commonly involved in older children and adolescents, these sites may be affected in infants and young children as well (Fig. 3.6). Typically, lesions of AD spare the groin and diaper area during infancy (Fig. 3.7), which aids in the diagnosis. This sparing likely reflects the combination of increased hydration in the diaper area, protection from triggers by the diaper, and inaccessibility to scratching and rubbing. The "headlight sign" has been used to describe the typical sparing of the nose and medial cheeks in AD, even when there is extensive facial involvement elsewhere (see Fig. 3.1).

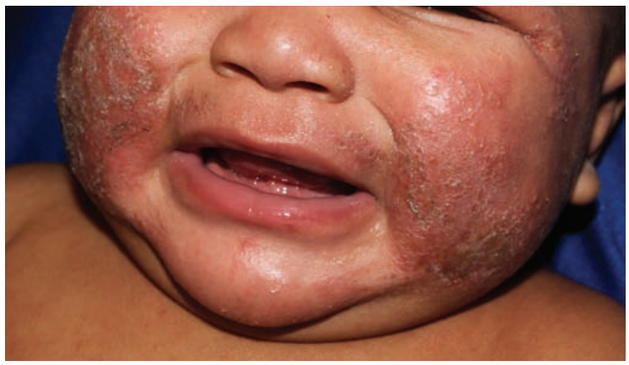


Fig. 3.1 Acute atopic dermatitis (AD) on the cheek of an infant. This boy shows the headlight sign, with relative sparing of the midface and immediate perioral area. The edema and exudation is typical of infantile AD and should not be confused with secondary bacterial infection.

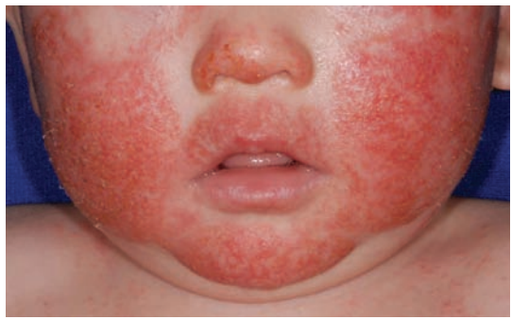


Fig. 3.2 Acute atopic dermatitis in an infant. Despite extensive perioral and nasal tip involvement, the immediate perinasal and infralabial areas are spared.

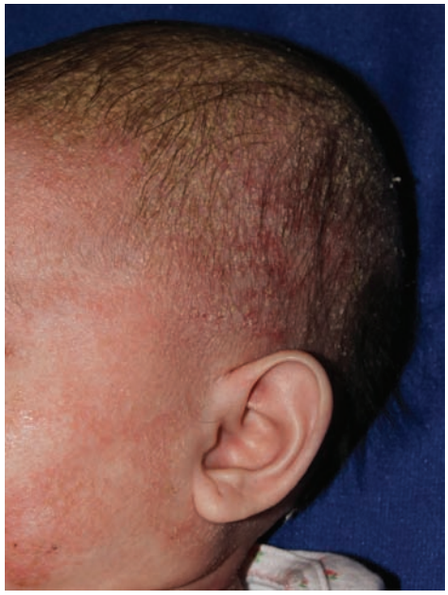


Fig. 3.3 Atopic dermatitis (AD) and seborrheic dermatitis. Seborrheic dermatitis and AD often occur concurrently, especially in infants with early atopic dermatitis. In addition to the presence of AD on the face, head rubbing or excoriations (suggesting scalp pruritus) and recalcitrance to traditional management for seborrheic dermatitis are clues to the combination.

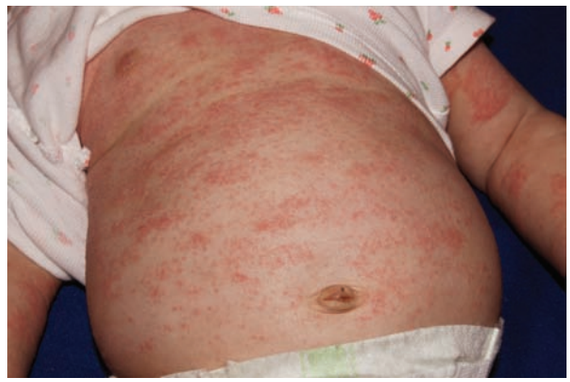


Fig. 3.4 Atopic dermatitis on the trunk and extremities of an infant. In this baby, note the accentuation at the nipple and relative sparing of the antecubital fold.

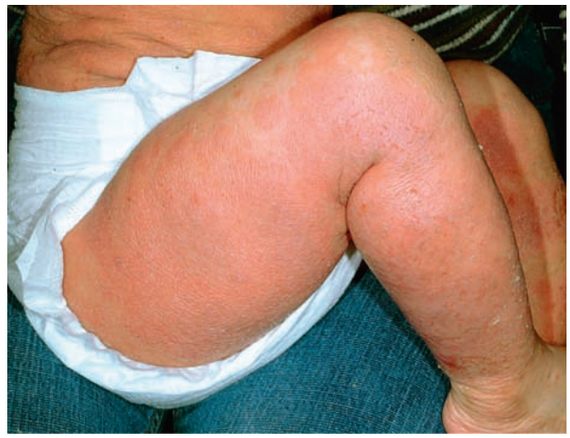


Fig. 3.5 Involvement of the extensor surfaces of the legs and arms is commonly seen during the infantile phase of atopic dermatitis beginning at about 8 months of age, concomitant with crawling and exposure to irritant and allergenic triggers.

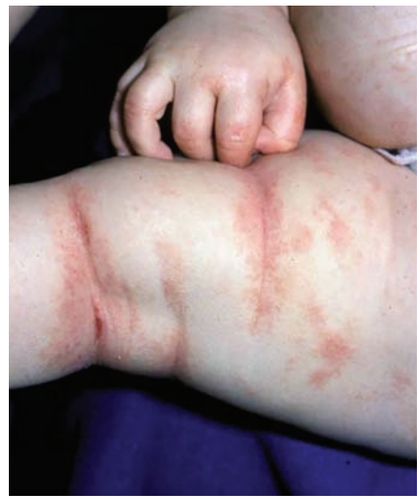


Fig. 3.6 Although antecubital and popliteal fossa involvement is typical of the childhood and adult phases of atopic dermatitis, infants not uncommonly will show involvement at these fold areas. This infant is demonstrating his response to the pruritus.

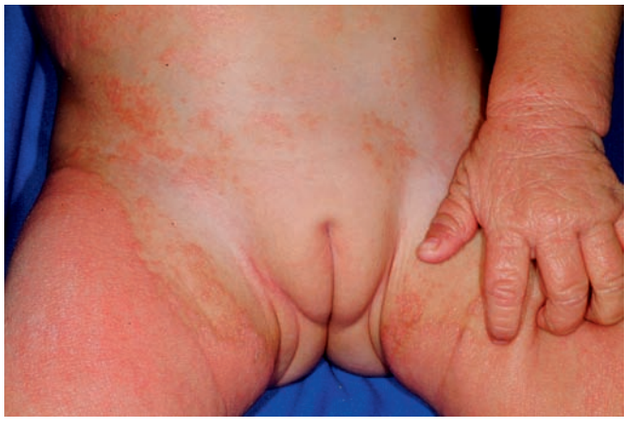


Fig. 3.7 Relative sparing of the diaper area is typical in infants with atopic dermatitis, likely because of the occlusion of this site and protection from scratching and rubbing, as well as from allergenic triggers.

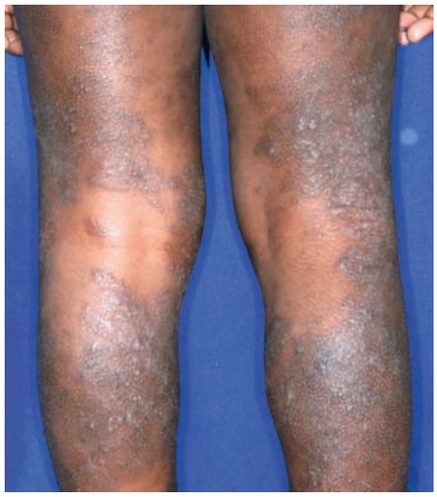


Fig. 3.8 Extensive lichenification on the legs of this affected toddler. Note the follicular accentuation and relative sparing of the popliteal areas.

Not uncommonly, infants initially show signs of seborrheic dermatitis, particularly during the first month or two of life. The associated pruritus and the dry (rather than greasier) scale suggest the combination of both disorders (see Fig. 3.3); the seborrheic component usually clears by 6 to 12 months, whereas the AD features persist. Alopecia may accompany the scalp involvement because of inflammation and chronic rubbing.

By about 2 years of age, children with AD are less likely to have exudative and crusted lesions and have a greater tendency toward chronicity and lichenification (Fig. 3.8). Eruptions are characteristically drier and more papular and often occur as circumscribed scaly patches. The classic areas of involvement in this group are the wrists, ankles, hands, feet, neck, and antecubital and popliteal regions (Figs. 3.9 and 3.10). Facial involvement switches from cheeks and chin to periorbital (Figs. 3.11 and 3.12) and perioral, the latter sometimes manifesting as "lip-licker's dermatitis" (see Fig. 3.56). Dermatitis of the nipples (Fig. 3.13) occurs in some infants and children and can be exacerbated by rubbing on clothing. Pruritus is often severe. Some children with AD show nummular or coin-shaped lesions with sharply defined oval scaly plaques on the face, trunk, and extremities (see Nummular Dermatitis section). In Black children, the lesions of

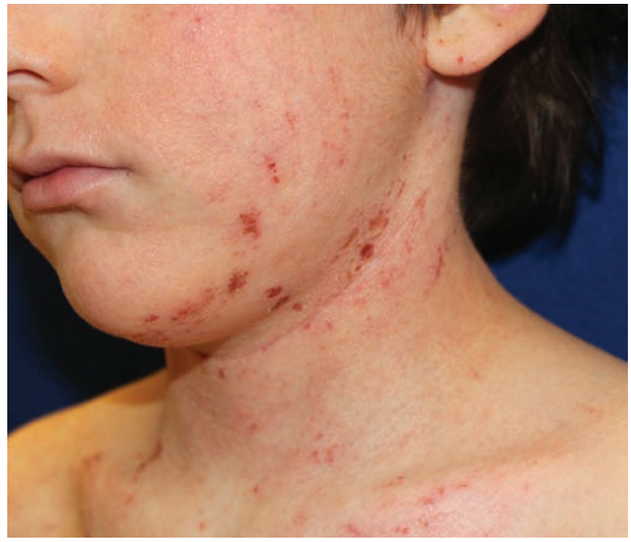


Fig. 3.9 Xerosis with erythema, fissuring, and crusting on the neck and face in this 10-year-old boy.

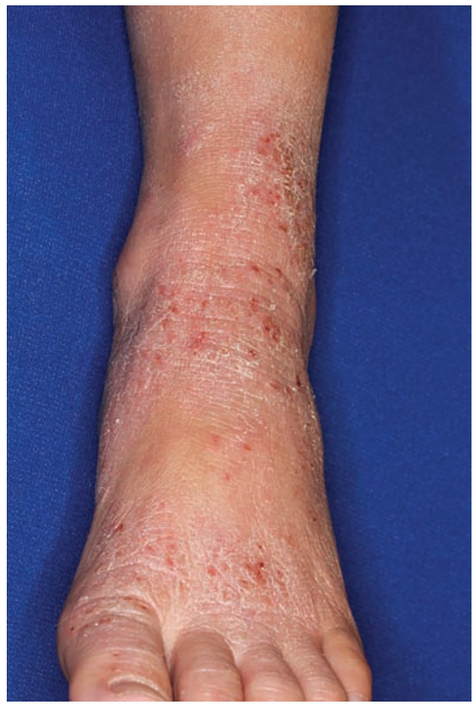


Fig. 3.10 Atopic dermatitis on the ankle and dorsal aspect of the foot. Note the lichenification and crusting.

AD are often more papular and follicular (Fig. 3.14). Although localization at flexural areas is more common, some children show an inverse pattern with involvement primarily of extensor areas. Lymphadenopathy may be a prominent feature in affected children (Fig. 3.15), reflecting the role of lymph nodes in handling local infection and inflammation. Nail dystrophy may be seen when fingers are affected, indicating involvement of the nail matrix; children may show secondary staphylococcal or pseudomonal paronychia.

By later childhood and adolescence, predominant areas of involvement include the flexural folds (Fig. 3.16), the face and neck, the

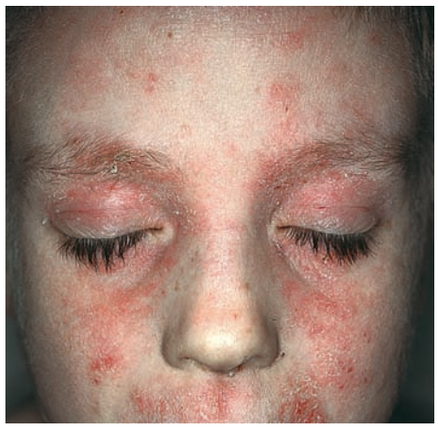


Fig. 3.11 Facial atopic dermatitis in children and adolescents typically affects the periorbital and perioral areas.

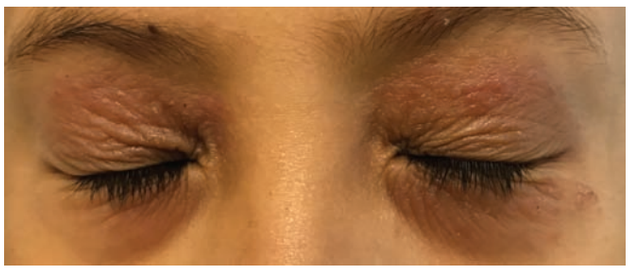


Fig. 3.12 The periorbital areas can be severely lichenified with chronic eyelid dermatitis. Consideration should be given to patch testing with chronic involvement at this site.

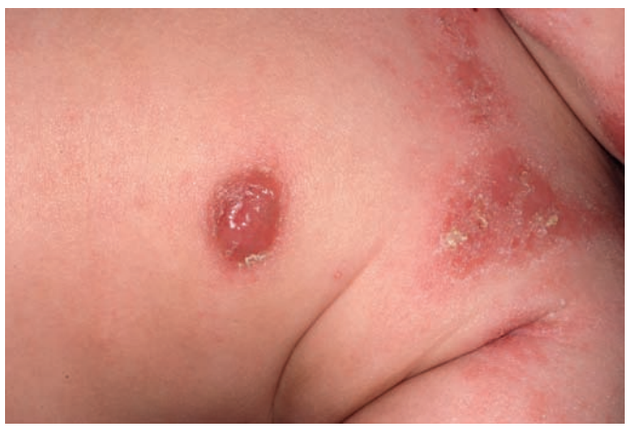


Fig. 3.13 Nipple eczema may occur in infants and children with atopic dermatitis, even without much truncal involvement elsewhere, and is exacerbated by the rubbing of clothes on the affected nipples.

upper arms and back, and the dorsal aspect of the hands, feet, Þngers, and toes. The eruption is characterized by dry, scaling erythematous papules and plaques and by the formation of large licheniÞed plaques from lesional chronicity. Weeping, crusting, and exudation may occur from the AD itself but usually is the result of superimposed staphylococcal infection or allergic contact dermatitis. Prurigo nodularis, characterized by well-circumscribed, usually hyperpigmented thickened papules, most commonly on the lower extremities, is most often seen during adolescence (Fig. 3.17).

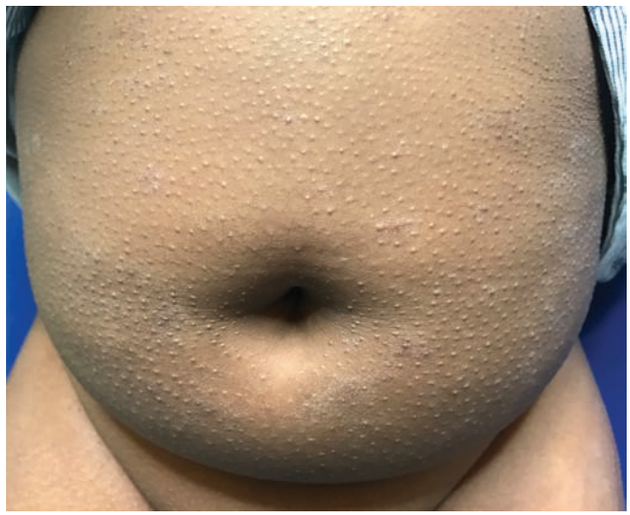


Fig. 3.14 Follicular (or papular) atopic dermatitis (AD) is more commonly seen in Black children with AD and can be difficult to distinguish from lichen nitidus (see Fig. 4.61) and, if on the elbows or knees, juvenile frictional lichenoid dermatosis (see Fig. 3.50).

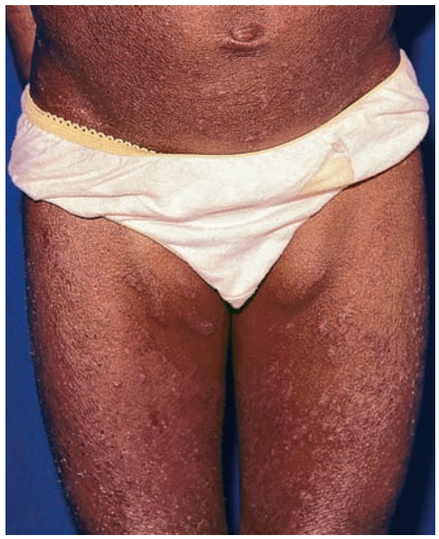


Fig. 3.15 Lymphadenopathy is a common accompanying feature of severe atopic dermatitis (AD), especially when the AD is associated with infection.

Postinßammatory reduction of pigmentation may occur at any age, especially in individuals with darker skin. Although postinßammatory hypopigmentation is more common (see Figs. 3.16 and 3.18), pigment reduction may be severe enough to be depigmented, resembling vitiligo (Fig. 3.19), especially on distal extremities. The pigmentary changes are transient and are reversible when the underlying inßammation is controlled; however, 6 months or more may be required for repigmentation (and years if vitiliginous), and sun exposure may accentuate the differences between uninvolved and hypopigmented skin areas. In contrast, hyperpigmentation is predominantly noted at sites of licheniÞcation (Figs. 3.12, 3.15, 3.17, and 3.20.), because the thickened epidermis accumulates epidermal melanin pigment, especially in darker skinned individuals. Children with licheniÞcation show accentuation of skin (Fig. 3.21). Parents may mistake the postinßammatory pigment change seen in some children for scarring or a toxicity of

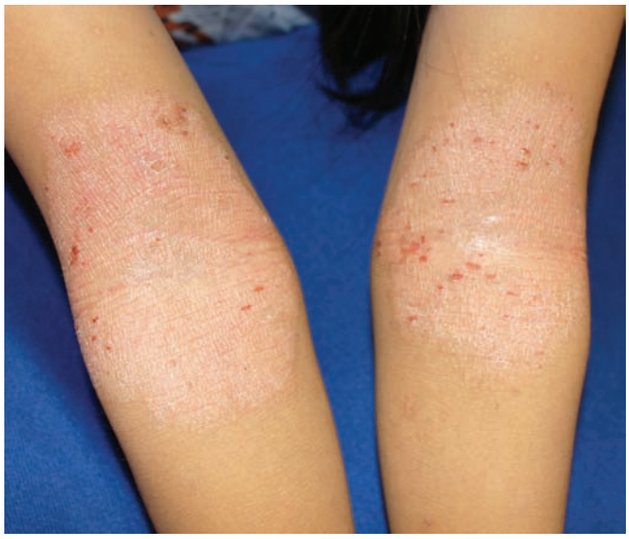


Fig. 3.16 Involvement of antecubital and popliteal areas is characteristic in children and adolescents with atopic dermatitis. Note the associated crusting and postinflammatory hypopigmentation.

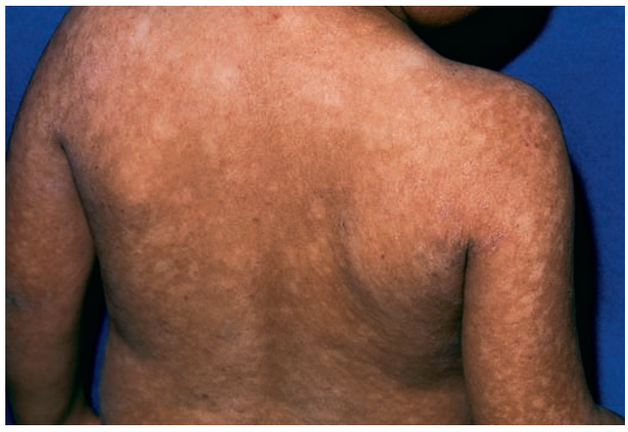


Fig. 3.18 Postinflammatory hypopigmentation of atopic dermatitis (AD). Postinflammatory hypopigmentation is a sequela of AD inflammation, is not related to use of topical steroids, and is not scarring. The postinflammatory hypopigmentation is particularly prominent during summer months, when the surrounding unaffected skin tans after exposure to ultraviolet light, and tends to clear spontaneously after several months if further flares of dermatitis at the site are prevented.

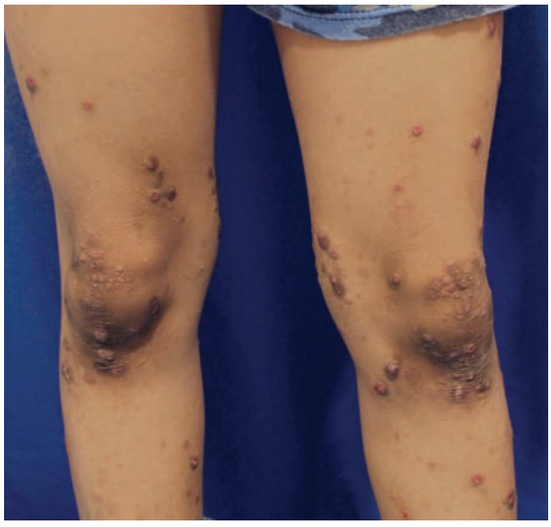


Fig. 3.17 Prurigo nodularis. Well-circumscribed, usually hyperpigmented lichenified papules appear most commonly on the lower extremities. Recurrent gouging of these intensely pruritic papules results in scarring.

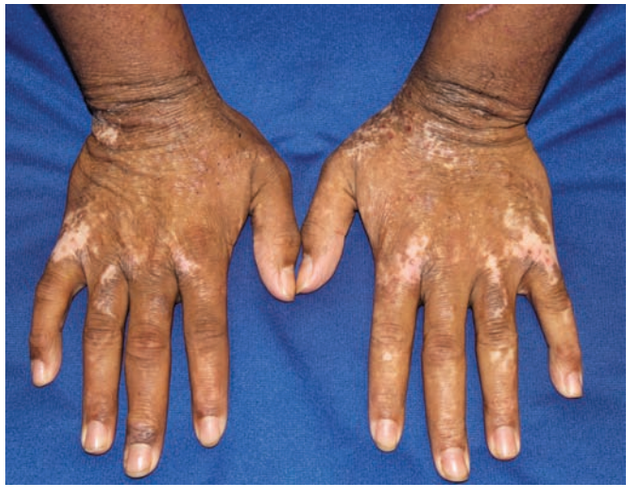


Fig. 3.19 Depigmentation resembling vitiligo occasionally occurs in severely affected children, particularly at sites of chronic atopic dermatitis (AD) on the dorsal aspect of the hands and feet, wrists, and ankles. Repigmentation can occur slowly with improved AD control at these sites.

topically applied medications and need reassurance. AD lesions are not usually scarring, but secondary infection and deep gouging of lesions can leave residual scarring and long-term pigmentary change.

OTHER CLINICAL SIGNS

Several other clinical signs are seen with increased incidence in children with AD, although they may appear in children without AD as well. Dermographism, a manifestation of the triple response of Lewis that occurs in approximately 5% of the normal population, is characterized by a red line, flare, and wheal reaction. A red line develops within 15 seconds at the exact site of stroking, followed within 15 to 45 seconds by an erythematous flare (because of an axon-reflex vasodilation of arterioles). The response finally eventuates in a wheal (because of transudation of fluid from the injured capillaries in the original stroke line) 1 to 3 minutes later. Individuals with AD often demonstrate a paradoxical blanching of the skin termed *white dermographism* (Fig. 3.22). The initial red line is replaced, generally within 10 seconds, by a white line without an associated wheal. Patients with AD may also show circumoral pallor, thought to relate to local edema and vasoconstriction.

Follicular hyperkeratosis, or chicken-skin appearance, particularly on the lateral aspects of the face, buttocks, and outer aspects of the upper arms and thighs, is termed *keratosis pilaris* (see Figs. 7.24 and 7.25).[63] Keratosis pilaris is not seen at birth but is common from early childhood onward and often persists into adulthood. Each lesion represents a large cornified plug in the upper part of the hair follicles, often with surrounding inflammation and vasodilation. Keratosis pilaris is more commonly associated with AD in children who have ichthyosis vulgaris. Moisturizers alone tend to be insufficient as therapy

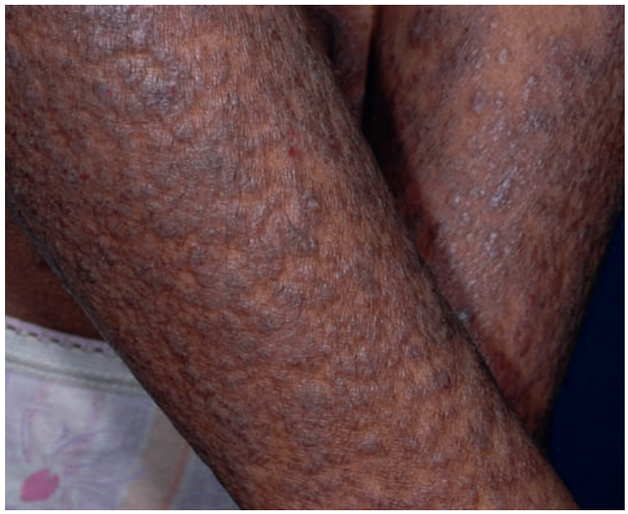


Fig. 3.20 Lichenification. Accentuation of skin markings are notable in thickened, lichenified skin of chronic atopic dermatitis. In darker-skinned individuals, hyperpigmentation tends to be associated with the lichenification.

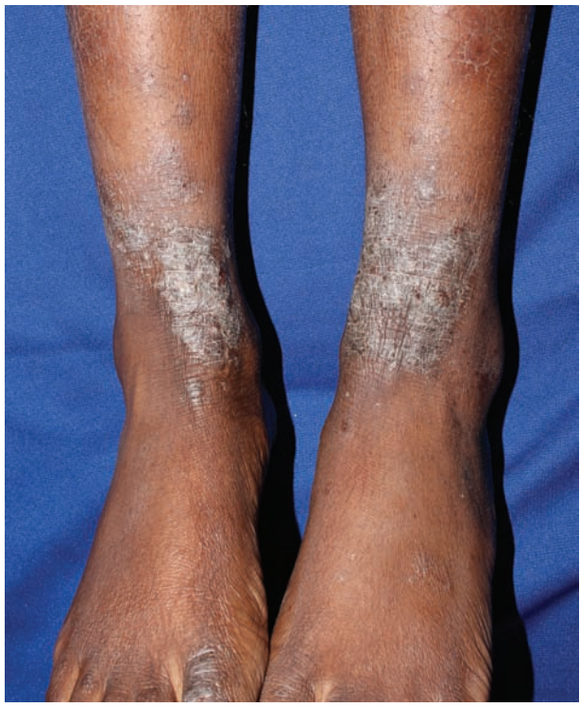


Fig. 3.21 Lichenification appears hyperpigmented in darker skin types (in contrast, see Fig. 3.10 with lichenification at the same site of a child with light skin).

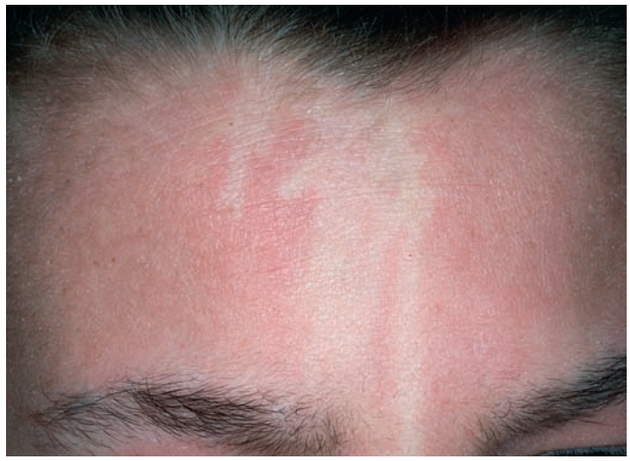


Fig. 3.22 White dermographism is the paradoxical blanching of skin after stroking.

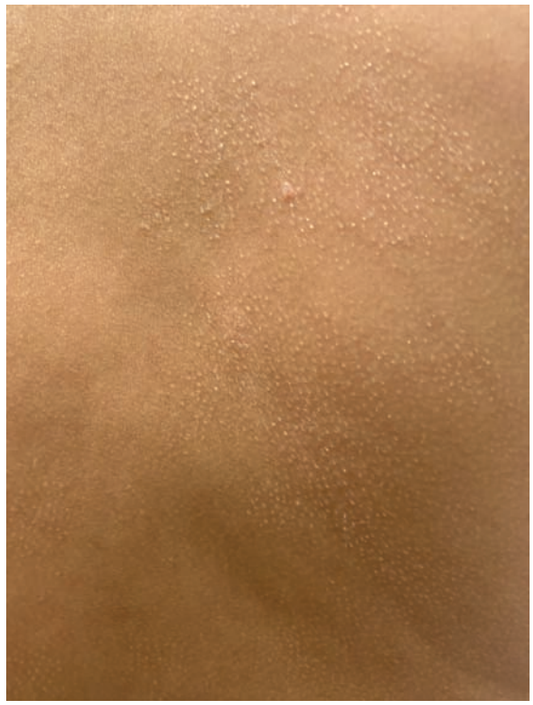


Fig. 3.23 Lichen spinulosus is commonly seen in children with dry skin and sometimes with atopic dermatitis. The characteristic collections of tiny, discrete flat-topped papules are usually asymptomatic.

for keratosis pilaris. Keratolytic agents such as urea or α-hydroxy acids may be helpful. Their use is limited, however, by the increased potential for irritation in children with AD. Treatment should be discouraged unless of significant cosmetic importance, because keratosis pilaris is almost always asymptomatic.

Lichen spinulosus manifests as round collections of numerous tiny, skin-colored to hypopigmented dry spiny papules (Fig. 3.23).[64] More common in Black children, lichen spinulosus usually occurs on the trunk or extremities. Lesions tend to be asymptomatic and may respond to application of emollients and mild topical corticosteroids. Children with AD also show an increased incidence of pityriasis alba, nummular dermatitis, dyshidrotic eczema, and juvenile plantar dermatosis (see related sections).

Individuals with atopic disorders have a distinct tendency toward an extra line or groove of the lower eyelid, the so-called "atopic pleat" (Fig. 3.24). Seen just below the lower lid of both eyes, the atopic pleat may be present at birth or shortly thereafter and is often retained throughout life. This groove (commonly referred to as a *Dennie–Morgan fold*) may result from edema of the lower eyelids and skin thickening; it represents a feature of the atopic diathesis rather than a pathognomonic marker of AD. The atopic pleat has been found with increased incidence in Black children.[65] Slate-gray to violaceous infraorbital discolorations ("allergic shiners"), with or without

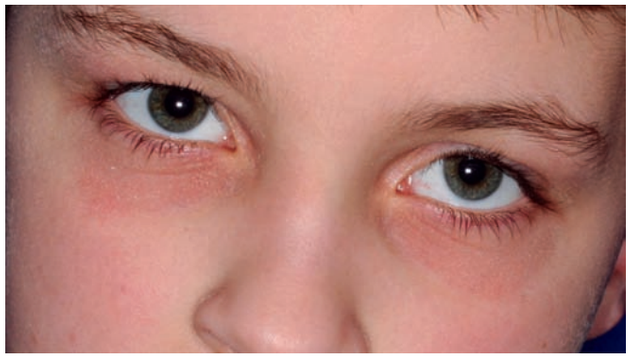


Fig. 3.24 Atopic pleats. Accentuated lines or grooves (Dennie–Morgan folds) are seen below the margin of the lower eyelids. This is a sign of the allergic diathesis and is not specific to atopic dermatitis. Note the mild periorbital dermatitis with hyperpigmentation.

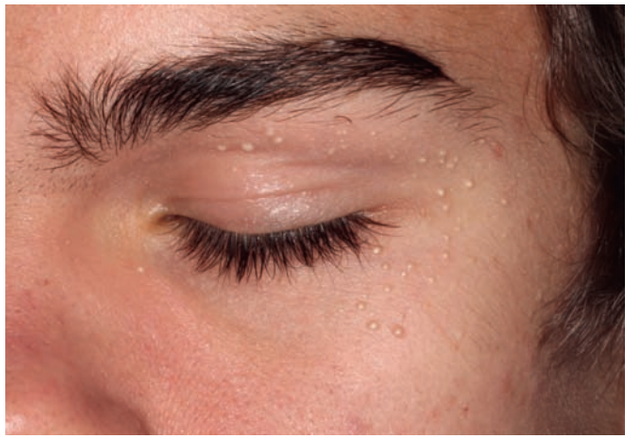


Fig. 3.25 Milia. Note that this child has numerous milia of the periorbital area, small inclusion cysts that are often a sign of chronic rubbing of the skin from periorbital dermatitis and/or allergic conjunctivitis. Milia clear spontaneously but after months to years.

swelling, are also seen in patients with allergies and in patients with AD. Allergic shiners are thought to be a manifestation of vascular stasis induced by pressure on underlying venous plexuses by edema of the nasal and paranasal cavities; the swelling and discoloration become more prominent as a result of repeated rubbing of the eyes and postinflammatory pigment darkening. Another clinical feature, an exaggerated linear nasal crease, is caused by rubbing of the nasal tip (the so-called "allergic salute") and occurs in 7% of schoolchildren.[66] Milia (tiny inclusion cysts; see Chapter 9) of the periorbital area are common in preadolescents (Fig. 3.25), may resemble acne, and are thought to result from the recurrent rubbing. Milia tend to resolve spontaneously, although years may be required; extraction may be performed but is rarely necessary.

Many patients with atopic conditions exhibit an increased number of fine lines and accentuated markings of the palms (Fig. 3.26). These accentuated palmar markings often are a clue to the concurrent diagnosis of ichthyosis vulgaris (see the previous discussion of the pathomechanism and also Chapter 5), a relatively common condition seen with increased incidence in children with AD. Ichthyosis vulgaris is considered a "semi-dominant" disorder because heterozygotes show manifestations (especially in drier, colder climates), but homozygotes tend to have greater severity. Most individuals with ichthyosis vulgaris merely think they have dry skin until the diagnosis is made when they are seen for AD. Diagnosis is based on the accentuated markings on

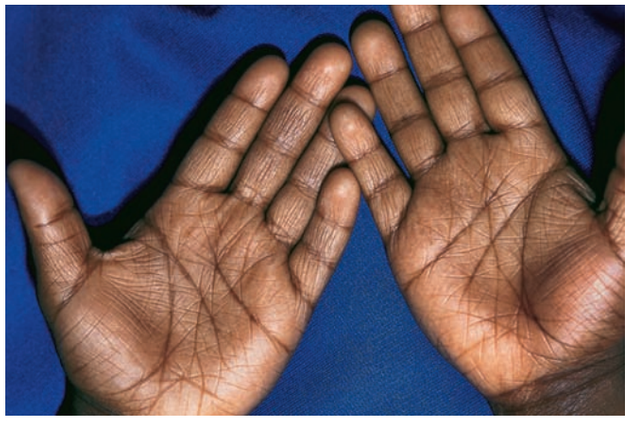


Fig. 3.26 Accentuated palmar creases. Hyperlinearity of the palms is a sign of concurrent ichthyosis vulgaris (see Chapter 5), a genetic disorder of skin associated with an increased risk of atopic dermatitis.

the palms and soles, the characteristic generalized scaling with larger and more severe scaling on the lower extremities, worsening during winter months, and often positive family history.

Allergic keratoconjunctivitis (AKC) is a chronic noninfectious inflammatory condition and is one of the most severe ophthalmic complications associated with atopic dermatitis. AKC has been described in up to 30% of children with AD. It typically begins during late teenage years but has been described as early as 7 years of age.[67] Patients experience chronic itching and pain of the eyes, as well as tearing, redness, and blurred vision. It requires prompt and effective treatment to prevent permanent vision loss; moderate to severe eye irritation, increased redness, discharge, and any visual symptoms are features that require more urgent referral to an ophthalmologist. Complications of AKC include cataracts, keratoconus, infectious keratitis, blepharitis, tear dysfunction, and steroid-induced glaucoma.[68] Treatment options include a combination of mast cell inhibitors, antihistamines, corticosteroids, and calcineurin inhibitors.

Posterior subcapsular cataracts have been described in up to 13% of adult patients with severe AD.[69] Rarely seen in children, these cataracts are usually asymptomatic. Keratoconus (elongation and thinning of the corneal surface) has been reported in about 1% of patients with AD and seems to develop independently of cataracts.[69] Keratoconus is exacerbated by continuous rubbing of the eyes and may require corneal transplantation.

EFFECT ON QUALITY OF LIFE

The quality of life in infants, children, and adolescents with moderate to severe dermatitis is significantly reduced,[70] and having severe AD during childhood can have a great impact on psychosocial development.[71] Infants with AD have been shown to be excessively dependent and fearful. Sleep disturbance affects up to 60% of children with AD overall and 83% of children during flares. Impaired sleep quality occurs in children with mild AD and even inactive AD but is particularly problematic in children with more severe disease,[72] especially wake after sleep onset.[73] Neurocognitive function is impaired in children with sleep problems.[74] Even in clinical remission, children with AD show more sleep disturbance than healthy children,[75] including increased nocturnal wakefulness and a longer latency to rapid-eye-movement (REM) sleep.[75]

Disfigurement associated with moderate to severe AD, coupled with the reduction in sleep, restlessness, and fatigue at school, as well as limitations in participation in sports, isolates the affected child and strains relationships with peers and with teachers.

As a chronic disorder that requires frequent attention, the family of a child with AD carries a high financial burden of parental missed days from work for doctor visits and home care; lost wages owing to interruption of employment; expensive medications; and the costs of

special or additional bedding, clothes, and food. The socioeconomic impact of AD in the United States alone is estimated to be $364 million to $3.8 billion annually.[76] The demonstrated average reduction by 1 to 2 hours of parental sleep nightly also translates into increased parental stress[77] and the tendency of affected children to cosleep with parents affects family dynamics.[78] These stressful psychological factors often exacerbate the AD, as may concurrent infectious illness or the stress of assignments at school.

COMORBIDITIES OF ATOPIC DERMATITIS

Allergic Disorders

AD is often associated with other forms of atopy, with 70% to 80% of affected children having an associated increase in IgE levels (extrinsic AD). Children with AD overall have a two- to threefold increased risk of developing asthma by 6 years of age and a threefold increased risk of developing allergic rhinitis (AR) compared with children without AD. Greater severity, earlier onset, persistence of the AD, polysensitization, having at least one variant in *FLG*, and parental history of allergic disease further increase the odds of developing these other atopic disorders.[79] Overall, asthma occurs by 6 years of age in approximately 30% of children with AD; AR develops in 43% to 80% of children with AD.[80]

The risk of food allergy is also increased with AD. In one study of almost 1100 infants with predominantly mild to moderate AD who enrolled at 3 to 18 months without a history of food allergy at baseline and were followed prospectively for 36 months, allergy to at least one food developed in 15.9% overall.[81] The most common triggers were peanut (6.6%), cow's milk (4.3%), and egg white (3.9%). The percentage with food allergies increases with greater AD severity, earlier onset, and AD persistence.[82]

Negative predictive values are high for antigen-specific IgE (sIgE), but positive predictive values for sIgE testing tend to be much lower,[81] especially if the cutoff values are low. True food allergy (based on clinical manifestations or food challenge) must be differentiated from the positive sIgE, which is common in infants and children with AD (including in 64% of those with AD beginning before 3 months of age).[83] In one study, 89% of food challenges based on positive sIgE testing were negative, consistent with a false-positive rate for true food allergy.[84] Food allergies to cow's milk and egg usually resolve during childhood, whereas peanut allergy tends to persist.

The approach to prevention of peanut allergy has dramatically changed during the past few years, based on the 2015 Learning Early About Peanut Allergy study, which showed that early introduction (4 to 11 months) of peanut reduced the risk of developing peanut allergy at 60 months of age (1.9%) compared with delayed introduction (13.7%). A panel of the National Institutes of Allergy and Infectious Diseases amended early guidelines[85] to recommend that children with severe AD, egg allergy, or both be exposed to peanut as early as 4 to 6 months of life, but only after evaluation by an allergy specialist (by skin prick testing [SPT], sIgE, or both). Severe AD has been defined as having persistent or frequently recurrent AD with typical morphology and distribution and requiring frequent application of prescription-strength topical antiinflammatory medications despite appropriate use of emollients.[85] Having a low peanut sIgE (<0.35; 6 to 7 g over three or more feedings) or minimal skin prick test reaction (0 to 2 mm) translates into an option to introduce the peanut at home or with supervision in the office setting; having an sIgE of 0.35 or greater should lead to referral to a specialist (given the poor predictive value for a positive sIgE). Having a SPT of 3 to 7 mm allows supervised administration in the office or oral food challenge, whereas having a reaction of more than 8 mm suggests a high likelihood of existent peanut allergy and requires appropriate management with strict peanut avoidance. For those with mild to moderate AD, peanut can be introduced at 4 to 6 months without further assessment (and as desired in those without AD, but ideally well before 1 year of age). Instructions for home feeding, including foods, amounts, subsequent observation, and signs of reaction have been published in the dermatology literature.[86] The expert panel did not recommend a broader panel of food allergen testing, given the poor positive predictive value and in an effort to avoid unnecessary dietary restriction.

The parallel increase in the prevalence of these various atopic disorders, including AD, suggests a shared mechanism or triggers. In fact, AD is often the first atopic feature in children who later develop asthma or AR, although food allergy not uncommonly precedes AD. The *atopic march* refers to the earlier occurrence of AD and later occurrence of one or more of these allergic disorders.[79] Having both AD and allergic sensitization greatly increases the risk of developing asthma and AR.[87]

The concurrence of allergic disorders with AD implicates the AD skin barrier abnormality in increasing the risk through promoting early local and systemic immune reactivity to antigens, with later development of food and environmental allergies, asthma, and allergic rhinitis. The importance of barrier integrity is supported by the association of *FLG* mutations with increased risk of asthma, allergic rhinitis, and food allergies,[88] but only in children with prior development of AD.[89–93] However, latent class analyses have suggested that AD occurs before asthma or AR less often than previously noted,[94] and studies have suggested the concept of multimorbidity with a shared underlying basis (e.g., genetic and/or environmental) driving these disorders.[79]

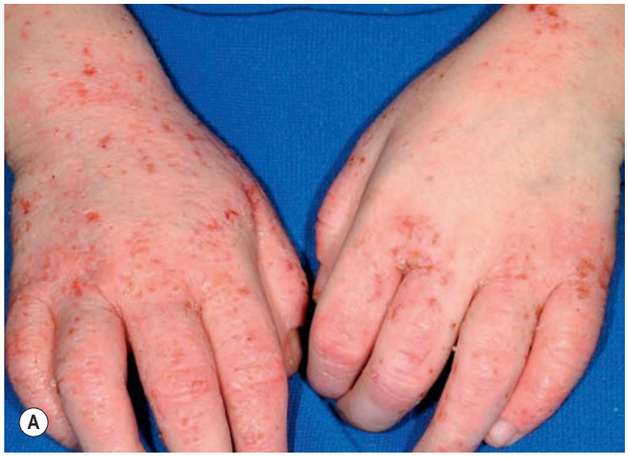
Biomarker and cluster analyses have begun to further subclassify patients according to phenotype (clinical features) or endotype (biologic/laboratory features[95–96] that are associated with clinical phenotypes). The ability to study biomarkers derived noninvasively through tape strips is likely to help subphenotype pediatric patients in the future,[97–99] allowing prediction of AD course, risk of comorbidities, and therapeutic responses.

INFECTIOUS COMPLICATIONS

In contrast to a prevalence of a carrier state in 5% to 20% of individuals who have no atopic condition, *S. aureus* is recovered in up to 90% of patients from lesions of AD up to 76% from uninvolved (normal) skin and 50% to 60% from the anterior nares.[100–102] The increased adherence of *S. aureus* to the epidermal cells of individuals with AD[103] and a failure to produce endogenous antimicrobial peptides in the inflamed skin of patients with AD may account for the high rate of *S. aureus* colonization and infection. Although secondary infection in AD is usually from *S. aureus* (72%), 16% of cultures in infected patients with AD yield *S. pyogenes,* and 14% are mixed cultures.[104] Patients infected with group A *Streptococcus* were more likely to be febrile, have facial and periorbital involvement, have bacteremia and cellulitis, and be hospitalized compared with those infected with *S. aureus* alone.[104]

The pyoderma associated with AD is usually manifested by erythema with exudation and crusting (Fig. 3.27, *A* and *B*), particularly at sites of scratching, and occasionally by small pustules at sites of dermatitis (Fig. 3.28). This complication must be considered whenever a flare of chronic AD develops or fails to respond to appropriate therapy. *S. aureus* exacerbates the AD through (1) release of superantigen toxins, which enhance T-cell activation; (2) activation of superantigen-specific and allergen-specific T cells[105]; (3) expression of IgE antistaphylococcal antibodies[106,107]; and (4) increased expression of Th2 cytokines (including IL-31 and TSLP, which are known to cause pruritus directly) and increased expression of IL-22,[108] which is associated with epidermal thickening. Superantigen production also increases the expression of an alternative glucocorticoid receptor that does not bind to topical corticosteroids, leading to resistance.[109] Other factors produced by *S. aureus* are likely to exacerbate AD as well.[110] These observations emphasize the role of *S. aureus* as an important trigger of AD and endorse therapies that decrease the numbers of bacteria on the skin.

Although MRSA colonization and superinfection of AD is increasing, the majority of children with AD harbor MSSA.[100,111] MRSA infection may manifest as pustules (Fig. 3.29, *A*), abscesses (see Fig. 3.29, *B*), or crusting that is indistinguishable clinically from MSSA infection but much more difficult to eradicate; suppression of MRSA often requires that the entire family (including pets, who can harbor MRSA) be treated initially or even on an intermittent basis to reduce colonization, such as with intranasal mupirocin



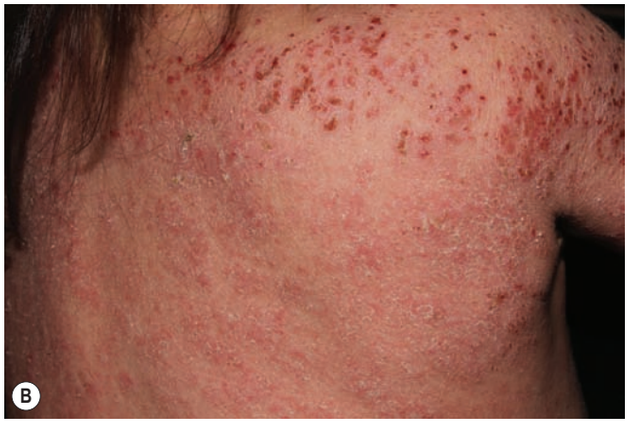


Fig. 3.27 Staphylococcal infection in atopic dermatitis. Sites of excoriation on the dorsal aspects of the hands **(A)** and upper back **(B)** are oozing and crusted. Note the erythema and mild associated edema. The dermatitis and the infection improved with oral administration of cephalexin, and the use of daily baths with sodium hypochlorite helped to maintain control while minimizing crusting.

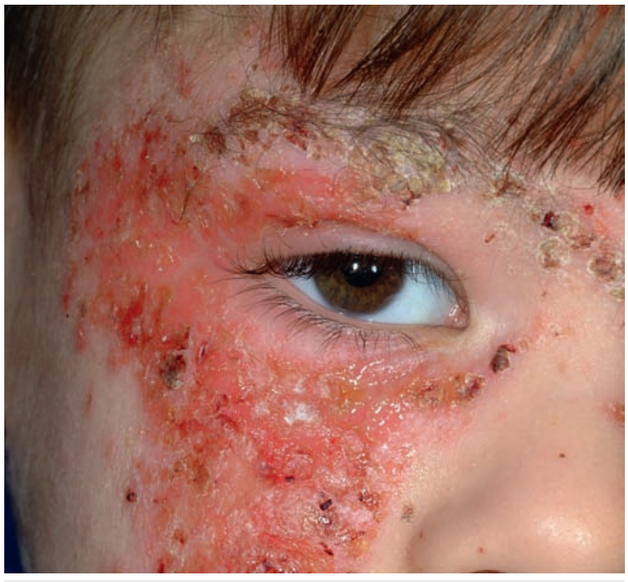
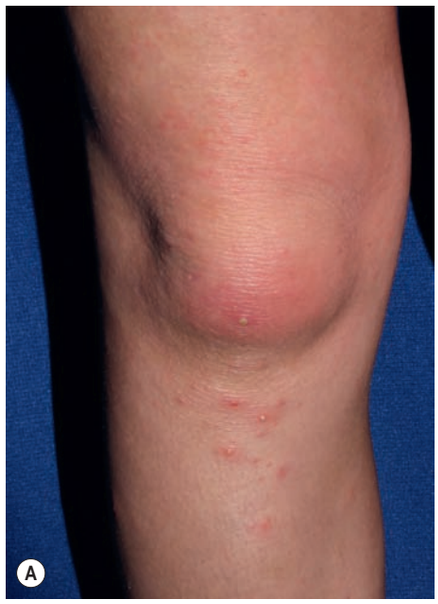


Fig. 3.28 Staphylococcal infection with pustules in atopic dermatitis (AD). Discrete nongrouped pustules and crusting overlying erythema and swelling of the periorbital area of a child with severe AD.



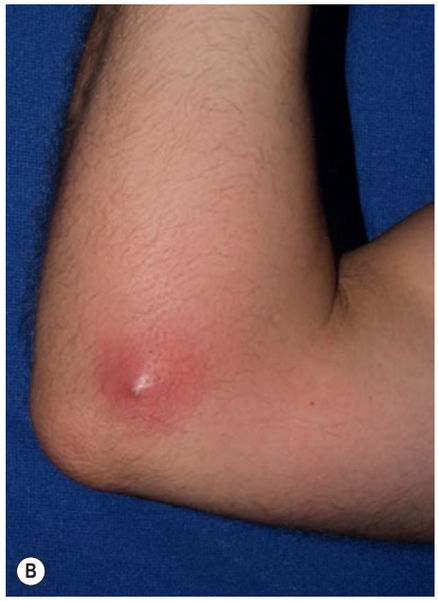


Fig. 3.29 Methicillin-resistant *Staphylococcus aureus* (MRSA) infection in atopic dermatitis (AD). **(A)** Staphylococcal pustulosis on the knees in a girl with severe AD and recurrent MRSA infections. **(B)** Her father has an MRSA abscess on the arm. Decolonization of the entire family is important.

ointment and once to twice weekly bleach baths or use of sodium hypochlorite–containing cleansers.

Greater cutaneous dissemination of certain viral infections has also been noted in children with AD and has been attributed to defects in the generation of antimicrobial peptide and the relative deficiency of Thl cytokine generation and cytotoxic T-cell function. Molluscum contagiosum is a cutaneous viral infection of childhood that most commonly affects the trunk, axillae, antecubital, popliteal fossae, and crural areas (see Chapter 15). Lesions are usually small, dome-shaped papules that often show central umbilication. The often-extensive molluscum lesions tend to be most numerous at sites of active dermatitis and can induce pruritus as well as dermatitis around the molluscum papules (“molluscum dermatitis”).

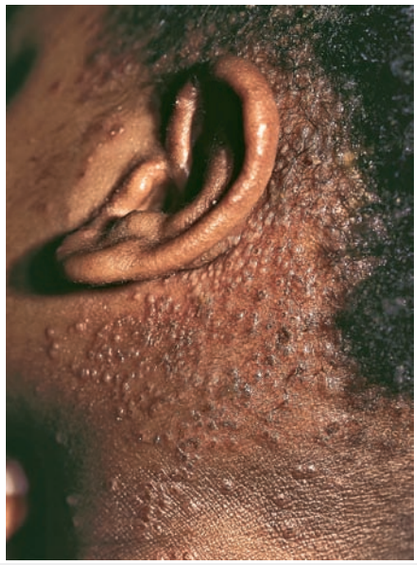


Fig. 3.30 Eczema herpeticum (Kaposi varicelliform eruption). Grouped vesiculopustular lesions on the face, retroauricular, and neck areas. Several of the pustules are beginning to show umbilication. The intense erythema is harder to appreciate in dark skin.

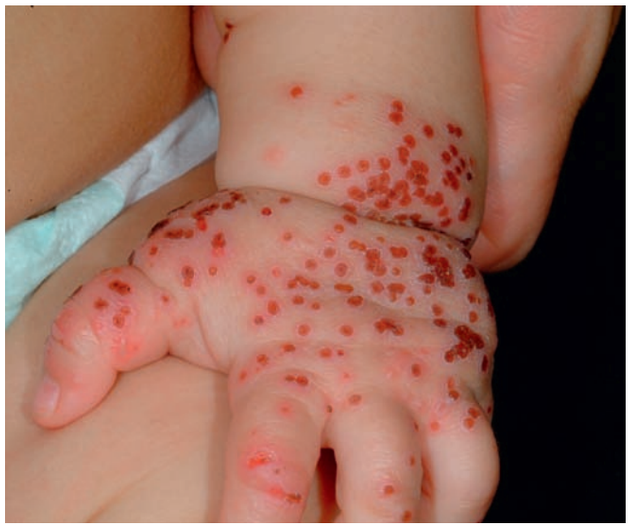


Fig. 3.31 Eczema herpeticum. These small, round umbilicated vesicles and punched out erosions are typical lesions of herpes simplex infection.

Eczema herpeticum (EH, also termed *Kaposi varicelliform eruption*) describes the explosive development of a vesiculopustular eruption caused by herpes simplex virus (HSV) in an individual with an atopic condition. Children with more severe AD and other atopic conditions are at greatest risk.[112] The tendency toward eczema herpeticum is associated with an elevated Th2 and reduced Th1 T-cell immune response to HSV1.[113,114] The clustering and often umbilication of the vesicles is characteristic (Figs. 3.30 and 3.31; see Fig. 8.15), with sites of the dermatitis most commonly affected. Nevertheless, with a confluence of vesicles and crusting, eczema herpeticum can be mistaken for bacterial infection (Fig. 3.32). The diagnosis can be verified by polymerase chain reaction (PCR) and viral culture. If these tests are not available, a Tzanck test can be performed by scraping the floor of vesicles and, after staining the smear with Giemsa or Wright stain, searching for multinuclear virus (giant cells) or balloon cells.

Hospitalization may be necessary, especially in infants younger than 1 year and in association with fever or other systemic symptoms.[115]

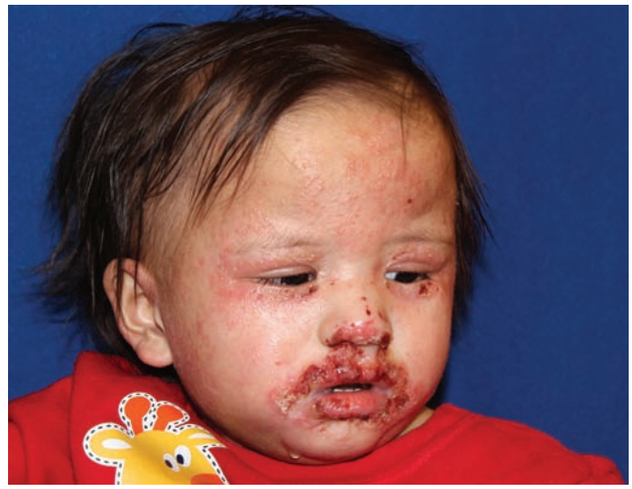


Fig. 3.32 Eczema herpeticum. Infection tends to occur at sites of atopic dermatitis, in this case the periorbital and perioral areas. Although eczema herpeticum with confluence of vesicles and extensive crusting can be confused with bacterial infection, some children also have secondary bacterial infection and need treatment with both acyclovir and antibiotic, such as cephalexin.

Early administration of acyclovir has been shown to lead to better outcomes for EH,[116] and use of topical corticosteroids or calcineurin inhibitors has not been associated with poorer outcomes in children hospitalized with EH.[117] Systemic antibiotics should be administered if secondary bacterial infection is strongly suspected but should not be used empirically.[118]

Eczema vaccinatum was a problem when smallpox vaccinations were compulsory, most commonly contracted by accidental contact with a recently vaccinated individual. The global threat of bioterrorism and consideration of smallpox vaccinations has again brought to attention the risk of eczema vaccinatum for patients, particularly children, with AD.[119] Eczema vaccinatum is characterized by the widespread cutaneous dissemination of vaccinia viral lesions that manifest as firm, deep-seated vesicles or pustules that are all in the same stage of development (see Chapter 15). Lesions may become umbilicated or confluent.

Eczema coxsackium (see Chapter 16) is a recently coined term to describe the unusual cutaneous concentration in sites of previous or current AD of vesicles and erosions from coxsackievirus A6 and, less commonly, coxsackievirus A16 infection, which could be confused with EH (Fig. 3.33).[120,121] Fever, oral erosions or ulcerations, and sore throat or mouth are among the most common associated symptoms. Lesions clear spontaneously in an average of 12 days but may persist for a month.

Reactivity to *Malassezia* has been blamed for recalcitrant AD of the head and neck in adolescents. Although there are no documented differences in *Malassezia* species colonization, patients with head and neck AD are more likely to have positive skin prick test results and *Malassezia*-specific IgE compared with healthy control subjects and patients with atopy without head and neck dermatitis. These patients may benefit from a 1- to 2-month course of daily itraconazole or fluconazole followed by long-term weekly treatment.[122]

Other Comorbidities

AD is also associated with several neuropsychiatric disorders, including anxiety, depression, attention-deficit/hyperactivity disorder (ADHD), conduct disorder, and autism.[123–126] In preschool children with AD, there is also a higher risk of enuresis, encopresis, and attachment disorder.[127] The risk of ADHD is highest in children with more severe disease and greater sleep deprivation,[128] reinforcing the impact of these factors on neurocognitive function. One provocative study suggested that use of sedating antihistamines increased the risk of developing ADHD,[129] but further study is needed. Although restlessness and inattention at school, common in sleep-deprived, itchy AD

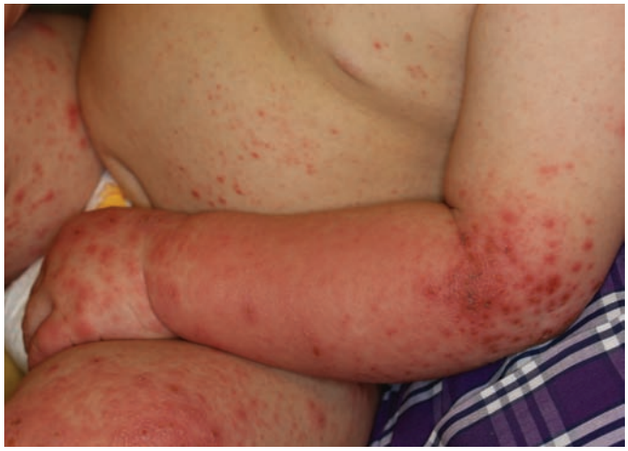


Fig. 3.33 Eczema coxsackium. Children with atopic dermatitis (AD) are at increased risk of widespread cutaneous lesions from coxsackie infection, especially coxsackie A6, which can cluster at sites of AD and be confused with eczema herpeticum.

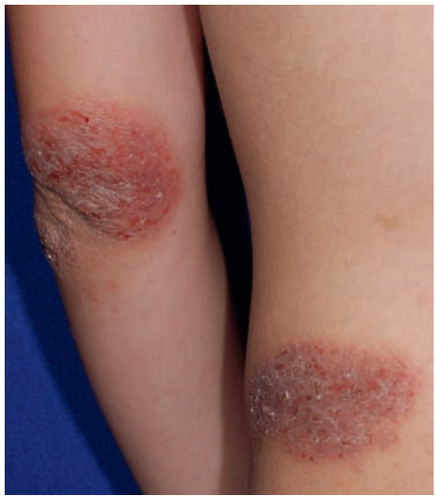


Fig. 3.34 Nummular dermatitis. Characterized by well-defined, round (coin-shaped or nummular) plaques of vesiculopapules overlying erythema and edema. Oozing and secondary infection are common.

children, may be features that resemble those of ADHD, these are not sufficient to meet screening criteria for ADHD for the majority of AD children.[130] Families are also affected, with higher risks of anxiety and depression in caregivers.[131] Children with AD have a higher risk of injury requiring medical attention, related both to comorbid psychiatric and behavioral disorders and their atopy.[132] Additional emerging comorbidities are autoimmune disorders (alopecia areata, vitiligo, rheumatoid arthritis, and inflammatory bowel disease[133]) and obesity,[134] especially during infancy and including central obesity.[135,136]

DIFFERENTIAL DIAGNOSIS

AD is a chronic fluctuating disease. The distribution and morphology of lesions vary with age, but itching is the cardinal symptom of this disorder. Although many skin conditions may occasionally resemble AD, certain characteristics assist in their differentiation. Three common forms of dermatitis that are seen often with AD are contact dermatitis (both irritant and allergic), seborrheic dermatitis, and nummular dermatitis. Each of these disorders is discussed in detail later in the chapters and, as such, is mentioned only briefly here as relevant to AD.

Seborrheic dermatitis is characterized by a greasy yellow or salmon-colored scaly eruption that may involve the scalp, cheeks, trunk, extremities, and diaper area. The major differentiating features include a tendency toward earlier onset, characteristic greasy yellowish or salmon-colored lesions with a predisposition for intertriginous areas, a generally well-circumscribed eruption, and a relative absence of pruritus (see later). Infants may show both atopic and seborrheic dermatitis (see Fig. 3.3), with progression or persistence of the atopic lesions as the seborrheic dermatitis subsides.

Irritant and allergic forms of contact dermatitis are common comorbidities of AD (see related section).[137] Primary irritant dermatitis is commonly seen in infants and young children on the cheeks and the chin (owing in part to the irritation of saliva), the extensor surfaces of the extremities (as a result of harsh soaps, detergents, or rough fabrics), and the diaper area (usually spared in AD; primarily from feces and vigorous cleansing). Irritant dermatitis may also result from bubble baths, personal care products, and handled materials such as modeling clays. Primary irritant dermatitis is generally milder, less pruritic to asymptomatic, and not as eczematous and oozing as the eruptions seen in association with AD. Irritant contact dermatitis to saliva and to exposure to harsh soaps and fabrics occurs more often in children with concomitant AD.

Allergic contact dermatitis (ACD), although relatively uncommon in the first few months of life, can mimic almost any type of eczematous eruption and is characterized by a well-circumscribed pruritic, erythematous, papular, and vesicular eruption. Although such eruptions involute spontaneously on identification and removal of the cause, this disorder often requires a carefully detailed history and

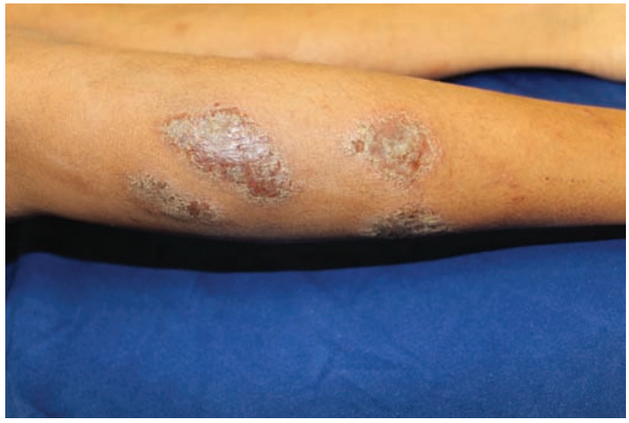


Fig. 3.35 Nummular dermatitis. Some patients show multiple nummular plaques.

prolonged observation before the true causative agent is identified. ACD to nickel occurs often in children with AD[138] and may be misdiagnosed as recalcitrant periumbilical AD. Patients with recalcitrant AD may have concomitant allergic contact reactions, particularly to nickel and less often to topically applied medications and emollients, suggesting the role for patch testing.[139] Positive patch tests for potential allergens other than nickel have been described in up to 45% of children with AD,[138,140,141] and more than half of these are reactions to components in their emollients (lanolin, neomycin, formaldehyde, sesquiterpene lactone mix [including parthenolide], compositae mix, and fragrances) or foaming products (cocamidopropyl betaine).[142] Topical corticosteroids are unusual contact allergens[144D145] but can be tested based on structural class with tixocortol-21-pivalate, budesonide, and hydrocortisone 17-butyrate.[140,146,147]

Nummular dermatitis is a distinctive disorder characterized by coin-shaped lesions. Measuring 1 cm or more in diameter, lesions of nummular dermatitis develop on dry skin and are more often seen during dry winter months. The eruption is characterized by discrete erythematous round plaques formed by the confluence of papules and vesicles (Figs. 3.34 and 3.35). Nummular lesions tend to be secondarily infected and often more recalcitrant to topical therapy. If the combination of medium-strength to potent topical steroid plus topical antibiotic does not suffice, a course of systemic antibiotic may be required. Dilute sodium hypochlorite baths should also be considered.

The lesions of psoriasis, another common skin disease of children, are bright red and topped with loosely adherent silvery micaceous scale (see Chapter 4). Psoriatic lesions usually show a sharply delineated edge and have a predilection for the extensor surfaces (particularly the elbows and knees), the scalp, the buttock, and the genital regions. Approximately 5% of children with psoriasis also show dermatitis, either as typical psoriasis and AD lesions or a psoriasiform dermatitis; these children often have a family history of both atopy and psoriasis.

Scabies in infants and children is commonly complicated by eczematous changes because of scratching and rubbing of involved areas or the application of harsh topical therapeutic agents. The diagnosis of scabies is best made by the history of itching, a characteristic distribution of lesions, the recognition of primary lesions (particularly the pathognomonic burrow when present), positive identification of the mite on microscopic examination of skin scrapings, and the presence of infestation among the patient's family or associates (see Chapter 18).

Langerhans cell histiocytosis (LCH) most commonly occurs before 3 years of age (see Chapter 10). In affected neonates, reddish-brown, purpuric, crusted papules or vesiculopapules are typically present. In infants this skin eruption is often characterized as a scaly, erythematous seborrheic eruption on the scalp, behind the ears, and in the intertriginous regions. On close inspection the presence of reddish-brown, petechial or purpuric lichenoid papules or vesicular or crusted papules in infants is typical. Cutaneous biopsy and identification of $CD1a^+$ Langerhans cells by immunostaining confirms the diagnosis of LCH.

Acrodermatitis enteropathica is an autosomal recessive disorder characterized by vesiculobullous eczematoid lesions of the acral and perioricial areas, failure to thrive, diarrhea, alopecia, nail dystrophy, and frequent secondary bacterial or candidal infection (see Chapters 2 and 24). The characteristic distribution of lesions accompanied by listlessness, diarrhea, failure to thrive, and low serum zinc levels differentiate lesions of acrodermatitis enteropathica from those of AD. Usually a disorder in formula-fed babies with the hereditary form, acrodermatitis enteropathica may also occur in breastfed babies as a result of deficient zinc secretion into maternal breast milk.

Dermatitis during the neonatal or infantile periods is also seen in immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, which manifests with early onset intractable diarrhea and type 1 diabetes mellitus.[148–150] The disorder is often fatal during the first year of life. The cutaneous manifestations are seen in 70% of affected babies and tend to be the first sign.[148] Although an atopic-like dermatitis is most common, the eruption has also been described as psoriasiform or resembling ichthyosiform erythroderma. Lesions are often pruritic, secondarily infected by *S. aureus*, and resistant to treatment with topical corticosteroids. Other common cutaneous manifestations include severe cheilitis, onychodystrophy, and alopecia. Infections of the upper and lower airways and gastrointestinal (GI) tract are common, and affected patients may succumb to sepsis. Food allergies and high levels of IgE and eosinophils are also associated. The autoimmune enteropathy is characterized by persistent, watery, and sometime mucoid or bloody diarrhea during the neonatal period, resulting in malabsorption and failure to thrive. Type 1 diabetes is difficult to control and results from lymphocytic infiltration of the pancreas. Other autoimmune symptoms, such as hypothyroidism, cytopenia, hepatitis, nephropathy, and arthritis can develop in patients who survive the initial acute phase. IPEX syndrome results from mutations in *FOXP3*, leading to absent or dysfunctional regulatory T cells and self-reactive T-cell activation and proliferation. Detection of enterocyte autoantibodies helps make the diagnosis.[151] Treatment generally includes supportive care and systemic immunosuppressive therapy (steroids, methotrexate, tacrolimus), although rapamycin has shown promise. Stem-cell transplantation is the curative treatment[150] if a suitable donor can be found.

Generalized erythroderma in association with atopic features can be seen in other disorders with barrier abnormalities, notably Netherton syndrome (biallelic mutations in *SPINK5*) and SAM syndrome (*s*evere skin dermatitis, multiple *a*llergies and *m*etabolic wasting; biallelic mutations in *DSG1*)[152]; failure to thrive, recurrent infections, and hypotrichosis are associated with both of these ichthyotic disorders (see Chapter 5).

Typical AD may be a feature of several forms of immunodeficiency, most notably in Wiskott–Aldrich syndrome (WAS) and the hyperimmunoglobulinemia E syndrome (HIES) (see related sections). These disorders are distinguished from AD by their recurrent noncutaneous infections and other characteristic features (e.g., thrombocytopenic purpura, bloody diarrhea, and purpuric lesions in WAS and facial and intertriginous staphylococcal abscesses in HIES).

MANAGEMENT

The overall goals of therapy are to reduce itch and maintain sufficient control to minimize any adverse effects of the AD on quality of life. In general, a multistep approach[153] is taken toward management that includes patient and parent education,[154] avoidance of irritants and allergic triggers, good moisturization, normalization of dysbiosis, and use of antiinflammatory medications[155] (Table 3.1). Patient compliance is the main reason for poor outcome and is fueled by concerns about the use of topical corticosteroids and calcineurin inhibitors (see later). Aggressively but safely managing AD flares is important in preventing the exacerbation of disease by delayed or inadequate treatment. The National Eczema Association (NEA) offers a website for education and patient support (www.nationaleczema.org). Age-specific structured educational programs have improved objective and subjective severity scores,[156] and educational videos may improve severity beyond direct education.[157] Written action plans have been shown to improve adherence to therapy.[158,159,161,162] Several guidelines for AD management in children have been published.[163–167]

Preventing the Development of Atopic Dermatitis

Infants in at-risk families (i.e., with at least one parent or sibling who has AD) have a 30% to 50% chance of developing AD by 2 years of age.[168] Limiting the use of skin cleansers is advised. Applying an oil-in-water emollient at least once daily appeared to lower the risk and severity[169–172] of AD, but larger studies have not confirmed this effect.[173,174]

Water hardness has been shown to be associated with an increased prevalence of AD[175,176] and may relate to increased sodium lauryl sulfate residue from washing, leading to greater impairment in barrier function and skin irritation.[177] Although ion-exchange water softeners do not lower the prevalence of AD,[178] they may mitigate the residue deposition seen with hard water.

Table 3.1 Management of Mild, Moderate, and Severe Forms of Atopic Dermatitis

Mild	Moderate	Severe
Bathing and barrier repair*	Bathing and barrier repair*	Bathing and barrier repair*
Avoidance of irritant and allergic triggers	Avoidance of irritant and allergic triggers	Avoidance of irritant and allergic triggers
Intermittent, short-term use of class VI or VII topical steroids (see Table 3.2) ± topical calcineurin inhibitors ± phosphodiesterase 4 (PDE4) inhibitor	Intermittent, short-term use of class III–V topical steroids (see Table 3.2) ± topical calcineurin inhibitors ± PDE4 inhibitor	Class II topical steroids for flares (see Table 3.2); class III–V topical steroids ± tacrolimus ointment for maintenance
Treat superinfection	Treat superinfection	Treat superinfection
	Oral antihistamines for sleep	Oral antihistamines for sleep
		Consider systemic immunosuppressants, immunomodulatory biologics (e.g., dupilumab), ultraviolet light therapy

*Barrier repair may be accomplished by application of effective emollients and/or barrier-repair agents.

Despite the fact that maternal dietary antigens are known to cross the placenta, most studies have provided no evidence that avoidance of maternal dietary antigens during pregnancy or lactation has a protective effect during the Þrst 18 months of life on the development of AD or on food sensitization by 7 years of age.[179D181] In fact, there is increasing evidence that early exposure to food antigens may reduce the risk of developing food allergies. As a result, breastfeeding without restricting maternal diet as a strategy to prevent food allergy is recommended until 4 to 6 months unless contraindicated for medical reasons. Although there is no evidence that breastfeeding protects against the development of pediatric AD at any age,[182,183] peanut, milk, and wheat intake during pregnancy may be associated with reduced allergy and asthma in children.[184,185] As a result, if available and affordable, hydrolyzed infant formulas, rather than cowÕs-milk or soy-milk formulas, can be given to at-risk infants who are not exclusively breastfed, although they may not affect the risk of AD. Solid foods, including potentially allergenic foods, should not be delayed beyond 4 to 6 months of age in at-risk infants.[186,187]

Probiotics have recently received considerable attention as a means of prevention of AD. Evidence that reduced diversity in the gut microbiota is a risk factor in the development of AD[188D191] provides further rationale for probiotic use. Although there is some evidence of beneÞt prenatally in prevention (for reviews[192D195]) there is insufÞcient evidence to recommend probiotics as part of standard management of infantile AD.[195,196] Of note, however, mixtures of probiotics appear to be more helpful than use of a single probiotic, and a recent trial of a mixture of different probiotic strains led to a signiÞcantly greater reduction in SCORAD during 12 weeks of therapy than placebo, with a greater use of topical steroids in the placebo arm.[197]

Although early studies suggest some beneÞt of prebiotics (Þber compounds that stimulate the growth of advantageous organisms) and fatty acids (such as the γ-linolenic acid alone or in combination with omega-3 fatty acids),[195] there is insufÞcient evidence to recommend these approaches for either reducing the risk of developing AD or treating AD.

Avoidance of Irritant Triggers

Certain climatic factors, such as temperature, air pollution/urban environment, and psychological stress, are linked to AD and difÞcult to control.[198] Many patients have problems with eccrine sweating and sweat retention during the summer months, leading to increased pruritus, especially in the face of licheniÞcation. The increased vasodilation of already inßamed skin from increased summer heat further contributes to pruritus and cutaneous erythema. Nevertheless, children with AD should be encouraged to participate as actively in sports as possible. Swimming is an excellent sport for children with AD if exposure to chlorinated pool water is tolerated. Children should be coated with an emollient (after sunscreen application) as a protectant against pool chemicals; rinsing immediately after swimming followed by application of emollient may decrease the risk of irritation. Children should also be kept cool after application of the thick emollient, or, if sweating is anticipated, a less occlusive moisturizer should be applied. Air-conditioning is important during hot weather to decrease pruritus. The pruritus and erythematous papules of miliaria rubra, which can develop when sweating and using an occlusive moisturizer, can be confused by parents with exacerbation of the dermatitis, setting up a cycle of worsening involvement from repeated application of the occlusive emollient. Recognition and education in decreasing the frequency of emollient application are vital in this situation.

Overdressing children during winter months should also be avoided to prevent overheating. The low humidity of winter months and use of indoor heating also increases skin xerosis and may promote dermatitis; humidiÞers may be useful but may increase the exposure to mold allergens if they are not cleaned often. Saliva is a major irritant for infants with AD, and exposure to large amounts of saliva with teething and eating, including saliva mixed with food, exacerbates the facial dermatitis. Protecting the face before meals or naptime with a thick, protective emollient may be helpful. Similarly, older children with AD are at risk for lip-lickerÕs dermatitis because of the irritant effects of saliva.

Attention to clothing is also important. Soft cotton clothing is recommended over traditional wool or other harsh materials, which tend to precipitate itching and scratching, and in one study fabric softener decreased skin dryness.[199] There is only low-quality evidence regarding AD improvement or decrease in bacterial colonization from use of special textiles, particularly silk and silver-coated cotton.[200D201] Affected children should avoid use of harsh soaps and detergents, fabric softener sheets, products with fragrance, and bubble baths. Cigarette smoking in homes of children with AD should be avoided, because it can lead to an increase in irritation and pruritus and may also increase the tendency toward subsequent development of asthma.[203]

Avoidance of Triggering Allergens

It may be possible to identify potential allergen triggers by taking a careful history and doing selective allergy tests.[204] However, triggers that can easily be avoided are difÞcult to Þnd for most affected individuals, and without a documented or proven food allergy, avoiding potentially allergenic foods as a means of managing AD is not recommended. Food allergy leading to dermatitis is unusual. Testing for allergy to milk, egg, peanut, wheat, and soy is only recommended in children younger than 5 years of age with moderate to severe AD who have persistent AD despite optimized management with topical therapy or who have a reliable history of an immediate reaction after ingestion of a speciÞc food.[205,206] Food antigenDspeciÞc IgE levels correlate better than a radioallergosorbent test and prick tests,[207] but the level of sIgE is not clinically useful for predicting the development of clinically relevant food allergy. Negative skin prick tests or serum allergen-speciÞc IgE levels are highly predictive at eliminating potential allergens. However, at 6 months of age, 83% of patients with severe AD show IgE food sensitization to milk, eggs, and/or peanuts, and 65% of these children retain food sensitivity by 12 months of age. In comparison, 5% of 6-month-old infants and 11% of 12-month-old infants without atopy show IgE food sensitization.[208] Fewer than 40% of children with moderate to severe AD with food sensitization show reactivity during food challenges,[209] and many of these eruptions are urticarial. In a longitudinal study, 16% of more than 1000 infants with AD (all severities) developed food allergies, particularly to peanut (7%), milk (4%), and egg (4%), with the highest risk in infants with greater AD severity.[81,209] Foods may also induce extracutaneous manifestations in pediatric patients with AD, particularly involving the GI tract. Foods may also act as irritants, especially citrus foods, and reactions to chemicals in foods, such as tartrazine or other colorings, may occur. For children in whom food allergies are suspected to be relevant, comanagement with a pediatric allergist is recommended.

The most common food allergens often contaminate other foods and are difÞcult to avoid entirely. Restrictions in diet should not worsen the quality of the patientÕs and familyÕs life more than the AD itself. Challenges of agents that may trigger IgE reactivity are best conducted under medical observation, because anaphylaxis has occasionally been reported. It should be remembered that excessively restrictive diets in atopic children may lead to weight loss, calcium deÞciency, hypovitaminosis, and kwashiorkor.[210] Proper nutritional counseling and supplementation should be included in management, including warning against the use of protein-poor rice and almond milk for cowÕs milk, hydrolyzed, and elemental formulas. After the Þrst few years of life, the risk of signiÞcant reactivity to food diminishes (particularly with eggs, milk, soy, and wheat). Unless a careful dietary history suggests food sensitivity as a trigger, improvement through dietary manipulation in children older than 5 years is rarely noted.

In contrast to potential reactivity to foods, reactivity of children and adolescents with AD to aeroallergens increases with age. The most common aeroallergen triggers are house-dust mites *(Dermatophagoides pteronyssinus)*, grass pollens, animal dander, and molds, particularly *Alternaria*. Plant pollens, particularly ragweed, also contain an oleoresin capable of producing sensitization and eczematous contact dermatitis. Airborne dermatitis may involve the exposed surfaces of the face, neck, arms, legs, and V area of the chest but can be distinguished from photosensitivity, which results in sharper lines of demarcation between normal skin and eczematous skin. Exacerbation of facial dermatitis during pollen season or after children contact a pet should alert parents to the possibility of allergy to an aeroallergen or contact allergen (see Allergic Contact Dermatitis section). Cat exposure during infancy

can increase the risk of developing AD,[211] especially in infants with an *FLG* mutation.[212] Cat exposure in children with AD has been shown to increase the risk of developing asthma, although dog exposure may be protective.[213] Epicutaneous application of aeroallergens by atopy patch test on unaffected atopic skin shows reactivity as an eczematoid patch in 30% to 50% of patients with AD but tends to be negative in patients with only respiratory allergy to these triggers or in healthy volunteers. However, patch tests have not been standardized, and their performance and interpretation vary widely.

The value toward AD control of mite-allergen avoidance measures (encasing mattresses and pillows, washing bedding in hot water weekly, vacuuming living areas and bedrooms frequently, keeping only soft nonfurry toys, cleaning carpets regularly or removing them, and eliminating pets) is controversial, and a meta-analysis found no value in encasing mattresses to prevent allergic diseases or symptoms.[214] Immunotherapy for food allergies or aeroallergens has long been controversial as treatment for AD, unlike its efficacy for treating AR and extrinsic asthma; recent double-blind, placebo-controlled studies, however, suggest some value of specific oral and sublingual immunotherapy, including to peanuts.[215,216]

Use of Bathing and Emollients

Although water exposure can increase xerosis through evaporative loss, daily baths hydrate the skin, especially if the water loss is prevented by emollient application within a few minutes after bathing. Baths are also fun for infants and children, contribute to parentÐ child bonding, and remove surface bacteria and desquamated scale. Whether to limit the duration of bathing is controversial, but many recommend limiting the bath to approximately 10 minutes. Older children and adolescents should be instructed to avoid excessively warm baths and showers. Only mild soaps with lower pH to suppress protease activation (such as Dove or Basis) or soapless cleansers (such as Cetaphil, CeraVe, or Aquanil) should be used if a cleanser is felt to be needed. Bubble baths can be irritating and are contraindicated in moderate to severe AD. Bath oils[217] have not been found beneficial and can be hazardous if they make the tub slippery.

The addition of dilute sodium hypochlorite (bleach) to the bath (¼ cup per half-tub of water with full-strength 5% to 6% commercial bleach [range commercially is 3% to 8%] or 1 mL/L for local soaks or compresses) or use of a sodium hypochlorite wash is helpful in controlling the dermatitis, especially for children with a history of skin infection when used as maintenance therapy (see Topical Antiinflammatory Medications section).[100] Although the antibacterial effect has been implicated in AD improvement, there is growing evidence that dilute sodium hypochlorite has direct antiinflammatory and barrier-promoting effects on skin[218] (see Treatment of Secondary Cutaneous Infections section), rather than being antibacterial, given its low concentration.[219] Children may complain about sitting in a tub bath because of stinging, particularly during acute exacerbations with raw skin and crusting. In such instances, the addition of 1 cup of salt or baking soda may make the bath more tolerable until more aggressive therapy with topical steroids and treatment of secondary infection with oral antibiotics leads to improvement.

In general, dryness is worse during cold months when it is aggravated by heat in the house and low humidity. Key to maintaining hydration is the application of a good emollient, particularly within minutes after bathing. In general, the thicker and greasier the emollient, the higher the content of oil relative to water and the more effective the emollient (e.g., ointment is better than cream, which is better than lotion). Petrolatum itself has been shown to upregulate gene expression of Þlaggrin and antimicrobial peptides, increase stratum corneum thickness, and reduce cutaneous inßammation. Pure petrolatum is rarely a cause of contact dermatitis.[220] Nevertheless, nonointment emollients, particularly emollient creams, can be substituted when use of a greasy ointment is objectionable and may have inherent antiinßammatory properties. Some patients, especially those with sensory issues and poor tolerance of ointments and creams, Þnd oils to be helpful, although in general oils do not penetrate the skin as well as oilÐwater mixtures. PuriÞed sunßower seed and safßower seed oils improve the AD skin barrier, whereas olive oil and mustard seed oil are detrimental to skin barrier recovery and can cause erythema,[221D223] emphasizing that oils are not interchangeable. Similarly, virgin coconut oil is superior to mineral oil in reducing AD severity[224] and to olive oil in decreasing *S. aureus*,[225] although potential concern about contact sensitization have been raised. ÒBarrier repairÓagents, with additives such as N-palmitoylethanolamine,[226] ceramide,[227] and glycyrrhetinic acid,[228] also show mild antiinßammatory properties and may be beneÞcial for children with mild to moderate AD but are much more costly than emollients.

Wet wraps of plain water can be applied at night after bathing and emollition or after application of the topical antiinßammatory agent to decrease pruritus and the sensation of burning at night.[229D231] Short-term use (up to 14 days) of wet wraps over topical corticosteroids is more efÞcacious than wraps over bland emollients alone but can be associated with transiently increased steroid absorption. Although wet gauze bandage wraps (such as Kerlix or Kling) are often used in a hospital setting, dressing the young child at home in moist pajamas and socks that cling to the skin and are topped by a dry layer to avoid excessive cooling can be very soothing and promote sleep. Unna boots can also be loosely applied to the legs or arms at night (under self-adherent wraps) to decrease pruritus and protect from scratching.

Open wet compresses may be useful in children with weeping, oozing, or crusted lesions. Aluminum acetate (as in Burow solution, 1:20 or 1:40) is germicidal and suppresses the weeping and oozing of acutely inßamed lesions. Burow solution 1:40 is prepared by dissolving one packet or effervescent tablet (Domeboro) in a pint of cool or tepid tap water. These compresses are applied with a gauze or a soft cloth (e.g., a manõ handkerchief or strips of bed-sheeting) two to three times daily for 10 to 15 minutes for up to 5 days. Washcloths and heavy toweling interfere with evaporation and therefore are not as effective. Compresses should be lukewarm, moderately wet (not dripping), and remoistened at intervals. After the compress, the topical antiinßammatory agent may be applied.

Topical Antiinflammatory Medications

Topical corticosteroids have been the mainstay of treatment for AD (see Table 3.1) and are available in a wide range of potencies from the weakest class VII corticosteroids (e.g., hydrocortisone acetate) to the ultrapotent class I steroids (Table 3.2). The use of more potent topical corticosteroids when applied to large surface areas, under occlusion, or for long periods may lead to adverse effects (Box 3.2), most commonly local atropy. The face and intertriginous areas are the most susceptible sites and may show local effects, even when weaker steroids are used for prolonged periods. Because of their increased body surface area-to-weight ratio, small children have the greatest risk of systemic absorption of topically applied steroids.

The potency of a topical corticosteroid is largely determined by vasoconstrictor assay and is related to its vehicle as well as to its chemical formulation. The concentration of each topical corticosteroid is only signiÞcant with respect to potency relative to other corticosteroids of the same chemical formulation. Accordingly, hydrocortisone acetate 2.5% is much weaker than triamcinolone acetonide 0.1%, which in turn is weaker than clobetasol propionate 0.05%, even though the concentrations would suggest the opposite. It also should be recognized that hydrocortisone acetate differs chemically from hydrocortisone butyrate, hydrocortisone probutate, and hydrocortisone valerate, which as midpotency steroids are stronger than hydrocortisone acetate. Similarly betamethasone dipropionate is stronger than betamethasone valerate. Halogenated steroids are usually stronger than nonhalogenated steroids.

Ointments are the most commonly chosen vehicle for treating AD. Corticosteroid ointments afford the advantage of occlusion, more effective penetration, and in general greater efÞcacy than equivalent cream or lotion formulations. Ointments are particularly effective in the management of dry, licheniÞed, or plaque-like areas of dermatitis. Ointment formulations, however, may occlude eccrine ducts, inducing sweat retention and pruritus, and hair follicles, leading to folliculitis. As with emollients, formulations in ointments may not be as well tolerated during the summer months of increased heat, perspiration, and high humidity. Creams and lotions are more cosmetically elegant and afford the advantages of greater convenience and acceptability

Table 3.2 Relative Potencies of Topical Corticosteroids (from Most Potent to Weakest)

Class	Drug	Dosage Form(s)	Strength (%)
I. VERY HIGH POTENCY			
	Augmented betamethasone dipropionate	Ointment	0.05
	Clobetasol propionate	Cream, ointment, foam	0.05
	Diflorasone diacetate	Ointment	0.05
	Halobetasol propionate	Cream, ointment	0.05
II. HIGH POTENCY			
	Amcinonide	Cream, lotion, ointment	0.1
	Augmented betamethasone dipropionate	Cream	0.05
	Betamethasone dipropionate	Cream, ointment, foam, solution	0.05
	Desoximetasone	Cream, ointment	0.25
	Desoximetasone	Gel	0.05
	Diflorasone diacetate	Cream	0.05
	Fluocinonide	Cream, ointment, gel, solution	0.05
	Halcinonide	Cream, ointment	0.1
	Mometasone furoate	Ointment	0.1
	Triamcinolone acetonide	Cream, ointment	0.5
III–IV. MEDIUM POTENCY			
	Betamethasone valerate	Cream, ointment, lotion, foam	0.1
	Clocortolone pivalate	Cream	0.1
	Desoximetasone	Cream	0.05
	Fluocinolone acetonide	Cream, ointment	0.025
	Flurandrenolide	Cream, ointment	0.05
	Fluticasone propionate	Cream	0.05
	Fluticasone propionate	Ointment	0.005
	Mometasone furoate	Cream	0.1
	Triamcinolone acetonide	Cream, ointment	0.1
V. LOWER-MEDIUM POTENCY			
	Hydrocortisone butyrate	Cream, ointment, solution	0.1
	Hydrocortisone probutate	Cream	0.1
	Hydrocortisone valerate	Cream, ointment	0.2
	Prednicarbate	Cream	0.1
VI. LOW POTENCY			
	Alclometasone dipropionate	Cream, ointment	0.05
	Desonide	Cream, gel, foam, ointment	0.05
	Fluocinolone acetonide	Cream, solution, oil	0.01
VII. LOWEST POTENCY			
	Dexamethasone	Cream	0.1
	Hydrocortisone	Creams, ointments, lotions, solutions	0.25, 0.5, 1
	Hydrocortisone acetate	Creams, ointments	0.5–1

during hot weather and in intertriginous areas but often contain additives that may be irritating or sensitizing. Traditional gels and foams are not well tolerated in individuals with AD, but they may be most effective in the management of acute weeping or vesicular lesions. Topical corticosteroids in emollient-based foam formulations and hydrocolloid gels (in contrast to the alcohol-containing foams and gels) are particularly useful for hairy areas, to avoid occlusion, and for cosmesis. Oil preparations are most commonly used for scalp dermatitis. Best applied to a wet scalp, oil formulations can be shampooed out after exposure for at least 1 hour to overnight. Fluocinolone acetonide oil, however, spreads easily and has been shown to be helpful after the bath for children with extensive AD.[232]

Occlusion of treated areas with polyethylene Þlm such as Saran wrap or the use of ßurandrenolide-impregnated polyethylene tape enhances the penetration of corticosteroids up to 100-fold. This mode of therapy is particularly effective for short periods (8 to 12 hours a

Box 3.2 Potential Side Effects of Topical Corticosteroids

Local Cutaneous Side Effects

Atrophy
Striae
Periorificial granulomatous dermatitis
Acne
Telangiectasia
Erythema
Hypopigmentation
Ocular effects
Cataracts
Glaucoma

Systemic Side Effects

Hypothalamic–pituitary–adrenal axis suppression

day on successive days) for patients with chronic lichenified or recalcitrant plaques of dermatitic skin. Occlusive techniques, however, are contraindicated for prolonged periods and are not recommended in infected or intertriginous areas. Given that the diaper is an occlusive dressing, application of steroids in the diaper area of infants should be avoided or limited to short-term use of low-strength topical steroids.

Concern about the use of topical steroids has led to "steroid phobia" among families and even physicians[233–235] internationally.[236] As a result, compliance may be decreased and weak topical steroids insufficient for adequate control may be used. In a recent study, 81% of parents or adult patients with AD had fears about the use of topical steroids, and 36% admitted nonadherence as a result.[237] Considering the widespread use of topical corticosteroids, few local adverse reactions occur when topical steroids are carefully chosen and used appropriately based on site of application and severity of the dermatitis (Fig. 3.36).[238] Recently, topical steroid addiction has been cited as an adverse effect of topical corticosteroids, but it is virtually never seen in children with AD who use topical steroids and should not discourage the use of topical steroids in pediatric patients. In older patients with AD, this disorder is characterized by a burning or stinging, sharply delineated erythematous eruption, primarily on the face and genital region, occurring days to weeks after discontinuation of prolonged, inappropriate, and frequent use of moderate- to high-potency topical corticosteroids.[239]

In general, group I corticosteroids are not recommended for patients younger than the age of 12 years, should not be used in intertriginous areas or under occlusion, and require a rest period after 14 days of use. Use of this group of ultrapotent steroids is usually reserved for lichenified plaques and recalcitrant dermatitis of the hands and feet and should be limited. Potent topical corticosteroids (class II) may safely be used once or twice daily for up to 2 weeks, except in sensitive areas, and are often applied at the first sign of flare to rapidly reverse the itch and inflammation.

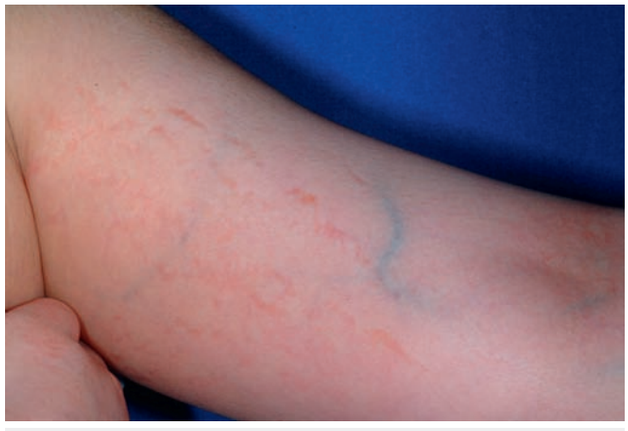


Fig. 3.36 Steroid-induced atrophy. Although unusual, steroid-induced atrophy in this patient with atopic dermatitis resulted from the twice-daily application of a class III–IV topical steroid over 1 year. Note the excellent control of the dermatitis but the obvious striae and prominence of veins because of atrophy of overlying skin.

A variety of steroid-free topical antiinflammatory agents have been introduced to allow patients to decrease their application of topical steroids and thus associated risks. Topical calcineurin inhibitors (TCIs; tacrolimus ointment 0.03% and pimecrolimus cream 1%) have been approved as alternative therapy for AD in children older than 2 years.[240,241] Several studies and anecdotal reports have suggested good efficacy and safety for tacrolimus ointment 0.1% (in children older than 2 years) and for tacrolimus 0.03% ointment and pimecrolimus cream in infants younger than 2 years, but their use is off-label.[242,243] Tacrolimus and pimecrolimus prevent the formation of a complex that includes calcineurin, a phosphatase.[244] Without this complex, the phosphate group from the nuclear factor of activated T cells (NF-AT) cannot be cleaved, the NF-AT transcription factor cannot be transported to the nucleus, and production of cytokines associated with T-cell activation is inhibited. Tacrolimus and pimecrolimus also inhibit mediator release from mast cells and basophils and decrease IgE receptor expression on cutaneous Langerhans cells.[245]

Tacrolimus ointment has good efficacy in children with moderate to severe AD.[246] The efficacy of the 0.1% ointment is comparable to a mid-potency topical corticosteroid,[247] and that of the 0.03% ointment to a low-potency steroid. Pimecrolimus cream is also comparable to a low-potency steroid and is indicated for pediatric patients with mild to moderate AD.[248,249] Assays of systemic absorption of tacrolimus and pimecrolimus have shown transient low levels in the blood, if at all, and no adverse effects on systemic immunity have been demonstrated.[246,250]

In 2006 the US Food and Drug Administration (FDA) placed a boxed warning on the class of calcineurin inhibitors based on the theoretical potential for TCIs to cause skin carcinogenesis and lymphoma. This theoretical risk was based on the known risk of malignancy (posttransplant lymphoproliferative disease and nonmelanoma skin cancer) in transplant patients who are profoundly immunosuppressed by systemically administered tacrolimus and in animal studies when treated with 26 to 47 times the maximum recommended dosage. Although a meta-analysis identified an increased risk of lymphoma in patients with severe AD, the number of malignancies and lymphomas is very low in AD children in postmarketing registries.[251–256] In addition, task forces of the American College of Allergy, Asthma, and Immunology; the American Academy of Allergy, Asthma, and Immunology; and the American Academy of Dermatology found no evidence to support the issuance of a black box warning.[257–260] Although preliminary data from a European cohort study suggested a borderline association of the use of tacrolimus in AD children and pediatric lymphoma, data did not account for disease severity.[261] There was also no evidence for an association of pimecrolimus with lymphoma. No lymphoma or nonmelanoma skin cancer occurred in a 10-year cohort study with almost 45,000 person-years of use of tacrolimus ointment.[262] Regardless of the limited evidence for risk, the boxed warning remains and patients need to be advised of potential risks and to practice sun protection during use.

To date, the only confirmed safety issue associated with the use of calcineurin inhibitors in children is burning or pruritus with application, described in the minority of affected children, particularly those with active inflammation. This sensation has been shown to result from stimulation of TRPV1 receptors in skin with depletion of substance P.[263] Calcineurin inhibitors do not have the atrophogenic potential of the corticosteroids and can be safely used on the head, neck, and intertriginous areas. Furthermore, no adverse effects on the eyes have been found, allowing safe application in periorbital areas. No increase in cutaneous infections has been noted in children.[264] Given that the potential local effect of TCI has been described more often when skin is inflamed, many practitioners recommend calming the

inßammation with a short course of topical corticosteroids, then continuing with TCI to maintain control.

In 2016 the Þrst topical phosphodiesterase 4 (PDE4) inhibitor (crisaborole) became commercially available for treating mild to moderate AD in children 2 years and older,[265,266] and subsequently 3 months of age. PDE4 activity is increased in AD and promotes degradation of cyclic adenosine monophosphate (cAMP). As a result, the cyclic AMP response is reduced and production of proinßammatory cytokines is increased in AD skin. Crisaborole has a good safety proÞle, although burning and stinging on application can occur in up to 50% of patients, particularly when applied to the face.[267]

The choice of topical steroid, TCI, or crisaborole depends on the severity and localization of the dermatitis, the age of the pediatric patient, and the history of use of topical antiinßammatory agents. For children with mild AD, intermittent use of a low-strength topical steroid with emollient application to maintain clearance usually sufÞces. However, children with moderate to severe disease often show a cycle of rapid recurrent ßaring when topical antiinßammatory suppression is discontinued. A commonly used regimen to maintain control in these children while minimizing the risk of chronic steroid application is to apply mid- to high-potency topical steroids for acute ßares (e.g., for a few days to up to 2 weeks twice daily), followed by a maintenance regimen. Alternative options for maintenance are Ò dialing downÓ to a low-strength topical corticosteroid, switching to a nonsteroidal topical agent (e.g., TCI or PDE4 inhibitor), or Ò proactive therapyÓ to retain control.[268Ð270] The typical regimen for proactive therapy is to taper use from twice daily (in response to a ßare) to once daily for a week or two, and then two to three times a week on areas that are now clear or almost clear but recurrently ßare without continued local immunosuppression.

For sites of severely licheniÞed dermatitis, salicylic acid can be compounded into preparations with steroids to improve penetration. Tar (liquor carbonis detergens or crude coal tar) can be also be used as an adjunctive therapy in patients with chronic dermatitis in the form of tar baths (e.g., Cutar) or compounded with topical corticosteroids (e.g., compounding triamcinolone 0.1% with 6% salicylic acid and 5% to 10% liquor carbonis detergens in Aquaphor ointment). The objectionable odor, staining properties, potential for irritation, risk of causing folliculitis, and low potential risk of later carcinogenesis make tar a choice only for only selected patients.

Several new nonsteroidal antiinßammatory medications are currently under development for AD and have shown promise in phase 2 trials. The topical aryl hydrocarbon receptor modulating agent (TAMA)[271] tapinarof was found to be superior to vehicle in patients with primarily moderate AD, approximately 30% of whom were adolescents. Several cytokines, including type 2 cytokines, require activation of the JAK/STAT signaling pathway. Topical formulations of JAK inhibitors (ruxolitinib and delgocitinib) have improved AD severity and reduced itch signiÞcantly more than vehicle[272,273] and numerically more than active comparators.

Role of Antihistamines

Reduction of the pruritus of AD is best achieved by reducing AD severity, generally through application of topical antiinflammatory medications. Sedating antihistamines (targeting the histamine 1 receptor), such as hydroxyzine, diphenhydramine, and doxepin, may help itchy children fall asleep, although they have little direct effect on the pruritus itself. Nonsedating antihistamines may be valuable as treatment for other atopic conditions such as AR and have been shown to decrease the risk of urticaria, but they have limited value in decreasing pruritus because they do not tend to be sedating.[274] Long-term use in young children has not led to behavioral, cognitive, or psychomotor developmental abnormalities.[275]

The histamine 4 receptor (H4R) is a recently discovered receptor subtype that has been shown to mediate the proinßammatory function of T cells, mast cells, eosinophils, and inßammatory dendritic epidermal cells. An oral antihistamine antagonist of H4R, adriforant, did not reduce the severity of adult moderate to severe AD when compared with placebo in a phase 2b trial.[276] Leukotriene antagonists such as montelukast, which are used extensively in asthma prophylaxis, have largely been ineffective.[277]

Treatment of Secondary Cutaneous Infections

Antistaphylococcal antibiotics are important in the management of patients with heavy *S. aureus* colonization or infection because of the role of *S. aureus* overgrowth in triggering dermatitis. Topical antibiotics, such as mupirocin or fusidic acid (the latter is not currently available in the United States), can be used for localized impetiginized lesions, but systemic antibiotics are required for more extensive involvement. Despite the increase in community-acquired (CA) MRSA nationally, most atopics still harbor MSSA.[100,105] As a result, cephalexin is still used most commonly (and successfully) to empirically treat secondarily infected dermatitis and will cover both staphylococcal and streptococcal organisms.[104] The chronic administration of antistaphylococcal therapy for AD should be avoided in an effort to minimize the risk of development of MRSA and *S. aureus* resistant to topical antibiotics.[278]

Dilute sodium hypochlorite (bleach) baths are now the standard of care as a maintenance measure for decreasing ßares in moderate to severe AD. The addition of ½ cup of 5% to 6% sodium hydroxide per full tub of water (1 mL/L or 4 mL/gallon) markedly reduces the severity and extent of the dermatitis in children with a history of staphylococcal infections, although likely not because of any anti-bacterial properties, given its low concentration of sodium hypochlorite.[100,279,280] Even daily maintenance dilute sodium hypochlorite baths are generally well tolerated and may be needed for more severe AD. A washcloth can be used to distribute the bleach-bath water to the head and neck, avoiding the eyes and mouth. If skin erosions from secondary infection make bathing uncomfortable, postponing bleach baths until after the Þrst few days of treatment may be necessary. If a bath is not possible, a 5- to 10-minute wet compress with bleach solution or a shower using a sodium hypochloriteÐcontaining wash (such as CLn), or soaks of hands or feet can be used.[281] Application of mupirocin ointment to the nares and hands of patients and caregivers twice daily for 5 sequential days each month, and use of gentle antibacterial soaps[282] may also decrease colonization.

Antiviral treatment of cutaneous herpes simplex infections is important in preventing widespread dissemination, which rarely is life threatening. Administration of oral acyclovir (100 mg tid to qid for children younger than 6 years; 200 mg qid for older children; or for adolescents 500 mg valacyclovir twice daily) for a week usually controls the infection. More extensive involvement may require hospitalization and intravenous acyclovir treatment, especially in younger children. For children with recurrent EH, a course of prophylactic administration of oral acyclovir or valacyclovir once daily for 6 months or longer effectively suppresses the recurrences. Adjunctive therapies include topical compresses and concurrent administration of topical or systemic antibiotics if bacterial infection is also suspected. In general, topical corticosteroids can be continued during the course of systemic acyclovir therapy without affecting clearance of the viral infection if the dermatitis is problematic. Molluscum infections (see Chapter 15) can be managed by curettage after application of topical anesthetics[283] or by cantharidin application.[284] Children with molluscum and AD (but not nonatopic children) may show improvement in both their dermatitis and the molluscum lesions by treatment with high doses of oral cimetidine (40 mg/kg per day divided twice daily) for a 3-month course.[285,286] Imiquimod has not been found beneÞcial in double-blind, randomized trials.

Other Considerations for Atopic Dermatitis that Fails to Respond: Adherence and Alternative Diagnoses

Moderate to severe AD may be recalcitrant to topical antiinßammatory therapy. Although secondary staphylococcal infection is a common reason for recalcitrance, several other factors should be considered before initiating systemic immunosuppressive therapy or phototherapy.[287] Poor adherence is a major reason for failure to respond. In one study with electronic-cap monitoring to detect opening of tubes, mean adherence of patients with mild to moderate AD was 32%, increasing on or near ofÞce visit days.[288] Shortening the time between prescription of the medication and the follow-up ofÞce visit[289]; prescribing once-a-day treatment; using sticker charts to engage children[290]; providing adequate education about the disease, the use of treatment, and why it is needed; and adapting instruction on medication use to existing elements of the family routine (e.g., linking to bathing or brushing the teeth)[291] may be helpful.

Chronic, unresponsive dermatitis, especially involving the face, hands, or feet, may result from ACD,[292] and comprehensive patch testing should be undertaken (see Contact Dermatitis section). Several other alternative diagnoses that may require different intervention are described (see Differential Diagnosis section).

Management of Children with Severe Atopic Dermatitis Requiring Systemic Immunosuppressive Therapy

Systemic immunosuppressive therapy[293,294] and ultraviolet light treatment have long been considered the alternatives for children and adolescents with recalcitrant moderate to severe disease. Narrow-band ultraviolet B light therapy, which avoids intervention with systemic immunosuppressive therapy, has been reported to cause at least moderate improvement in 89% of children and complete clearance in 40% during a median of 3 months.[295] Significant reductions in severity can be seen in as little as 3 weeks after initiation.[296] Nevertheless, the requirement for frequent treatments in a medical office (two to three times weekly) and holding still in a hot, enclosed box while wearing protective goggles, as well as the unknown risk of long-term cutaneous damage from ultraviolet light, complicate the use of this form of therapy for most pediatric patients. Home-based therapy may be an option, but phototherapy units are costly.

Systemic immunosuppressants have more often been the choice as intervention, and have been used by approximately 1% of AD patients overall[296–298] (despite 7% with AD having severe disease). Pediatric AD guidelines for the two most commonly used immunosuppressants, cyclosporine and methotrexate, are similar to those for pediatric psoriasis.[299] Their use has been limited by the potential risks of immunosuppressant therapy and requirement for laboratory monitoring. Dupilumab, the first targeted AD therapy, inhibits the shared receptor for IL-4 and IL-14 (IL-4R). Dupilumab was FDA approved for adolescents in 2019 and for children ages 6 to 11 years in 2020.

Systemic Immunosuppressant Therapy

Systemic corticosteroid therapy is effective for most patients with AD, but the rapid rebound after discontinuation of therapy and high risk of potential side effects make its use impractical for patients with AD and contraindicated for most pediatric patients.[300] Systemic administration of nonsteroidal antiinflammatory medications to children with AD has largely replaced the use of systemic corticosteroids by pediatric dermatologists in the management of more recalcitrant severe AD, but systemic steroids are still the most commonly used systemic medication overall for pediatric AD.[298]

Cyclosporine has the most rapid onset of action and greatest efficacy among the nontargeted systemic agents, but also the highest risk of potential side effects.[301] Therapy is initiated with 3 to 5 mg/kg per day (microemulsion for preferred). Response may be seen within 1 to 3 months, but medication should be tapered once significant improvement is achieved; trough levels can be determined in patients without a sufficient response to determine if a higher dosage can be administered. Discontinuation of treatment usually leads to relapse flares, but low-dose continuing treatment or intermittent courses in children can be effective.[302–304] In one study that predated the availability of dupilumab, cyclosporine was the most common first-line agent for treating pediatric AD severe enough to require medication.[305] Several experts now recommend initial treatment with cyclosporine to rapidly suppress the severe AD (e.g., for 3 months) followed by continued treatment with an alternative, safer immunosuppressant, such as methotrexate or mycophenolate mofetil, or with ultraviolet light, should immunomodulatory agents be inavailable or ineffective. Renal and hepatic function and blood pressure must be carefully monitored during cyclosporine therapy.

Methotrexate is a safer alternative to cyclosporine as first-line or maintenance therapy after cyclosporine-induced improvement.[306–308] Its major limitation is the delay in onset of action compared with cyclosporine, a limitation that is shared with mycophenolate mofetil and azathioprine. Continued improvement in severity and quality of life can occur beyond 10 months after initiation.[306] However, methotrexate can be effective or very effective in 75% of children with severe AD. In general, treatment is well tolerated (in one study, 14% experienced minor nausea and 14% had slight elevation in hepatic transaminases) and serious adverse events are quite rare. Low-dose therapy (0.3 to 0.5 mg/kg per week)[309] is administered with folic supplementation. Although not studied in AD, for pediatric psoriasis a 6- to 7-day per week regimen of folic acid was found to be more effective in limiting gastrointestinal toxicity than weekly folic acid administration. The need for a small test dose of methotrexate has not been demonstrated. Complete blood cell counts and hepatic transaminates should be monitored at least monthly during the first 6 months and then quarterly.

Mycophenolate mofetil has been found to cause at least 60% improvement in 91% of treated children with a dosage of 40 to 50 mg/kg per day for children and 30 to 40 mg/kg per day for adolescents with maximal effects at 8 to 12 weeks.[310] Complete blood cell counts and liver function testing should be performed.

Azathioprine (2.5 to 3.5 mg/kg per day) has effectively suppressed severe, recalcitrant AD in 58% to 92% of children during a 3-month trial.[311–313] Pretreatment determination of thiopurine methyltransferase level can predict the risk of developing myelosuppression, and hepatic functions should also be monitored. In one study the thiopurine methyltransferase (TPMT) levels changed unpredictably during treatment in 25% of patients, suggesting that periodic assessment of TPMT levels is warranted to optimize clinical response.[313] Azathioprine should be used with caution, given its recent link with hepatosplenic T-cell lymphoma.

Interferon-γ downregulates Th2 lymphocyte function, and treatment with recombinant interferon-γ (50 μg/m^2 daily or every other day) has led to improvement in some patients, including pediatric patients.[314–316] Flu-like symptoms are particularly common early in the treatment course. The high price and benefit for only a subset of individuals also limit the use of interferon-γ in children who are severely affected with AD.

Targeted Immunomodulatory Agents

The increased understanding of the pathogenesis of AD, including in children, has led to an extensive pipeline of new therapeutics in trial for AD[317] and generation of biologics that specifically target Th2 pathway components. As noted, dupilumab inhibits activation of the shared receptor (IL4Rα) of key type 2 cytokines IL-4 and IL-13. For all dosing, a loading dose double the treatment dose is given. The pivotal double-blind, randomized controlled trial in 251 adolescents with moderate to severe AD showed achievement of the co-primary endpoints of Investigator Global Assessment (IGA), clear (0) to almost clear (1) (24% on dupilumab every 2 weeks vs. 2% on placebo), and at least a 75% reduction from baseline on the Eczema Area and Severity Index (EASI-75) in 42% using dupilumab every 2 weeks vs. 8% placebo.[318,319] In general, administration every 2 weeks was superior to every 4 weeks. In *post hoc* analyses, 80% of adolescents taking dupilumab every 2 weeks (versus 24% on placebo) who did not achieve IGA 0/1 at week 16 achieved meaningful improvement from baseline ($p < .0001$).[319] Dosing is weight based at 200 mg every other week for those less than 60 kg and 300 mg every other week for those 60 kg and more; a loading dose of twice the standard dose is given initially. In the phase 3 trial for 6- to 11-year-olds, approximately 30% achieved IGA 0/1 and approximately 70% EASI-75, regardless of whether given every 2 or every 4 weeks, versus 11% and 27% on placebo, respectively.[319,320] However, dosing of 300 mg every 4 weeks for children <30 kg and 200 mg every 2 weeks gave superior blood levels and efficacy, resulting in these on-label dosing recommendations. At the time of writing, trials were ongoing for pediatric patients as young as 6 months.

The side effect profile of dupilumab in pediatric patients shows the risk of injection site reactions, as with other biologics. Conjunctivitis has been seen at about twice the frequency in those on dupilumab versus placebo in trials, but rarely leads to discontinuation (Fig. 3.37). In the adolescent trial the occurrence of bacterial infection was reduced and dupilumab improved comorbid asthma and allergic rhinitis, reducing IgE concentrations for food and aeroallergens.[319] Dupilumab has not been found to suppress vaccine-induced immunity[321] in adults.

Increased facial erythema, despite improved severity elsewhere, is not an uncommon experience with dupilumab and may be related to unmasking of contact dermatitis[322–324] (see Contact Dermatitis section). In fact, recall dermatitis at the site of previous positive patch tests has been shown to occur after injection of dupilumab[325] and patch testing may still be possible although sometimes suppressed.[323] Other possible causes of increased facial erythema include *Malassezia* reactivity, Demodex, or the need for higher dosing. Psoriasis-like

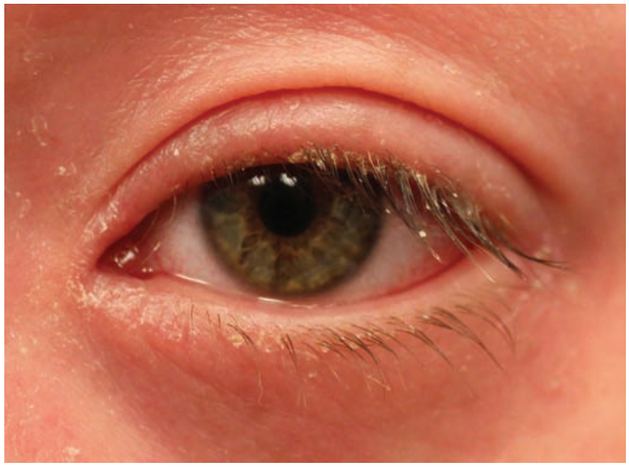


Fig. 3.37 Conjunctivitis, blepharitis, and concomitant periorbital dermatitis (edema, erythema, and scaling) that developed while using dupilumab therapy. Inflammation of the bulbar conjunctiva is occasionally seen with use of dupilumab, but the eyelids and periorbital area are a common site of allergic contact dermatitis.

lesions have been reported in a minority of patients given dupilumab after clearance or near-clearance of the dermatitis. In addition, although alopecia areata has been reported to reverse with treatment in those with concomitant AD and alopecia areata,[326–330] dupilumab-induced alopecia during dupilumab therapy with reversal after drug discontinuation has also been described.[331,332]

Several additional targeted systemic approaches to improving AD are currently being studied and appear promising in early trials. Most advanced are the IL-13 inhibitors (lebrikizumab[333] and tralokinumab),[334] based on the predominance of the type 2 cytokine IL-13 in AD skin, and JAK inhibitors (baricitinib,[335] abrocitinib [primarily JAK1],[336] and upadacitinib[337] [primarily JAK1]), based on the concept that signaling in AD is primarily through JAK1. Nemolizumab targets the "itch-specific" cytokine IL-31 and strongly suppresses the itch but has little antiinflammatory effect.[338–340]

Use of Complementary Treatment Approaches

The impact of vitamin D_3 levels and potential value of vitamin D_3 supplementation remain controversial. Low levels of vitamin D_3, including in cord blood,[341] have been associated with childhood AD,[342,343] and AD severity may be greater with lower vitamin D levels.[344] Oral vitamin D_3 has been shown to upregulate the expression of cathelicidin, including in the skin of individuals with AD. However, topically applied vitamin D_3 analogue irritates AD skin and has been used to generate a mouse model of AD. Although one small open-label study of oral vitamin D_3 supplementation in children with AD who were vitamin D deficient showed clinical improvement,[345] small double-blind trials show improved serum levels of vitamin D_3 with supplementation but no clinical improvement in AD.[344,346] At this time there is insufficient evidence to recommend vitamin D_3 supplementation for AD.[347]

Alternative medicine, particularly herbal remedies and homeopathy, is used in 42.5% to 63.5% of patients with AD.[348,349] More than half reported no improvement but tried the therapies based on recommendation from nonphysicians, concern about the potential risks of topical steroids, and dissatisfaction with conventional treatment. Of concern is that these complementary approaches have potential side effects, have not been adequately tested for safety and efficacy, and require time and effort that might otherwise be directed toward use of physician-prescribed treatment. The benefit from administration of traditional Chinese herbal therapy has been variable.[350–352] Regardless, the demonstration of hepatic toxicity, cardiac adverse events, and idiosyncratic reactions from this therapy has raised concerns; furthermore, the discovery of glucocorticoid contamination in some preparations warns that these alternative agents be used with caution.[353]

Massage therapy has been advocated as a means to improve the clinical signs of AD in young children, in addition to improving the psychological well-being of the patients and family members.[354] Psychological counseling, behavioral modification, hypnotherapy, and biofeedback can also be helpful in decreasing scratching.[157] Psychological intervention for families can also be beneficial, because increased parental stress and depression correlate with higher levels of biologic markers of inflammation.[355]

Pityriasis Alba

Pityriasis alba is a common cutaneous disorder, especially in children with darker skin, characterized by asymptomatic hypopigmented patches, usually on the face, neck, upper trunk, and proximal extremities (Figs. 3.38 and 3.39).[356,357] Individual lesions vary from 1 cm or more in diameter and may show a fine scale. This disorder is thought to represent a nonspecific dermatitis with residual postinflammatory hypopigmentation and occurs more often in individuals with darker skin types.[358] Histologic evaluation shows normal numbers of melanocytes but decreased epidermal melanosomes and melanocyte degeneration.[359] Most cases appear after sun exposure because

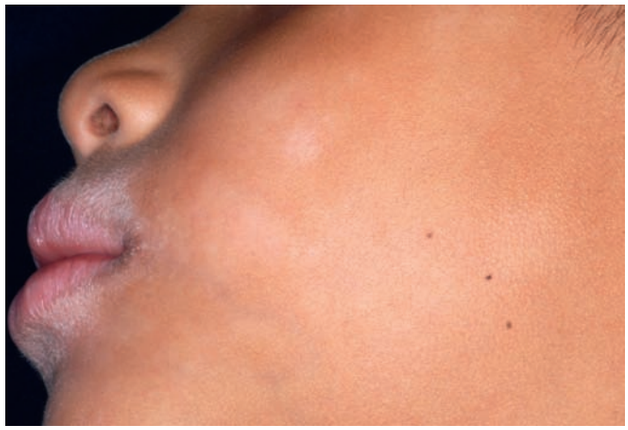


Fig. 3.38 Pityriasis alba. Circumscribed scaly hypopigmented lesions on the cheek. These patches are thought to represent postinflammatory hypopigmentation and are most easily visible in children with darker skin. Note the concomitant lip-licker's dermatitis.

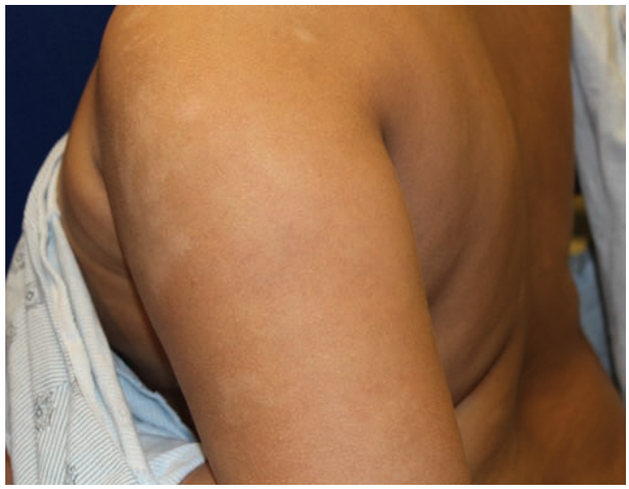


Fig. 3.39 Pityriasis alba. The upper arm is another common site.

of the contrast that results between areas that can show a pigmentary response to ultraviolet light and the pityriasis alba areas that do not.

The differential diagnosis of the hypopigmented macules of pityriasis alba includes tinea versicolor, vitiligo, and the white macules seen in association with tuberous sclerosis; nevus depigmentosus; cutaneous T-cell lymphoma; leprosy; postinßammatory hypopigmentation secondary to atopic dermatitis, psoriasis, tinea corporis, or pityriasis rosea; and, in light-skinned individuals, nevus anemicus. Application of mild topical corticosteroids or calcineurin inhibitors for a few weeks followed by frequent moisturization and protection of the sites and surrounding area from sun exposure allows repigmentation of involved areas. Patients and parents should be warned that, as with any form of postinßammatory hypopigmentation, repigmentation may take several months to years. Effective moisturization during drier months may help prevent recurrence of the pityriasis alba in subsequent summers.

Hyperimmunoglobulinemia E Syndrome

HIES[360D364] is a rare immunodeÞciency disorder characterized by very high levels of IgE in association with AD and recurrent cutaneous and sinopulmonary infections.[365D367] The AD is seen in 100% of patients, usually within the Þrst 6 months, and is of variable severity (Fig. 3.40). Most patients have an autosomal dominant form (AD-HIES), a subset of which has been called *Job syndrome*. AD-HIES results from mutations in the gene encoding signal transducer and activator of transcription 3 *(STAT3)*.[368,369]

Many neonates or infants with AD-HIES have pruritic papulopustules, especially on the face, which show eosinophilic folliculitis or eosinophilic dermatitis by biopsy of lesional skin.[370] Infections often begin during the Þrst 3 months of life. Cutaneous candidiasis may also be an early clinical feature (83%). Cutaneous *S. aureus* infections may take the form of excoriated crusted plaques, pustules, furuncles, cellulitis, paronychia, lymphangitis, or abscesses, especially on the neck, scalp, periorbital areas, axillae, and groin (Fig. 3.41). The abscesses are slightly erythematous and tender but not nearly to the degree expected for a normal individual. Although some patients demonstrate cutaneous manifestations only,[371] patients with HIES usually have recurrent bronchitis and pneumonias with resultant empyema, bronchiectasis, and in 77% of patients, pneumatocele formation. The pneumatoceles tend to persist and become the site of further infections with bacteria *(Pseudomonas)* or fungi *(Aspergillus, Scedosporium)*. Rarely, massive hemoptysis ensues. Other common sites of infection include the ears, oral mucosae, sinuses, and eyes. Visceral infections other than pneumonia are unusual.

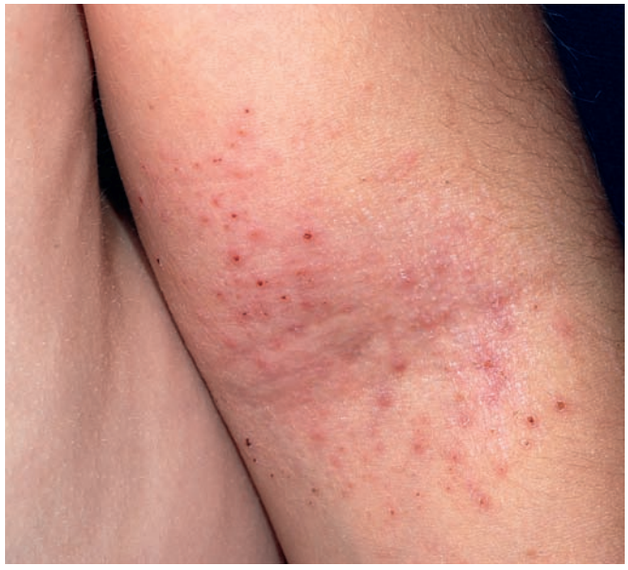


Fig. 3.40 Hyperimmunoglobulinemia E syndrome with atopic dermatitis of the antecubital area.

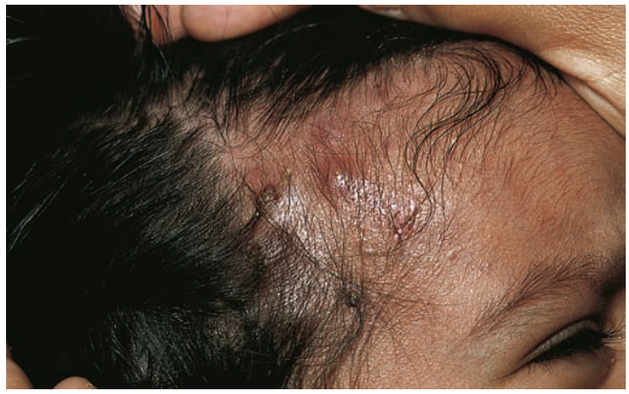


Fig. 3.41 Hyperimmunoglobulinemia E syndrome (HIES). In addition to atopic dermatitis, most infants and children with HIES show erythematous, slightly purulent cold abscesses, shown here on the forehead and scalp. (Reprinted with permission from Bolognia JL, Jorizzo JL, Rapini RP. *Dermatology*. St. Louis, MO: Elsevier; 2003.)

By late childhood and adolescence, patients with HIES begin to develop characteristic facial features with thickened, doughy skin, prominent forehead, broad nose, deep-set eyes, pitted scars, and prominent follicular ostia,[365] perhaps reßecting bony abnormalities and recurrent facial abscesses. Osteopenia is usually detected by adolescence or early adulthood, and patients have an increased risk of bone fractures, often because of unrecognized or minor trauma.[372] Scoliosis occurs in 64% of patients 16 years of age or older, and hyperextensibility of joints has been reported in 70% of patients. Dental abnormalities associated with HIES syndrome include retention of primary teeth, lack of eruption of secondary teeth, and delayed resorption of the roots of primary teeth.[373] Focal brain hyperintensities and an increased incidence of lymphoma are other features. Patients with HIES of intermediate phenotypes that include staphylococcal and mucocutaneous candidal infections may have *STAT3* mosaicism.[374]

The abnormalities in *STAT3* signaling impair Th17-cell development, leading to insufÞcient expression of IL-17 and IL-22, which drive expression of antimicrobial peptides, thus promoting *S. aureus* and candidal infections.[375]

The diagnosis of HIES is largely based on clinical Þndings and the presence of very high levels of IgE. There are no speciÞc tests to conÞrm the diagnosis other than the Þnding of HIES-related mutations. Patients have markedly elevated levels of polyclonal IgE. Although levels of more than 2000 IU/mL are needed to consider the diagnosis in older children and adults, the normal levels of IgE in infants (0 to 50 IU/mL) are considerably lower than those in older children. A 10-fold increase in IgE levels above normal levels for age should trigger consideration of HIES, although these levels of IgE are more common in AD without HIES.[376] Affected individuals tend to have IgE antibodies directed against *S. aureus* and candida. Levels of IgE are not related to clinical course and may decrease to normal in affected adults. Approximately 93% of patients have eosinophilia of the blood and sputum. Abnormal polymorphonuclear leukocyte and monocyte chemotaxis has been noted but is intermittent and not correlated with infection. Cell-mediated immunity (Th1 driven) is often abnormal as well and may manifest as anergy to skin testing, altered responses in mixed leukocyte culture, and impaired blastogenic responses to speciÞc antigens such as *Candida* and tetanus. The decrease in memory ($CD27^+$) B cells is noted in 80% of patients, in contrast to individuals with AD and high levels of IgE.[377]

Autosomal recessive HIES (AR-HIES)[367,378,379] is much less common than AD-HIES. In 78% of cases, it results from loss-of-function mutations in *DOCK8* (dedicator of cytokinesis 8), which is highly expressed in lymphocytes and regulates the actin cytoskeleton.[379] In a large series of 64 DOCK8-deficient patients, 62% had low IgM levels, less than 50% were able to mount recall immune responses, and 20% had lymphopenia, in addition to the typical hyper IgE and eosinophilia.[379] Early AD was a feature in 97% of patients, with almost 70% having severe AD. The neonatal eosinophilic skin eruption was only described in 35%. Abscesses occur in 60% but tend to be more inflamed than the cold abscesses of AD-HIES. Upper respiratory infections and allergies (>70%) are also shared features with AD-HIES. Cardinal features that are not part of the *STAT3*-deficient form include severe viral infections (extensive warts and molluscum, herpes, and life-threatening cytomegalovirus infections), early malignancy (cutaneous and mucosal squamous cell carcinomas in 8%[380]) neurologic changes (primarily aneurysms and strokes; 36%), and an increased risk of autoimmune issues (anemia, thrombocytopenia, and vasculitis).[381,382] In contrast to STAT3 deficiency, pneumatoceles and parenchymal lung abnormalities are unusual, and patients fail to show the bone fractures and retention of primary teeth of the dominant form. DOCK8 deficiency leads to impaired migration of dendritic cells to lymph nodes and defective CD4 T-cell priming. In B cells, DOCK8 also serves as an adaptor protein upstream of STAT3, which likely accounts for some of the overlap with AD-HIES. The T-cell lymphopenia and low interferon-γ production contribute to the high risk of viral infections.

The majority of patients AR-HIES without *DOCK8* mutations have biallelic mutations in *PGM3*,[383] the gene encoding phosphoglucomutase 3, leading to impaired synthesis of UDP-GlcNAc (uridine diphosphate N-acetylglucosamine), which is an important precursor for protein glycosylation. Although *PGM3* mutations may lead to SCID, patients with milder disease have high levels of IgE, atopy, and frequent sinopulmonary infections with bronchiectasis, as well as neurocognitive impairment. Autoimmune disorders and increases in Th17 cells are distinguishing features. Joint hyperextensibility and scoliosis have been described. AR-HIES can also result from homozygous mutations in *TYK2* (which activates STAT3), although *TYK2* mutations are usually associated with more profound immunodeficiency. Nontuberculous mycobacterial infections are a characteristic feature of patients with *TYK2* mutations.[384,385]

HIES must be distinguished from a number of other disorders in which IgE levels may be elevated. Most common is AD (including *CARD11* heterozygous loss-of-function mutations), which shows similar inflammatory cutaneous features and often very high levels of IgE, especially if severe[376]; the concurrent presence of abscesses, coarse facies, noncutaneous infections, and dental and bony abnormalities in HIES may enable differentiation. WAS can be distinguished by thrombocytopenia with cutaneous petechiae and hemorrhagic episodes. Eosinophilia and elevations of IgE levels with dermatitis can also be seen in patients with DiGeorge syndrome, the Omenn syndrome type of SCID, graft-versus-host disease (GVHD), and selective IgA deficiency. Loss-of-function mutations in *ERBB2IP,* including ERBIN, leads to a phenotype with hyper IgE, eosinophilic esophagitis, and allergic manifestations of AD-HIES but without mucosal *Candida* infections and with the addition of hypermobility and vascular abnormalities.[386] Homozygous mutations in *IL6ST,* encoding the GP130 cytokine receptor subunit required for cytokine signaling (e.g., IL-6, oncostain M; all through JAK-STAT signaling), lead to hyper IgE, eosinophilia, AD, recurrent infections, bronchiectasis, and scoliosis, as well as craniosynostosis.[387]

The mainstay of therapy for HIES is antistaphylococcal antibiotics, and patients are usually treated prophylactically with trimethoprim-sulfamethoxazole. When other bacterial or fungal infections develop, infections must be treated with appropriate alternative antibiotics. Recombinant interferon-γ has shown inconsistent efficacy. The cutaneous and pulmonary abscesses often require incision and drainage. The pneumatoceles should be removed surgically, especially if present for longer than 6 months, to prevent microbial superinfection. Therapy for AD as discussed in previous sections is also useful for HIES; omalizumab has improved the severe dermatitis of a recalcitrant patient with a relatively low level of IgE.[388] Alendronate sodium may alleviate the osteopenia.[372]

Early stem cell transplantation is an important intervention for patients with AR-HIES from *DOCK8* mutations,[389] which has a 34% mortality rate.[379] Hematopoietic stem cell transplantation is not a treatment of choice for AD-HIES unless there are severe complications, such as lymphoproliferative disease.

Wiskott–Aldrich Syndrome

WAS is a rare X-linked recessive disorder that in its classic form consists of dermatitis that meets criteria for AD, bleeding from microthrombocytopenia and platelet dysfunction, and recurrent severe pyogenic infections.[390–392] Bleeding is the most common manifestation, but the presence of mild to severe AD distinguishes WAS from X-linked thrombocytopenia and X-linked neutropenia with myelodysplasia, which are both allelic. The majority of patients are male, but full expression has been reported in girls.[393]

The dermatitis usually develops during the first few months of life and fulfills criteria for AD (Fig. 3.42). Excoriated areas commonly have serosanguineous crust and often show petechiae or purpura. IgE-mediated allergic problems such as urticaria, food allergies, and asthma are also seen with increased frequency.

The hemorrhagic diathesis results from both quantitative and qualitative defects in platelets. Platelets from patients with WAS are small and structurally abnormal with a reduced half-life, although megakaryocyte numbers are normal. Epistaxis and bloody diarrhea are often the initial manifestations. Mucocutaneous petechiae and ecchymoses (Fig. 3.42), spontaneous bleeding from the oral cavity, hematemesis, melena, and hematuria are common, but the severity varies.

Recurrent bacterial infections begin in infancy as placentally transmitted maternal antibody levels diminish and include staphylococcal impetigo, furunculosis, otitis externa and media, pneumonia, pansinusitis, conjunctivitis, meningitis, and septicemia. Infections with encapsulated bacteria such as pneumococcus, *Haemophilus influenzae*, and *Neisseria meningitidis* predominate. With advancing age, T-cell function progressively deteriorates and patients become increasingly susceptible to infections caused by herpes and other viruses and to *Pneumocystis jiroveci*.

Additional clinical features may be hepatosplenomegaly, lymphadenopathy, and autoimmune complications. The most common autoimmune complication is hemolytic anemia, occurring in 36% of patients and usually before 5 years of age.[394] Other autoimmune disorders that clearly seem linked to WAS are autoimmune neutropenia (25%),

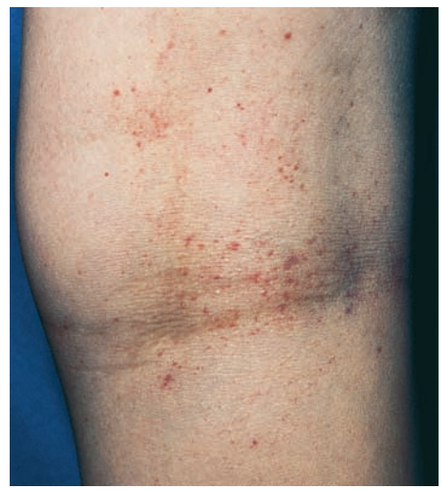


Fig. 3.42 A bleeding diathesis as a result of thrombocytopenia and platelet dysfunction, the most common manifestation in patients with Wiskott–Aldrich syndrome (WAS), may appear as petechiae, ecchymoses, and purpuric patches. The dermatitis of patients with WAS is indistinguishable from atopic dermatitis.

arthritis (29%), IgA nephropathy, and central nervous system vasculitis and painful cutaneous small-vessel vasculitis (22%), which can appear as purplish induration of skin and soft tissues.

The clinical course of WAS is progressive, usually resulting in death by adolescence without transplantation. Overall, 40% of patients die of infection, 21% of hemorrhage (usually intracranial), and 25% of malignant neoplasia. Lymphoreticular malignancies occur overall in 13% to 22% of patients,[395] with an average age of onset of 9.5 years. Non-Hodgkin lymphoma[395,396] is the most common malignancy and is often linked to EpsteinDBarr (EBV) infection, and extranodal and brain involvement predominate. Fewer than 5% who develop lymphoma survive more than 2 years.

Individuals with WAS have mutations in the gene that encodes WAS protein (WASp), and the extent of WASp depletion correlates with disease severity. WASp, through complexing with other proteins, activates Arp2/3 and ultimately polymerizes the actin cytoskeleton to enable cell movement, formation of dendrites and of immune synapses, T-cell activation, and B-cell homeostasis. Platelet abnormalities result from defective migration in proplatelet formation, inherent platelet defects increasing fragility, and autoimmunity against platelets. T-regulatory cell dysfunction has been blamed for the increased risk of autoimmune complications. The mechanism for the AD is not deÞned but could relate to T-cell activation defects and the abnormal interactions of WAS Langerhans cells with T cells after antigenic stimulation.

Laboratory studies show thrombocytopenia in 100% of patients, with platelets usually less than 80,000/mm^3 and often less than 20,000/mm^3. Platelets tend to be small, and aggregation is sometimes defective. Eosinophilia is common, but lymphopenia is not usually seen until after 6 to 8 years of age. Total serum γ-globulin is usually normal, but levels of IgM are often low, with variable IgG levels and increased levels of IgA, IgE, and IgD. The number of T lymphocytes and response *in vitro* to mitogens may be normal in early life but often decreases with advancing age. Delayed hypersensitivity skin-test reactions are usually absent, and antibody responses to polysaccharide antigens are markedly diminished.

Several conditions may be confused with WAS. Many other immunodeÞciencies are characterized by dermatitis, increased susceptibility to infections, and the development of malignancy but do not share the bleeding diathesis. The clinical Þndings of hemorrhage, petechiae, and recurrent sinopulmonary infections in WAS help to differentiate WAS from AD.

Bone marrow transplantation with human leukocyte antigen (HLA)-identical marrow is the treatment of choice. Full engraftment results in normal platelet numbers and functions, immunologic status, and, if T lymphocytes engraft, clearance of the dermatitis.[397] Optimal survival occurs with matched sibling donors and allogeneic transplantation before age 5 years (87%). Despite the good result of matched unrelated donors in young children (71%), there is a higher risk of acute GVHD after transplant (56%) versus matched siblings (16%).[398] Mixed chimerism (i.e., engraftment of T cells but not myeloid or B cells) increases greatly the risk of chronic GVHD. If a matched donor is unavailable, infusion of autologous stem cells modiÞed *ex vivo* by gene therapy is an alternative approach.[399]

Appropriate antibiotics and transfusions of platelets and plasma decrease the risk of fatal infections and hemorrhage. Intravenous infusions of γ-globulin are also useful in patients. Topical corticosteroids may improve the dermatitis, and chronic administration of oral acyclovir is appropriate for patients with EH. Splenectomy has been used selectively for patients with severe platelet abnormalities; however, splenectomy increases the risk of infection by encapsulated organisms, markedly increasing the risk of mortality after transplantation. Children with WAS are unable to mount immune responses after administration of vaccines against encapsulated organisms. Rituximab has been used successfully in some children with EBV-induced lymphoma to prolong survival.[400]

Lichen Simplex Chronicus

Lichen simplex chronicus (circumscribed neurodermatitis) is a localized, chronic pruritic disorder characterized by patches of dermatitis that result from repeated itching, scratching, and rubbing of the involved area. The pruritus may begin in an area of normal-appearing skin or may be initiated in a preexisting lesion of atopic, seborrheic, or contact dermatitis, lichen planus, or psoriasis.

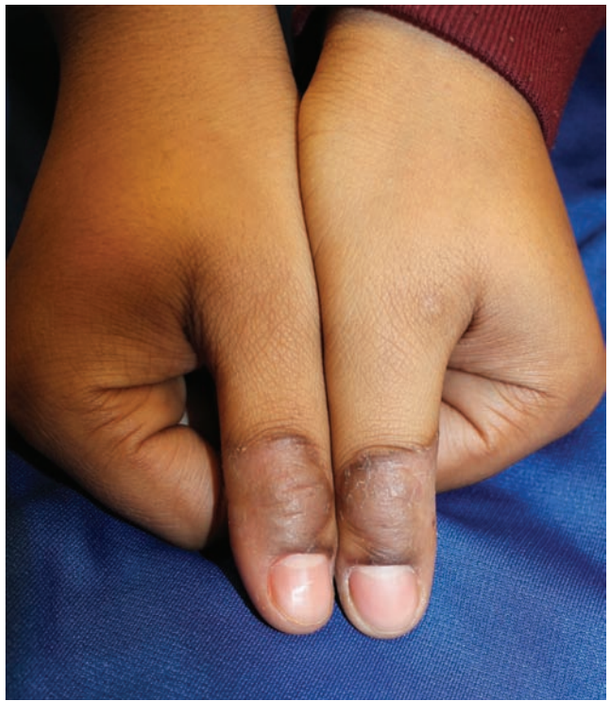


Fig. 3.43. Lichen simplex chronicus. Localized plaques of dermatitis result from repeated rubbing or scratching of the involved area.

Lesions of lichen simplex chronicus generally occur in adolescents or adults but may be seen in younger children. The disorder may develop at any location on the body, but the most common areas of involvement are those that are easily reached and may be scratched unobtrusively (particularly during periods of tension and concentration). These include the nape or sides of the neck, wrists, ankles, hands, and pretibial areas. Other common sites of involvement include the inner aspects of the thighs, vulva, scrotum, and perianal areas.

The clinical features of lichen simplex chronicus include single or multiple oval plaques with a long axis that usually measure up to 15 cm in diameter (Fig. 3.43). During the early stages, the skin is reddened and slightly edematous with exaggerated skin markings. Older, more typical lesions are characterized by well-circumscribed, dry, thickened, scaling, pruritic, often hyperpigmented plaques.

The diagnosis of lichen simplex chronicus is dependent on the presence of pruritic licheniÞed plaques in the characteristic sites of predilection. Lesions of tinea corporis may be differentiated by a lack of licheniÞcation, by the presence of a scaly border (often with clearing in the center), by demonstration of hyphae on microscopic examination of skin scrapings, and by fungal culture. Psoriatic plaques generally may be differentiated by a characteristic thick, adherent white or silvery scale, their underlying deep red hue, and characteristic areas of involvement. Lesions of AD may be differentiated by history, more poorly demarcated lesions, the presence of atopic stigmata, and a tendency toward involvement in antecubital and popliteal areas.

The successful management of lichen simplex chronicus depends on an appreciation of the itch-scratch-itch cycle and the associated scratching and rubbing that accompany and perpetuate this disorder. Topical application of potent corticosteroids, under occlusion if necessary, and the administration of systemic antihistamines (such as diphenhydramine or hydroxyzine) usually induces remission of the

pruritus and the eruption within a period of several weeks. Use of tap water compresses before application of the topical corticosteroid or compounding topical steroid with salicylic acid (e.g., 6% salicylic acid and 0.1% triamcinolone powder in hydrophilic ointment) may increase penetration of the topical antiinflammatory agent. Other techniques include application overnight of flurandrenolide-impregnated tape, protection from scratching and rubbing by occluding with adherent dressings, and injection of intralesional triamcinolone acetonide (e.g., 5 to 10 mg/mL) in tolerant adolescents.

Seborrheic Dermatitis

Seborrheic dermatitis refers to a self-limiting erythematous, scaly, or crusting eruption that occurs primarily in the so-called "seborrheic areas" (those with the highest concentration of sebaceous glands), namely the scalp, face, and postauricular, presternal, and intertriginous areas. Seborrheic dermatitis in the pediatric population is most commonly seen in infants and adolescents. The cause of seborrheic dermatitis is not well understood. Its predilection for areas of high sebaceous gland density and the correlation of activity with increased hormonal levels during the first year of life[401] and adolescence suggests a relation to sebum and sebaceous glands. Seborrheic dermatitis of adolescence and adulthood has been attributed to *Pityrosporum ovale (Malassezia ovalis)*, a lipophilic yeast normally found in abundance on the human scalp.[402] However, the relationship between seborrheic dermatitis in infants and that of adolescents and adults is controversial. It is unclear if this organism plays a causal role in disease in infants.[403,404] Many infantile cases improve with topical ketoconazole, suggesting that overgrowth of yeast may, at least in some instances, play a role in the pathogenesis of this disorder.

Seborrheic dermatitis appears in infancy between the second and tenth week of life (usually the third or fourth) and peaks in incidence at 3 months of age.[405] Infantile seborrheic dermatitis often begins with a noneczematous, erythematous, scaly dermatitis of the scalp (termed *cradle cap*) or the diaper area and is manifested by thin dry scales or sharply defined round or oval patches covered by thick, yellowish brown, greasy crusts. Although the condition is limited to the scalp in most affected infants, it may progress to the forehead, ears, eyebrows, nose, and back of the head (see Figs. 3.3 and 2.27). Erythematous greasy, salmon-colored, sharply marginated scaly patches may also involve the intertriginous and flexural areas of the body, the postauricular areas, the trunk, umbilicus, anogenital areas, and groin (Fig. 3.44). Pruritus is slight or absent, and the lesions usually lack the dry, fine scaling character associated with AD. Overlap of seborrheic dermatitis and AD, however, may occur with the features of AD becoming more prominent as the seborrheic dermatitis subsides. In one study, 49% of infants with AD had a history of infantile seborrheic dermatitis, in contrast to 17% of controls.[406]

The differential diagnosis of seborrheic dermatitis during infancy includes AD, psoriasis, LCH, and immunodeficiency. Lesions of AD are almost always pruritic, are poorly defined, and have dry, fine scaling. In addition, the occluded diaper area is usually spared in AD, in contrast to the common diaper area involvement of seborrheic dermatitis. Psoriasis can be quite difficult to differentiate because it can present in infants in a fashion very similar to that of seborrheic dermatitis, with sharply marginated, brightly erythematous scaling patches. Psoriasis tends to show a slower response to topical corticosteroid therapy and can be distinguished, if necessary, by skin biopsy. Although LCH can at times be mistaken for seborrheic dermatitis, the presence of discrete 1- to 3-mm yellowish to red-brown crusted or eroded papules, purpuric lesions, hepatosplenomegaly, or lymphadenopathy supports the diagnosis of LCH; histopathologic and immunohistochemical examination of cutaneous lesions confirms the diagnosis of LCH. When the erythema and scaling of infantile seborrheic dermatitis becomes severe, generalized, and exfoliative, the diagnosis of immunodeficiency must be considered. The lack of constitutional findings (diarrhea, fever, weight loss), alopecia, associated infections, and the spontaneous clearance or rapid response to therapy of seborrheic dermatitis help to distinguish the conditions. Severe generalized seborrhea-like dermatitis in association with failure to thrive, recurrent skin and other infections, and chronic diarrhea (once called *Leiner syndrome*) can be seen in several immunodeficiency disorders, including C3 and C5 complement deficiencies, C5 dysfunction, hypergammaglobulinemia E syndrome, SCID (especially Omenn syndrome), and X-linked agammaglobulinemia.[407]

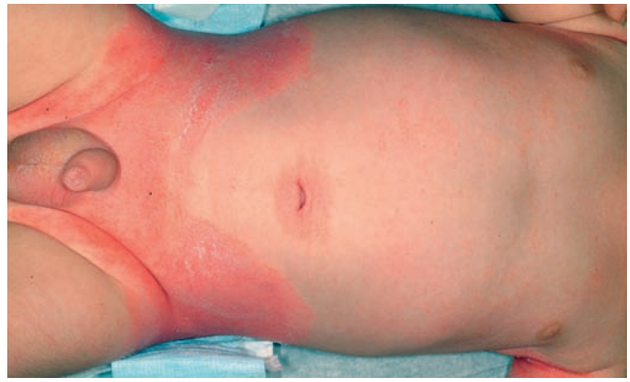


Fig. 3.44 Seborrheic dermatitis. A cause of diaper rash in young infants, seborrheic dermatitis is difficult to distinguish clinically from infantile psoriasis but tends to be less erythematous, to have thinner scaling, and to respond more quickly to topical antiinflammatory medications.

Between puberty and middle age, seborrheic dermatitis may appear on the scalp as a dry, fine, flaky desquamation, commonly known as *dandruff*. This seborrhea is an extreme form of normal desquamation in which scales of the scalp become abundant and visible, often overlying inflammation. Erythema and scaling of various degrees may also involve the supraorbital areas between the eyebrows and above the bridge of the nose, nasolabial crease (Fig. 3.45), lips, pinnae, retroauricular areas, and aural canals. Blepharitis is a form of seborrheic dermatitis in which the eyelid margins are red and covered with small, white scales. Seborrheic dermatitis may also involve the sideburns, beard, and mustache areas, with diffuse redness, greasy scaling, and pustulation. The severity and course of seborrheic eruptions of the eyelids and bearded areas are variable and have a tendency to chronicity and recurrence.

Occasionally an adolescent patient may have an eruption that has clinical features of both seborrheic dermatitis and psoriasis. Such eruptions may be termed *sebopsoriasis*. Lesions of seborrheic dermatitis can be differentiated from those of psoriasis by a lack of the characteristic vivid red hue or micaceous scale, a predisposition toward flexural rather than extensor aspects of the extremities, and the fact that lesions of seborrhea generally tend to remain within the confines of the hairline. Lesions of psoriasis (or sebopsoriasis) commonly extend beyond the hairline and in general are more resistant to standard antiseborrheic therapy.

The prognosis of infantile seborrheic dermatitis is excellent. In some patients, the disorder clears within 3 to 4 weeks, even without treatment, and most cases clear spontaneously by 8 to 12 months of age. The condition generally does not recur until the onset of puberty, although mild scaling of the scalp, particularly at the vertex, can be seen in some affected children through preschool years. Treatment of infantile scalp seborrheic dermatitis is best managed by frequent shampooing.[408] Although antiseborrheic shampoos, including ketoconazole shampoo,[409] may be useful, in infants or young children, these products may be drying or irritating to the eyes. A gentle "no-tears" shampoo usually suffices. If the scales are thick and adherent, removal can be facilitated by the thin application of mineral or baby oil followed by gentle scalp massage with a soft toothbrush and then shampooing. Antiseborrheic shampoos are alternatives if therapy with no-tears shampoo is not effective. If there is a significant inflammatory component, a topical corticosteroid lotion, oil, or solution, with or without 3% to 5% salicylic acid, may be applied once to twice daily. For involvement other than the scalp, a low-strength topical corticosteroid or topical antifungal agent is usually effective when applied once to twice daily.

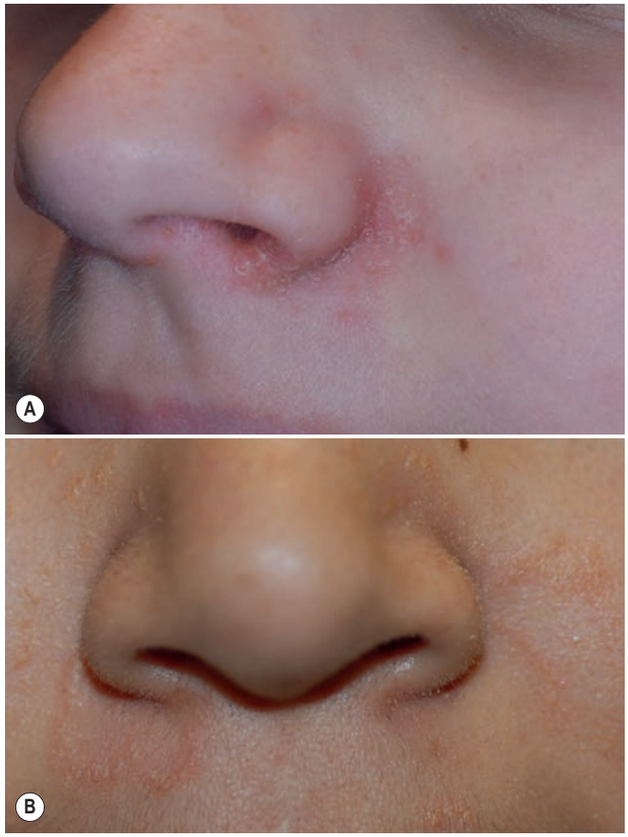


Fig. 3.45 Seborrheic dermatitis. **(A)** Facial seborrheic dermatitis in adolescents typically involves nasolabial folds and may result from overgrowth of lipophilic yeasts of the normal flora. In **(B)** tinea faciei was considered, but the distribution and bilaterality are atypical for tinea.

Adolescents with seborrhea of the scalp may try a variety of antiseborrheic shampoos, tar shampoo, ketoconazole shampoo, or 5% tea tree-oil shampoo.[408,410] Antiseborrheic shampoos may contain selenium sulfide (e.g., Sebulex, Exsel, and Selsun), salicylic acid (e.g., T-Sal), or zinc pyrithione (e.g., Head and Shoulders or DHS Zinc). If the scale is extremely thick and adherent, it can be loosened by warmed mineral oil massaged into the scalp or by the use of P&S Liquid (Baker Cummins), ideally left on overnight. Scales are then loosened by scrubbing gently with the fingers or a soft brush, and the scalp is shampooed. For patients with associated erythema or pruritus, topical corticosteroid lotions, gels, oils, or foams may be used. Seborrheic dermatitis of the face or intertriginous areas in adolescents usually responds quickly to the application of a mild corticosteroid, calcineurin inhibitor, or antifungal medication. If these are too greasy, a foam preparation of ketoconazole is available.[411]

Blepharitis may be managed by warm-water compresses, gentle cleansing with a dilute solution of a nonirritating or baby shampoo, and mechanical removal of scales when necessary. Topical corticosteroids on the eyelids or eyelid margins should be used with caution, although calcineurin inhibitors (e.g., tacrolimus or pimecrolimus) or PDE4 inhibitors (e.g., crisaborole) may be used safely in this area.

Seborrheic dermatitis of the intertriginous or diaper areas occasionally may be complicated by secondary candidal or bacterial infection. Candidal infection is usually seen in the diaper areas as discrete erythematous scaling papules and sometimes pustules, especially at the periphery of the affected area. Secondary bacterial infection is more commonly seen as oozing at the neck fold and other intertriginous sites. In such instances, topical anticandidal or antibacterial agents are generally helpful. For patients with disease refractory to topical treatment or for those with significant secondary bacterial infection, bacterial cultures and appropriate systemic antibiotics are necessary.

Intertrigo

Intertrigo is a superficial inflammatory dermatitis that occurs in areas where the skin is in apposition (Fig. 3.46; see also Fig. 17.43). As a result of friction, heat, and moisture, the affected areas become intensely erythematous in a well-demarcated pattern, macerated, and often secondarily infected by bacteria or *Candida* or, in adolescents, by dermatophytes (see Chapter 17). Intertrigo with secondary streptococcal infection often presents with oozing and can be associated with bacteremia.[412,413] Treatment is directed toward elimination of the macerated skin. Open wet compresses, dusting powders (such as Zeasorb), topical corticosteroid lotions, and, when indicated, appropriate antibiotics or fungicidal agents may be used.

Dyshidrotic Eczema

Dyshidrotic eczema (pompholyx) is an acute recurrent or chronic eczematous eruption of the palms, soles, and lateral aspects of the fingers, characterized by deep-seated, variably inflamed lesions that range from tapioca-like vesicles to large, tense bullae (Figs. 3.47

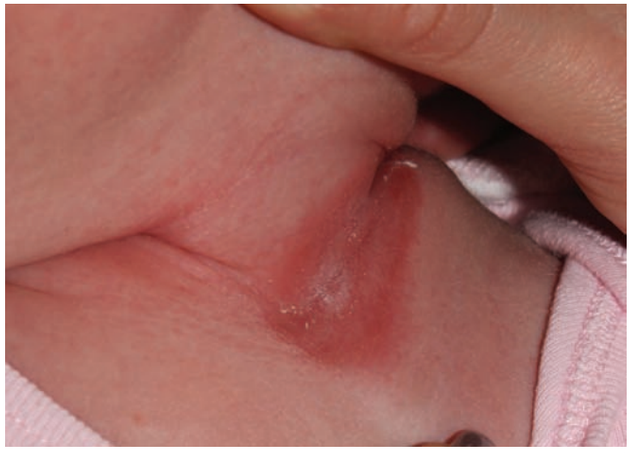


Fig. 3.46 Intertrigo of the neck fold. Intertrigo is a superficial inflammatory dermatitis that occurs at sites of skin apposition, most commonly involving the neck, inguinal, and antecubital and popliteal folds. Secondary bacterial or yeast infection is common.

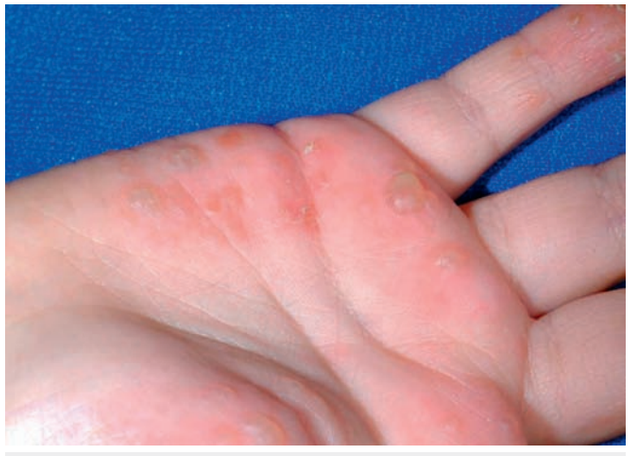


Fig. 3.47 Pompholyx, or dyshidrotic eczema. An acute recurrent or chronic eruption of the palms, soles, and lateral aspects of the fingers with deep-seated tapioca-like vesicles to large, tense bullae.

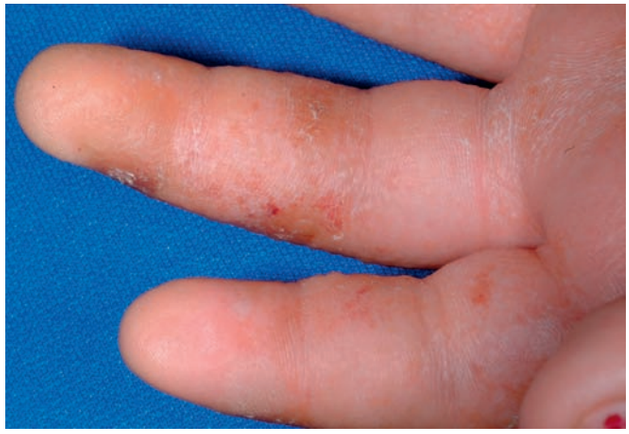


Fig. 3.48 Pompholyx, or dyshidrotic eczema. Superficial crusting and desquamation often replace the ruptured tiny vesicles of dyshidrotic eczema.

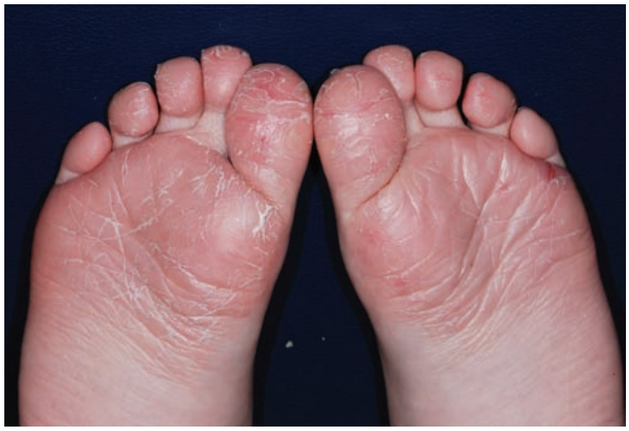


Fig. 3.49 Juvenile plantar dermatosis. Scaling, lichenification, and fissuring in chronic juvenile plantar dermatitis. Note the sparing of toe regions without contact. This patient also has ichthyosis vulgaris, which explains the hyperlinear soles.

and 3.48).[414] The distribution of lesions generally is bilateral and somewhat symmetric. Patients complain of considerable pruritus and/or burning. Hyperhidrosis is often associated. Attacks usually last a few weeks, but relapses are frequent, often several times per year.

Dyshidrotic eczema may be confused with contact dermatitis or tinea, disorders commonly unilateral or more localized. ACD (see Allergic Contact Dermatitis section) on the feet or hands most commonly results from exposure to potassium dichromate (for tanning leather) or rubber but occasionally is caused by paraphenylenediamine (PPD; in hair dyes and as an additive to henna), nickel, fragrance mix, and colophony (in glues and also in violin rosin).[415] Fungal culture and patch testing can be performed to distinguish these disorders from tinea and contact dermatitis, respectively. Id reactions and pustular psoriasis must also be considered in the differential diagnosis of this disorder and are most commonly bilateral. Juvenile plantar dermatosis is limited to the feet and tends to be bilateral (Fig. 3.49). A reaction on the palms and soles resembling dyshidrotic eczema has also been described after intravenous immunoglobulin (IVIG), most commonly after the first IVIG treatment in adults with neurologic disorders.[416,417] In a minority of these cases, eczematous lesions may be extensive. Severe dyshidrotic eczema may also occur after IVIG therapy for Kawasaki disease[418] or Stevens–Johnson syndrome.[416]

The natural course of dyshidrotic eczema is one of frequent recurrence. Open wet compresses tend to open the vesicles, and application of moderate to potent topical corticosteroids, although not curative, helps relieve the manifestations of this disorder. Topical tacrolimus 0.1% ointment has been used successfully as an alternative that allows rotational therapy.[419] When infection is present, antibiotics may be administered topically or systemically. Although not a disorder of eccrine glands *per se*, the use of topical aluminum chloride in concentrations of 12% (e.g., Certain Dri) to 20% (e.g., Drysol) or topical glycopyrronium may decrease the associated hyperhidrosis and help to control the disorder if not too irritating. Hyperhidrosis can also be controlled by oral administration of glycopyrrolate if topical application of drying agents is ineffective or too ineffective. For adolescents with recalcitrant hyperhidrosis, intradermal injections of botulinum toxin might be considered.[420] Phototherapy with either narrow-band ultraviolet B light or high doses of ultraviolet A1 light[421] and even short courses of oral corticosteroids with gradual tapering have been used.

Juvenile Plantar Dermatosis

Juvenile plantar dermatosis (dermatitis plantaris sicca or "sweaty-sock dermatitis") is a common dermatosis of infancy and childhood, most commonly localized to the distal aspect of the soles and toes, particularly the great toes, but sparing the interdigital spaces. Associated with hyperhidrosis and thought to represent a frictional irritant dermatitis, the disorder is manifested acutely by a symmetric, smooth, red, glazed, and fine scaling but can become lichenified with chronicity (see Fig. 3.49). Similar changes have also been reported on the fingertips in up to 5% of patients with excessive perspiration. Untreated juvenile plantar dermatosis generally tends to persist for several years, and although there is no seasonal pattern, some patients report slight worsening of the condition during the summer and in cold weather.

The differential diagnosis of juvenile plantar dermatosis includes tinea pedis, palmoplantar psoriasis, pityriasis rubra pilaris, and shoe-related contact dermatitis. Tinea pedis can manifest as scaling and erythema of the plantar foot but is more likely to involve the interdigital spaces. Associated pustulation of tinea may be mistaken for secondary staphylococcal infection. Potassium hydroxide scrapings and culture may be required to distinguish tinea pedis and juvenile plantar dermatosis. The plaques of psoriasis are often thicker and more erythematous. Pityriasis rubra pilaris may closely resemble psoriasis but often shows a salmon-orange coloration on the palms and soles. Both psoriasis and pityriasis rubra pilaris usually show lesions elsewhere. Contact dermatitis owing to a component of shoes is more commonly on the dorsum of the foot, but the plantar foot is occasionally involved (see Shoe Dermatitis section).

Although treatment is not always completely successful, children with hyperhidrosis of the feet should wear all-cotton socks and avoid occlusive footwear whenever possible, remove their shoes when indoors, change their socks whenever they are damp, dust an absorbent powder into shoes and socks (to help lessen perspiration), and use an emollient cream as soon as the shoes and socks are removed. Patients do not usually tolerate topical agents for hyperhidrosis, but oral glycopyrrolate tends to be very effective and may reduce the severity of the dermatitis; dosing is 1 to 5 mg per day, and the most common complications are dry mouth and eyes. Use of a medium-strength to potent topical steroid is usually effective in diminishing the pruritus and inflammation associated with juvenile plantar dermatitis. Low-strength topical steroids are often not effective, given the thick overlying stratum corneum of the plantar surface. Topical or systemically administered antistaphylococcal antibiotics may be needed if patients show crusting or pustulation suggesting secondary infection. Careful application of a cyanoacrylate (e.g., Super Glue) to fissured areas often provides relief from the associated discomfort.

Frictional Lichenoid Dermatitis

Frictional lichenoid dermatitis (frictional lichenoid eruption, juvenile papular dermatitis, recurrent summertime pityriasis of the elbows

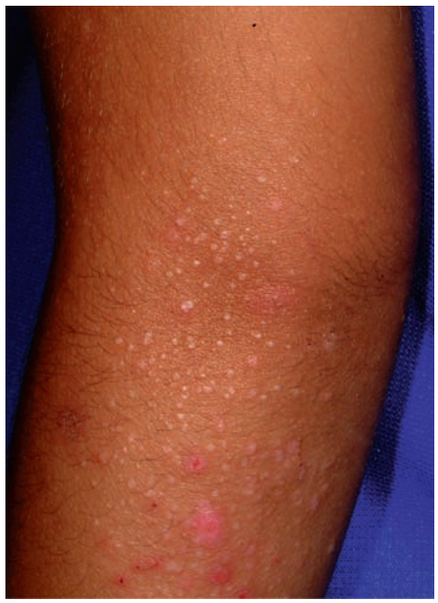


Fig. 3.50 Frictional lichenoid dermatosis. Aggregates of lichenoid papules occur primarily on the elbows, knees, knuckles, and backs of the hands of children. Although many of the papules are monomorphic and tiny, suggesting lichen nitidus (see Chapter 4), the associated pruritus, localization, and concurrent presence of lichenoid papules of various sizes on the elbows allow the diagnosis to be made clinically.

and knees) is a recurring cutaneous disorder affecting children, especially boys, between 4 and 12 years of age.[422] Most cases are seen in the spring and summer when outdoor activities are common, and many cases have been associated with playing in sandboxes (sandbox dermatitis) or on grass. Approximately half of the affected children have AD, allergic rhinitis, or asthma.[423] The eruption is characterized by aggregates of discrete lichenoid papules, 1 or 2 mm in diameter, which occur primarily on the elbows, knees, and backs of the hands of children in whom such areas are subject to minor frictional trauma without protection of clothing (Fig. 3.50). Lesions may be hypopigmented, and associated pruritus is often severe but may be absent. It tends to occur in children with a predisposition to atopy.

The differential diagnosis of this disorder includes psoriasis, AD, molluscum, flat warts, lichen nitidus, and the papulovesicular acrolocated syndrome (Gianotti–Crosti syndrome; see Chapter 16). The management of frictional lichenoid dermatitis includes avoidance of frictional trauma to the involved areas (as might occur with leaning on elbows and knees) and application of topical corticosteroids and emollient, especially to ease any associated pruritus.

Nummular Dermatitis

Nummular dermatitis (also called *nonmular eczema*) is characterized by discoid or coin-shaped plaques. The name is derived from the Latin word *nummulus* ("coin-like"), because of the shape and size of the lesions. The plaques of nummular dermatitis are composed of minute papules and vesicles, which enlarge by peripheral extension to form discrete, usually round or oval, erythematous, often lichenified and hyperpigmented plaques that measure 1 cm or more in diameter (see Figs. 3.34 and 3.35). They usually occur on the extensor surfaces of the hands, arms, and legs as single or multiple lesions on dry or asteatotic skin. Pruritus is usually associated and may be intense. Occasionally the face and trunk may be involved. The surrounding skin may be xerotic, particularly in children with AD and nummular dermatitis, but in many patients is normal. Secondary staphylococcal infection is common and manifests as crusting and exudation.

Nummular dermatitis must be differentiated from ACD, AD (which may be seen concurrently), psoriasis, and superficial dermatophyte infections of the skin. History of exposure, patch testing if appropriate, fungal culture, and biopsy of lesional skin can help to distinguish these conditions.

Effective therapy requires application of class II to IV topical corticosteroids, preferably in an ointment base or under occlusion. The combination of a refined tar preparation (liquor carbonis detergens 5% to 10%) in a strong corticosteroid used twice daily is an alternative means of treatment. Secondary staphylococcal infection should always be considered, especially in recalcitrant lesions, and commonly requires systemic administration of antibiotic (such as cephalexin) in addition to a potent topical steroid. Although in general the use of topical antibiotic with topical steroid is discouraged for AD beyond for mild secondary infection, nummular dermatitis often responds better to concurrently applying topical steroid and topical mupirocin. For severe cases that are recalcitrant to topical medication, methotrexate is the treatment of choice.[424]

Winter Eczema

Winter eczema, also known as *asteatotic eczema*, *eczema craquelé*, or *xerotic eczema*, is a subacute eczematous dermatitis characterized by pruritic scaly erythematous patches, usually associated with dryness and dehydration (asteatosis) of the epidermis. Generally seen on the extremities and occasionally on the trunk, these changes are most common during winter when the humidity is low, particularly in adults and adolescents who bathe or shower often with harsh or drying soaps. Frequent bathing with incomplete drying and resultant evaporation of moisture causes dehydration of the epidermis, with redness, scaling, and fine cracking that may resemble cracked porcelain (hence the term *eczema craquelé*). Treatment of winter eczema is centered in the maintenance of proper hydration of the stratum corneum and is dependent on the routine use of emollients, limiting the time and temperature of showers, use of mild soaps, and topical therapy with corticosteroids (preferably those in an ointment base) for individual lesions.

Lichen Striatus

Lichen striatus is a self-limiting inflammatory dermatosis that follows Blaschko lines, the path of ectodermal embryologic development of skin.[425,426] Although not considered contagious or inherited, lichen striatus has been described in more than one family member.[427,428] It has followed viral infections, vaccination (e.g., hepatitis B virus), and trauma, but its cause is unknown. The inflammatory infiltrate of lichen striatus shows plasmacytoid dendrocytes and, similar to other lichenoid disorders, a type I interferon signature.[429] The mean age of onset is 4 years of age, although older children may be affected. Girls appear to be affected two to three times more often than boys. In a large series, 60 of 115 affected children were atopic.[426]

The eruption is usually asymptomatic (but sometimes is pruritic) and reaches its maximum extent within a few weeks to months. Only 6% of affected children show more than one band. Lesions begin as 2- to 4-mm erythematous to hypopigmented, slightly scaling, flat-topped papules that rapidly coalesce to form the curvilinear band. The line of involvement tends to be narrow but can range from several millimeters to 1 or 2 cm in width. Most commonly lichen striatus affects an extremity but occasionally the face (Fig. 3.51),[430] neck, trunk, or buttocks is affected. Nail involvement is seen, typically by extension of an extremity lesion.[431,432] In dark-skinned or tanned individuals the eruption may appear as slightly scaly (Fig. 3.52) or as a band-like area of hypopigmentation (Fig. 3.53). Although the band is usually continuous, it may occasionally be interrupted by or interspersed with coalescent plaques several centimeters in diameter along a line of Blaschko.

The differential diagnosis of lichen striatus most commonly includes inflammatory linear verrucous epidermal nevus (ILVEN), which tends to be more psoriasiform (Fig. 3.54; see also Chapter 9 and Fig. 9.40) and blaschkitis[433] (more eczematous) (Fig. 3.55). In contrast to lichen striatus, blaschkitis is usually papulovesicular, pruritic,

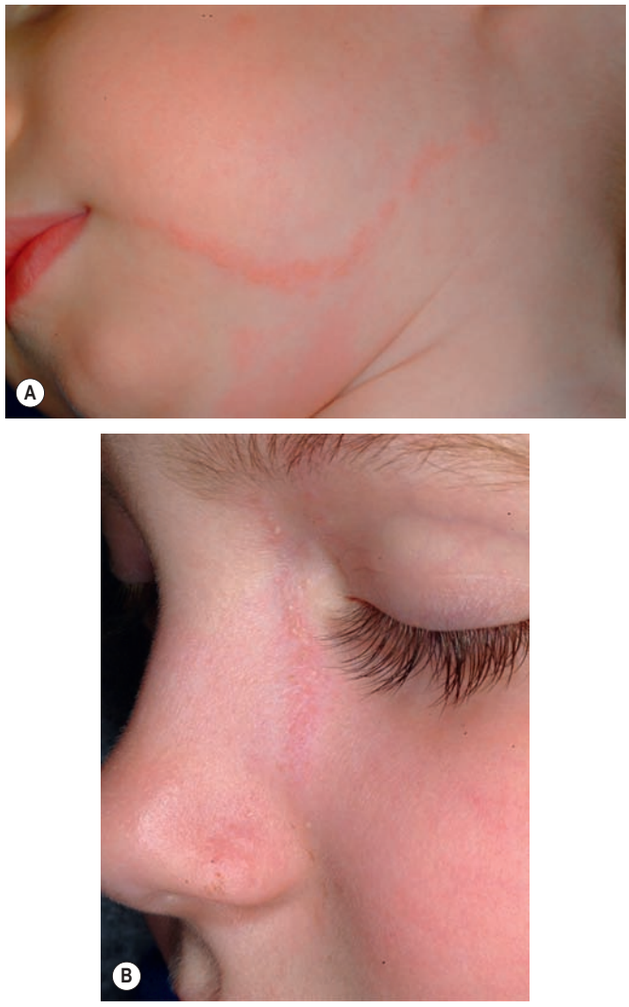


Fig. 3.51 (A and **B)** Lichen striatus. A self-limiting, usually unilateral linear or curvilinear collection of small, erythematous, flat-topped papules that follows one of the Blaschko lines, lines of the embryologic development of skin. Lines on the face tend to be particularly thin.

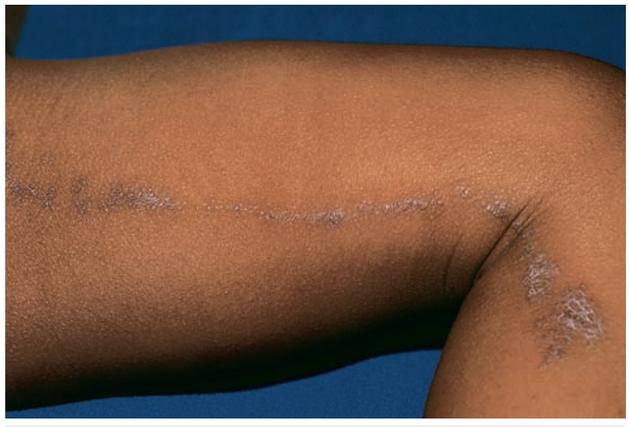


Fig. 3.52 Lichen striatus. Linear collection of papules of lichen striatus, most commonly seen on the extremities. The erythema is more difficult to appreciate on darker skin, but the mild scaling may be more apparent.

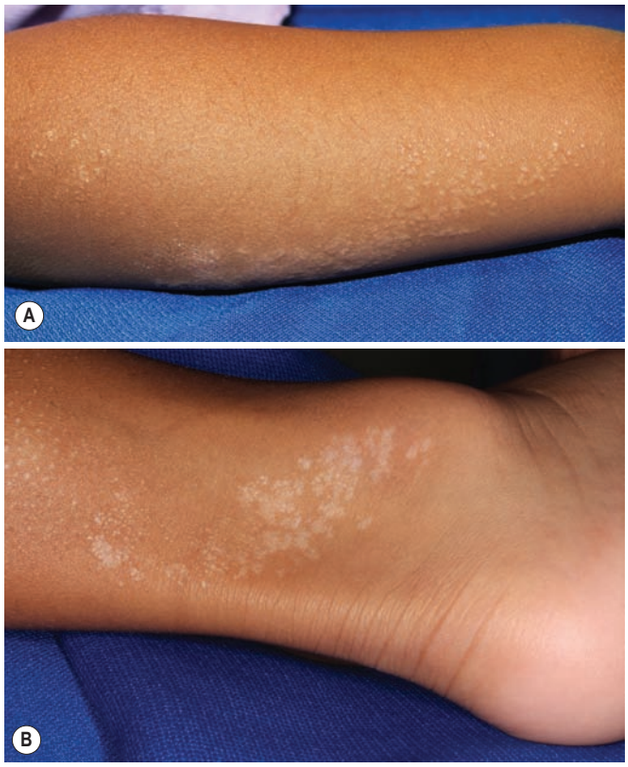


Fig. 3.53 (A and **B)** Lichen striatus. The linear and curvilinear streaks of lichen striatus may be collections of hypopigmented papules or macules from the onset, particularly in children with darker skin types.

involves multiple bands, tends to last for about a month, recurs often, and tends to respond to topical antiinßammatory medication. Biopsy of blaschkitis shows pure spongiosis without a lichenoid inÞltrate. Other acquired inßammatory lesions distributed along lines of Blaschko can include linear forms of lichen planus, linear lichen nitidus, lichenoid drug eruptions,[434] lichenoid chronic GVHD, lupus erythematosus, AD, and linearly arranged (Ò koebnerizedÓ) lesions of verruca plana. When the diagnosis remains in doubt, histopathologic examination of a cutaneous biopsy specimen will help exclude other possible linear eruptions.

Lichen striatus usually resolves spontaneously within 3 to 24 months (mean duration, 6 months)[426] but occasionally lasts longer (up to 3.5 years)[435] and often leaves an area of hypopigmentation that subsequently disappears. Recurrences occur in 2% of children. Therapy is generally unnecessary, and topical corticosteroids do not tend to hasten resolution but can reduce pruritus if present. However, facial lesions have responded to tacrolimus,[436] and combination of a topical tazarotene and topical steroid has been associated with lesional clearing.[437]

Contact Dermatitis

Contact dermatitis may be deÞned as an eczematous eruption produced either by local exposure to a primary irritating substance (irritant contact dermatitis) or by an acquired allergic response to a clinically relevant sensitizing substance (allergic contact dermatitis [ACD].[147] A contact allergen can sensitize but does not cause a reaction on Þrst exposure. With continued or repeated exposure, the allergen may trigger a contact dermatitis based on a type IV allergic reaction. An irritant, on the other hand, may be deÞned as a substance that produces an eczematous response on the basis of irritation rather than by immunologic means and can occur in anyone; allergens only

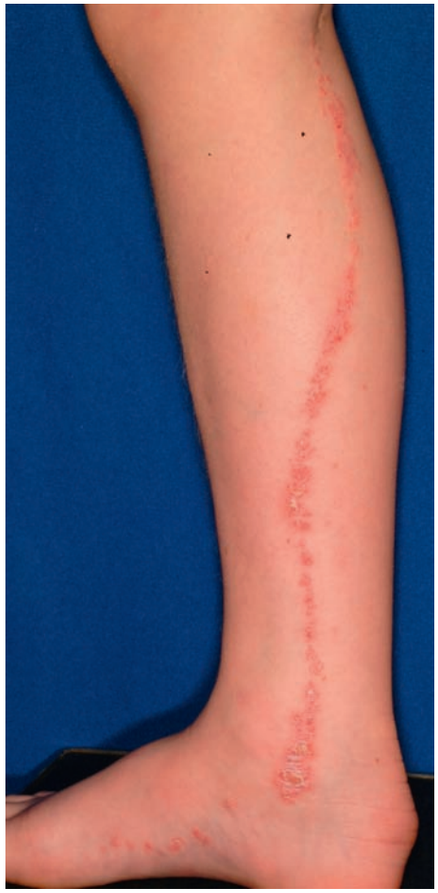


Fig. 3.54 Inflammatory linear verrucous epidermal nevus (ILVEN). Lichen striatus must be differentiated from ILVEN, a persistent mosaic lesion that follows the lines of Blaschko (see Chapter 9). The papules of ILVEN tend to be more erythematous, less discrete, more scaly, and more pruritic than those of lichen striatus, but biopsy or observation over 2 to 3 years may be necessary to determine the diagnosis.

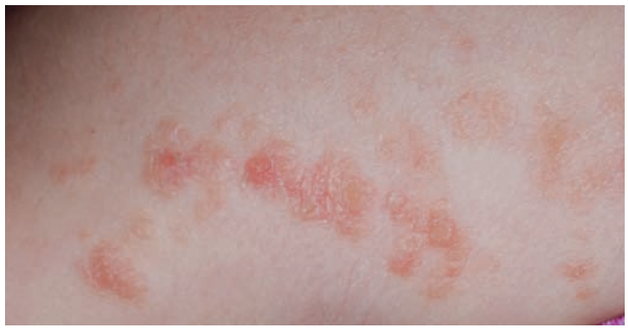


Fig. 3.55 Blaschkitis. Although distributed along a Blaschko line, lesions of blaschkitis are eczematous, are often multiple, and last for just a few weeks, in contrast to those of lichen striatus or ILVEN.

can trigger contact dermatitis in susceptible individuals. Photocontact reactions (see Chapter 19) such as phytophotodermatitis after contact with the juice or rinds of certain lemons and limes (and several other plant-based products) occur only when the skin is exposed to ultraviolet light. ACD should be distinguished from contact urticaria, which can be diagnosed by the morphology of the lesions (urticarial) and is best treated with antihistamines.[438,439]

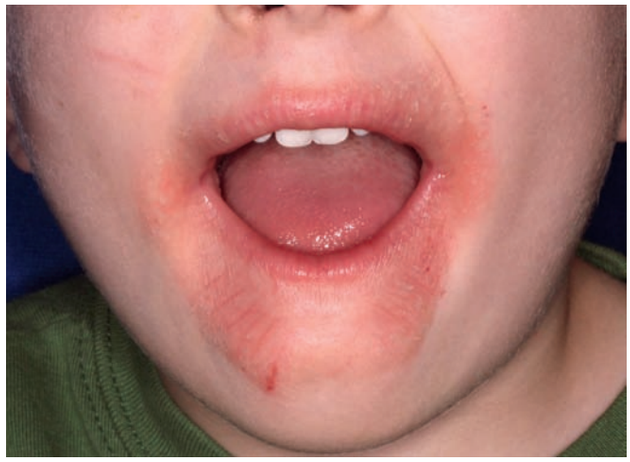


Fig. 3.56 Lip-licker's dermatitis. Chronic contact dermatitis with lichenification and hyperpigmentation in the shape of licking from the tongue and sometimes beyond.

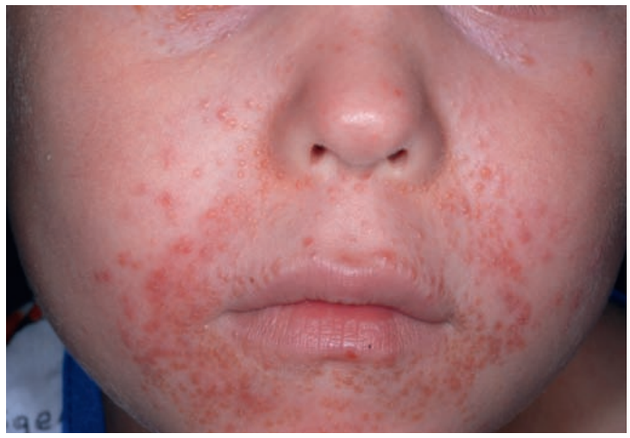


Fig. 3.57 Periorificial granulomatous dermatitis. The discrete, tiny, noneczematous papules are usually seen in a perioral distribution but may be perinasal and/or infraorbital. The morphology and distribution help to distinguish periorificial granulomatous dermatitis from perioral irritant or allergic contact dermatitis.

PRIMARY IRRITANT DERMATITIS

Common substances that produce primary irritant dermatitis include harsh soaps, bleaches, detergents, solvents, acids, alkalis, bubble baths, certain foods, saliva, urine, feces, and intestinal secretions. The severity of the dermatitis varies from person to person or from time to time in the same person as a result of the condition of the skin at the time of exposure, the strength of the irritant, the location of the eruption, the cumulative effect of repeated exposures to the irritating substance, and local factors such as perspiration, maceration, and occlusion.

In children, the lips and adjacent skin commonly become dry and, as a result of a licking habit, inflamed and scaly (lip-licker's dermatitis) (Fig. 3.56). If extensive, lip-licker's dermatitis must be distinguished from ACD, especially that caused by mango (see Fig. 3.63), and perioral granulomatous dermatitis (Fig. 3.57), which is characterized by small erythematous papules of the perioral and often suborbital areas and is exacerbated by application of topical corticosteroids (see Chapter 8). Saliva also commonly becomes trapped between the thumb and mouth of thumb suckers, and a similar reaction is commonly seen

in toddlers who continue to use paciÞers for long periods. In infants with AD, saliva is a signiÞcant irritant associated with the extensive drooling from teething and contributes to the dermatitis on the cheeks and chin. In the infant and young child, circumoral erythema may also represent a contact dermatitis in response to foods such as citrus foods, carrots, shrimp, and spinach. The dermatitis is caused by direct contact with the skin, not from ingestion of the offending food substances, although exposure is aggravated by regurgitation of food particles, dribbling of saliva, and rubbing of the involved areas.

Diaper dermatitis is the most common form of irritant contact dermatitis in infancy (see Chapter 2), with a peak age of incidence of 9 to 12 months of age. ACD in the diaper area is rare. Irritant diaper dermatitis typically affects the exposed convex surfaces and spares the folds, which are protected. Toddlers and younger children who use pull-up diapers at night and children with enuresis not uncommonly show an irritant dermatitis of the buttocks region related to exposure to urine and limited absorbency of the pull-up. Perianal dermatitis is often irritant related as a result of exposure to stool but must be distinguished from perianal psoriasis (see Chapter 4) and perianal streptococcal cellulitis (see Chapter 14).

Juvenile plantar dermatosis has been linked to exposure to sweat and is more commonly seen in children with plantar hyperhidrosis (see previous discussion). Excessive handwashing, especially during winter months and in compulsive handwashers, is the most common cause of dermatitis on the dorsum of the hands. The increased attention to handwashing as a means to decrease the spread of infectious disease has markedly increased the risk of developing irritant hand dermatitis in school-aged children. ÒSlime,Ó a concoction often made at home with boric acid salt, glue, and water, is a growing cause of irritant hand dermatitis, particularly on the palm[440Đ442] and palmar aspects of the Þngers (Fig. 3.58). Although most commonly an irritant dermatitis, ingredients in the detergents, shaving cream, shampoos, or contact lens solution that are used as the source of the boric acid or the glue may trigger ACD because they contain fragrance, methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), isothiazolinones, and other potential allergens (see Allergic Contact Dermatitis).

Soccer and hockey shin guards typically trap sweat and cause friction, leading to an irritant contact dermatitis on the anterior aspect of the lower legs of school-aged children that can become licheniÞed if chronic. Strategies to reduce friction, such as wearing a cotton sock under the guard and coating the area with absorbent powder or petrolatum before using the guards, together with topical antiinßammatory therapy for the dermatitis as needed, have been helpful.[444] Should the dermatitis persist or worsen, ACD should also be considered, particularly as related to the rubber compounds and neoprene components in sporting equipment (Table 3.3). Irritant dermatitis can develop under tight rings or watches because of the trapping of sweat, detergents, or other irritants (Fig. 3.59). Irritant reactions may also occur from exposure to Þberglass particles attached to clothes after exposure to Þberglass insulation panels or drapes.[445] Because clothes washed in a washing machine in which Þberglass materials have been washed are also capable of inducing this cutaneous reaction, children whose parents have been exposed may also be affected. Fiberglass dermatitis presents as a pruritic, patchy folliculitis or subacute dermatitis. Microscopic examination of skin scrapings from involved areas or suspected articles of clothing may reveal pale, greenish, granular rodlike Þbers one to two times the width of a hair. The use of methylphenidate transdermal patches in children with ADHD often leads to irritant reactions conÞned to the site of patch application; ACD to the patch is rare.[446]

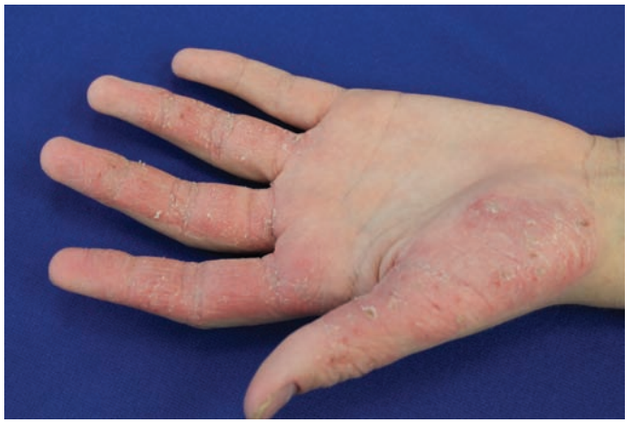


Fig. 3.58 Hand dermatitis. Slime, made at home from boric acid salt, glue, and water, is a cause of irritant (and sometimes allergic) contact dermatitis on the palms.

Avoidance of the irritant is key to improvement. Low-potency topical corticosteroids or calcineurin inhibitors are used to treat the dermatitis of face and intertriginous areas; medium-strength topical steroids, or even potent topical steroids for hands and feet, may be required. Moisturizing creams or ointments lubricate and protect the affected areas. The treatment of irritant diaper dermatitis is discussed in Chapter 2.

ALLERGIC CONTACT DERMATITIS

ACD may account for up to 20% of all dermatitis in childhood and is likely to be underdiagnosed.[146,147,447] Key areas of involvement are the eyelids, neck, hands, axillae, anogenital area, and lower extremities. ACD represents a type IV immunologic (delayed hypersensitivity or cell-mediated) reaction in which antigenic contact with cutaneous Langerhans cells and T-lymphocyte activation are key. Despite their clinical similarity, nickel sensitization involves Th1/Th17 and Th22 lymphocytes, but fragrance allergy and, to a lesser extent, rubber allergy largely involve Th2 lymphocyte activation.[448,449] After sensitization to the offending allergen, ACD will develop on reexposure to the sensitizing substance. Sensitization may occur after only a few exposures to the offending substance, or allergy may occur after years of contact. Once the area has become sensitized, however, reexposure to the offending allergen may result in an acute dermatitis within a relatively brief period (generally 8 to 12 hours after exposure to the sensitizing allergen).

Reactions to *Rhus* family of contact allergens (e.g., poison ivy) are the most common triggers in children. Other major sources of clinically relevant ACD in children are metals (especially nickel, chromates, cobalt, and occasionally gold), fragrances and Balsam of Peru, lanolin/wool alcohols, cocamidopropyl betaine (CAPB; foaming product in Òno-tearsÓ shampoos and cleansers),[450] topical antibiotics (neomycin and bacitracin), formaldehyde, and rubber products[146,147,451] (see Table 3.3). Other triggers to consider in children are PPD contaminating temporary henna tattoos,[452] disperse dyes in clothing,[453] and the preservatives MCI and MI, which are sometimes in wet wipes. Girls are at greater risk for developing contact allergy, especially during adolescence and on the face, because of their greater exposure to ear piercing (nickel), cosmetics (preservatives and fragrances), and hair products. Initial sensitization to common allergens and occasionally ACD itself may occur during infancy.[454] Of tested children, 23% to 49% have AD, although it is unclear whether this high number represents a referral bias or truly increased risk[139,455Đ457]; the greatest relevant reactivity in this group is to allergens in the emollients.[140]

In a recent study of baby and child products, the most prevalent allergen found in commercially available products was fragrance (48%) to give the Ò fresh babyÓ smell.[458] Betaines were found in 18% of products, especially cocamidopropyl betaine, derived from coconut oil or fatty acids. Lanolin was still in 10% of products, and propylene glycol was found in 9%. Propylene glycol is not only in topical products but is also used in food products, tablets, and liquid medications (including hydroxyzine syrup), increasing the risk of systemic contact dermatitis.[459] At this time, only 3% of products each had MCI/MI and formaldehyde releasers, which is much lower than the frequency of use less than 10 years ago (10% of products), suggesting response to concerns about sensitization risk. A second study from the United Kingdom similarly evaluated 438 Òbaby productsÓ and found that 88% had at least one potential contact allergen (especially parabens, fragrances, cetyl/stearyl alcohol, methylisothiazolinone, sodium lauryl sulfate, and lanolin). Interestingly, branded products and those marked as Òsensitive,Ó Ògentle,Ó Òorganic,Ó or Ò fragrance-freeÓ had more reference allergens than those without this marketing.[460]

Table 3.3 Most Common and Relevant Sensitizers in Children and Their Sources*

Group	Allergen	Sources	Typical Distribution	Other Comments
Plant	Urushiol	Poison ivy, sumac, oak	Extremities in linear streaks; face, genitals	If aerosolized, can be extensive and on face resemble angioedema
Metal	Nickel	Jewelry, snaps, buckles, eyeglasses, keys, coins, cell phones, tablets, laptop computers, orthodontics	Subumbilical, face, eyelids, earlobes, neck, wrists	Detect with glyoxime on objects
Topical antibiotic	Neomycin	Antibiotic-containing ointments	Face, eyelids	Bacitracin can also sensitize
Fragrance and balsam of Peru	Fragrance mix Balsam of Peru *(Myroxylon pereirae)*	Cosmetics, perfumes, sunscreens, toothpaste, flavoring agents in food and drink, lozenges, lip balms, topical healing agents, insect repellents	Face, eyelids, mouth, lips, neck, hands	Cross reacts with eugenol/isoeugenol (essential oils from several spices, such as cloves and cinnamon); vanilla, tiger balm, benzoin, propolis, colophony, citrus peel
Preservative	Thimerosal	Creams, lotions, mascara, vaccines	Torso, face	Largely removed
Metal	Cobalt	Buttons, snaps, jewelry, cement, ceramics, vitamin B_{12}	Umbilical, earlobes, neck, hands	Contaminant with nickel
Metal	Chromate	Leather (tanned), cement, paints, matches, green felt	Umbilical, hands, soles	
Metal	Gold	Jewelry, occupational exposure to jewelry, medicinal use; rarely dental gold	Face, eyelids, earlobes, neck wrists, fingers; rarely mucosal	Long-lasting patch reaction
Rubber accelerant	Thiuram	Elastic (waistband, socks), gloves, shoes (soles and insoles), pesticides	Waistline, feet, hands	Washing clothes with bleach causes release
Emollient	Lanolin/wool alcohols	Emollients, lip balms, soaps, aftershave, baby and bath oil, hand sanitizers	Hands, body	Sheep wool products
Emulsifier	Propylene glycol	Skin care products and cosmetics, topical medications, foods, coated oral medications	Face; can be generalized or scattered	More often causes an irritant dermatitis
Preservative	Formaldehyde/formaldehyde releasing	Lotions, cosmetics, shampoo, newsprint, wrinkle-resistant clothes	Hands, face, ears, trunk (sparing axillae)	
Oxidative chemical	Paraphenylenediamine	Hair dyes, printer ink, contaminant in henna tattoos (black)	Hairline, ears, hands, sites of tattoos	
Preservative	Methylchloroisothiazolinone/ methylisothiazolinone (MCI/MI)	Many infant products, such as wet wipes, protective creams, liquid soaps, shampoos, household cleaners, paints	Especially hands; can be head and neck, feet, diaper region, generalized	
Surfactant	Cocamidopropyl betaine (CAPB)	Cleansing products for children (such as tear-free formulations)	Face, hands	
Dye	Disperse dyes	Diaper material, colored synthetic garments (school and athletic uniforms)	Areas of high friction (e.g., around the axillae sparing the vault, anterior thighs)	
Rubber accelerant and antioxidant	Mixed dialkyl thiourea	Neoprene in computer mouse pads, wetsuits, shoes, athletic braces, shin guards, protective pads	Areas of friction and sweating under athletic equipment	
Adhesives	p-tert-butylphenol formaldehyde	Glues, surface coating and adhesives in shoes, ECG pads, leather goods, upholstery, hobbies	Hands, feet	

ECG, Electrocardiogram.
*For additional information, see http://www.truetest.com and choose the specific antigen.

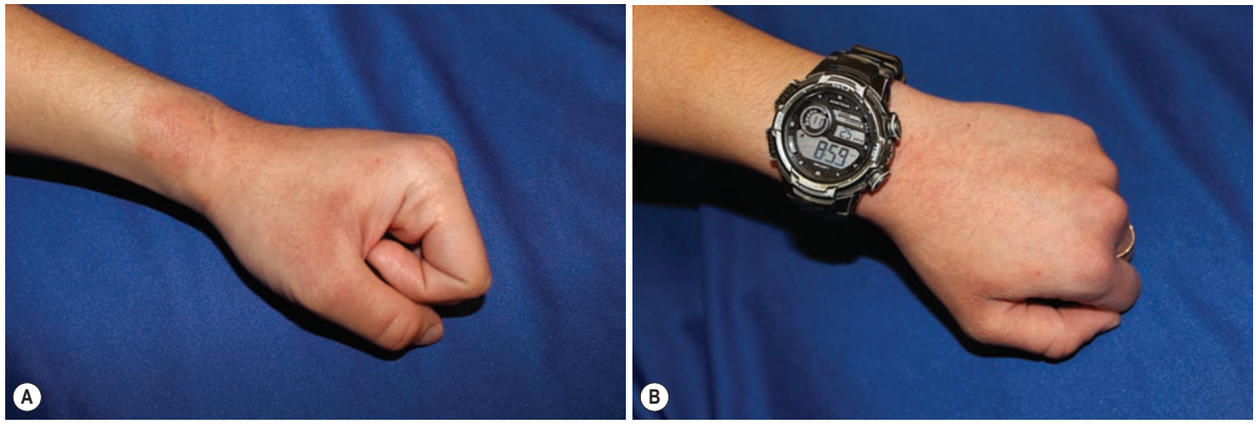


Fig. 3.59 Irritant contact dermatitis. **(A)** Tight watches or rings can trap sweat or water with detergent to cause irritation. **(B)** Allergic contact dermatitis might also be considered, but watch backs are largely stainless steel and do not contain releasable nickel or other components that can trigger allergic reactions.

The diagnosis of ACD is based on the appearance and distribution of skin lesions and aided when possible by a history of contact with an appropriate allergen (Table 3.4; see Table 3.3). Appearance on exposed areas only, linearity, and sharp edges are also clues to a reaction to a contactant, although ACD usually expands beyond the contact area in contrast to irritant contact dermatitis. For example, linearly distributed vesicles and bullae overlying erythema are typical of poison-ivy reactions. Dermatitis can appear at a distant site because of allergen transfer from one body site to another or by Òrecall reactions,Ó which are flares at sites of prior allergen exposure. Contact dermatitis can also occur from exposure of a child to a contact allergen from a family member *(connubial dermatitis)*. Particularly common are fragrances, hair products, and henna contaminated by paraphenyldiamine (PPD).[461D463]

Dermatitis on the eyelids, hands, feet, and legs is most commonly associated with positive reactions on patch testing. Eyelid dermatitis often results from preservatives in cosmetics, fragrances, or emollients applied to the hands. Shoe dermatitis occurs more often on the dorsal aspect of the feet; in children, the most common allergens are potassium dichromate, thimerosal, cobalt chloride, mercapto mix, colophonium, mercury, and nickel.[464] Subumbilical or earlobe dermatitis is typical of nickel contact allergy, and axillary-vault dermatitis should lead to investigation of sensitivity to deodorant or fragrances, whereas axillary dermatitis sparing the vault may relate to clothing dyes. Toilet seat dermatitis (buttock and posterior thighs) could result from ACD to essential oils, lacquer, or paint in a wooden toilet seat but now more commonly is irritant contact dermatitis from detergents or ACD to a cleansing component (Fig. 3.60) and responds well to treatment of the dermatitis followed by prevention with the use of toilet seat covers.[465] Occasionally, oral lichenoid reactions occur after ingestion of allergens. The histopathologic picture of ACD usually does not allow differentiation from primary irritant dermatitis or AD.

The acute lesions of ACD are characterized by intense erythema accompanied by edema, papules, vesiculation (sometimes bullae), oozing, and a sharp line of demarcation between involved and normal skin. In the subacute phase, vesiculation is less pronounced and is mixed with crusting, scaling, and thickening of the skin. Chronic lesions, conversely, are characterized by licheniPcation, Pssuring, scaling, and little or no vesiculation.

Table 3.4 Distribution of Dermatitis and Possible Triggers

Localization	Triggers
Eyelids	Cosmetics, emollients (hands), fragrances, hair dyes, metals, nail products
Hairline, postauricular, ear helix	Hair dyes, hair products
Earlobes, neck	Fragrance, metal jewelry
Periaxillary	Textile dyes, formaldehyde and formaldehyde releasers
Axillary vault	Deodorants
Subumbilical	Metal (snaps, belt buckles)
Extremities, linear streaks	Poison ivy and oak, phytophotodermatitis
Plantar aspect of feet	Adhesive, rubber in shoes
Dorsal aspect of feet	Leather (chromates, dyes), rubber, adhesive

Autosensitization Dermatitis or Id Reaction

Id reaction (autosensitization dermatitis, autoeczematization) describes a hypersensitivity disorder characterized by the acute onset of small edematous papules or papulovesicles. Id reactions to nickel are

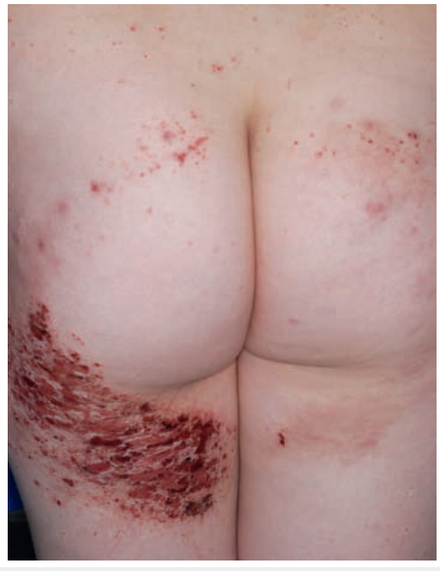


Fig. 3.60 Toilet seat dermatitis. This boy's mother used wipes with iodopropynyl butylcarbamates and fragrance to clean the seat. The dermatitis cleared after a switch to dilute bleach water.

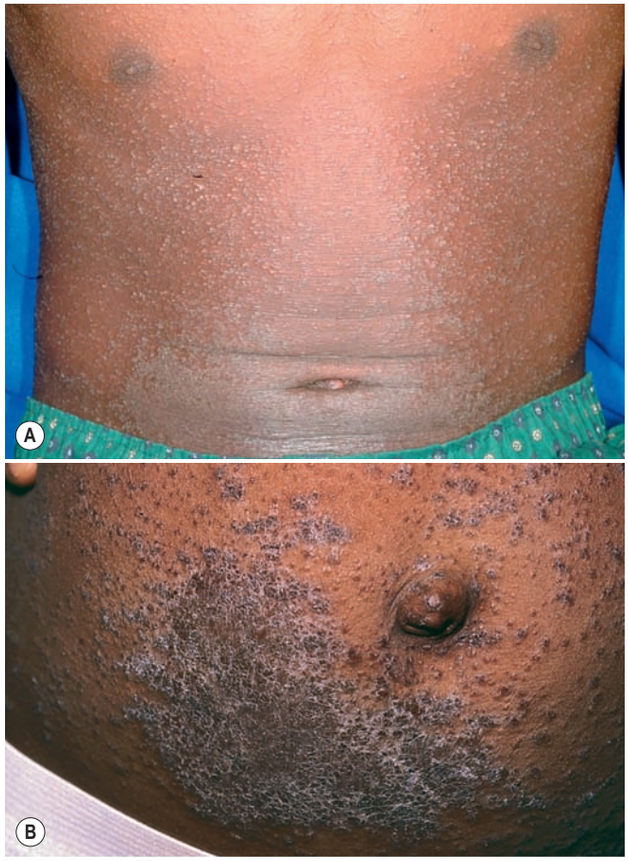


Fig. 3.61 Nickel contact dermatitis with id reaction. **(A)** Note the characteristic subumbilical (or periumbilical) hyperpigmented plaque of dermatitis in this patient with nickel contact dermatitis. **(B)** The lichenification and hyperpigmentation indicate a chronic dermatitis. The tiny discrete papules seen around the plaque extend across the entire trunk and represent an id reaction to the dermatitis.

found in up to 50% of patients[466] and may appear on the trunk (Fig. 3.61), forearms, flexor aspects of the upper arms, and extensor aspects of the upper arms and thighs and, less commonly, the face. The eruption is nearly always symmetric but may demonstrate light sensitivity or an isomorphic response (the Koebner phenomenon), in which trauma elicits new lesions. Lesions are generally associated with moderate to severe pruritus. The disorder usually appears acutely over a few days and nearly always is preceded by an exacerbation of the preexisting dermatitis by infection, rubbing, or inappropriate therapy. The acute eruption may subside spontaneously in a few weeks if the primary dermatitis is controlled. Relapses, however, are common, particularly when the initial local lesion flares and is followed by a further disseminated eruption.

The diagnosis of id reaction is made clinically on the basis of a generalized papulovesicular eruption that develops in the wake of preexisting eczematoid dermatitis. Treatment depends on the use of open wet compresses, antihistamines, and topical corticosteroid preparations. Control of the primary lesion is critical to prevent further or recurrent antigenic stimulation. Although seldom indicated, a 2- to 3-week course of systemic corticosteroids may at times be necessary in cases unresponsive to more conservative therapy.

Id reactions may also be seen in response to infectious agents, particularly in bacterial and dermatophyte infections. The tiny papules of the id reaction associated with tinea capitis most commonly are localized to the head and neck. Often, the id reaction of tinea capitis occurs after initiation of treatment with oral antifungal agents and is erroneously considered to be a drug reaction. Recognition of the underlying infection and continuing the antimicrobial treatment is critical for clearance.

Table 3.5 Allergen Components in the Commercially Available T.R.U.E. Test Kit

Panel 1.2	Panel 2.2	Panel 3.2
Nickel sulfate	p-tert-butylphenol formaldehyde resin	Diazolidinyl urea
Wool alcohol (lanolin)	Epoxy resin	Quinoline mix
Neomycin sulfate	Carba mix	Tixocortol-21-pivalate
Potassium dichromate	Black rubber mix	Gold sodium thiosulfate
Caine mix	Cl^+ Me^- isothiazolinone (MCI/MI)	Imidazolidinyl urea
Fragrance mix	Quaternium-15	Budesonide
Colophony	Methyldibromo glutaronitrile	Hydrocortisone 17-butyrate
Paraben mix	p-phenylenediamine	Mercaptobenzothiazole
Negative control	Formaldehyde	Bacitracin
Balsam of Peru	Mercapto mix	Parthenolide
Ethylenediamine dihydrochloride	Thimerosal	Disperse blue 106
Cobalt dichloride	Thiuram mix	Bronopol

T.R.U.E., Thin-Layer Rapid Use Epicutaneous.

Patch Testing

Patch tests may be used to confirm the diagnosis of ACD if a specific agent is suspected, even in young children.[467] Different panels of antigens for patch testing are available in Europe, the United States, and Japan, which has led to efforts to standardize testing internationally. In the United States, the Thin-Layer Rapid Use Epicutaneous (T.R.U.E.) patch test kit (Allerderm; http://www.truetest.com) is commercially available and has been expanded to 36 allergens (Table 3.5). These test kits have allergens for reactivity against the most common contact allergens measured and preloaded onto hypoallergenic tape for easy use; however, the potential allergens are not inclusive and lack flexibility. Of the most relevant allergens in children,[468] dialkyl thioureas and CAPB are not found in the latest T.R.U.E. test kits. Also, although MCI/MI is in this kit, MI alone is not but is often positive (and thus missed).[469] A Pediatric Dermatology Workgroup of the American Contact Dermatitis Society designated the 38 most important allergens for testing in children 6 to 17 years of age (FDA-approved ages for patch testing), noting that a typical back of a child can hold 40 to 60 patches.[470] Of these 38, 15 are not included (or are only partially represented) in the T.R.U.E. test kits at this time.[471] The North American Contact Dermatitis Group (NACDG) and American Contact Dermatitis Society screening allergen series are more extensive sets of test substances.[472] Among these 38, the ones most likely to cause ACD per the Pediatric Contact Dermatitis Registry are nickel (13.0%), fragrance (9.4%), Balsam of Peru (6.5%), propylene glycol (5.0%), bacitracin and CAPB (both 4.6%), and neomycin and formaldehyde (both 4.4%). A list of 21 key allergens for testing in preschool children has also been published.[473]

When patch testing is performed, patches should be placed on grossly normal, nonhairy skin such as the back or volar forearm.[474] Distraction techniques such as having the child watch a video are very useful, particularly for testing smaller children.[475] Patch testing should be deferred in the presence of extensive active dermatitis; false-positive reactions may be obtained, and a strongly positive patch-test reaction may cause acute exacerbation of the dermatitis. Antihistamines affect type I reactions and not type IV reactions; thus their administration is not a contraindication to patch testing. Systemic corticosteroid and immunosuppressive therapy might mask patch-test responses, and it is preferable that oral steroids be discontinued at least 3 weeks before patch testing. Potent topical steroids have also

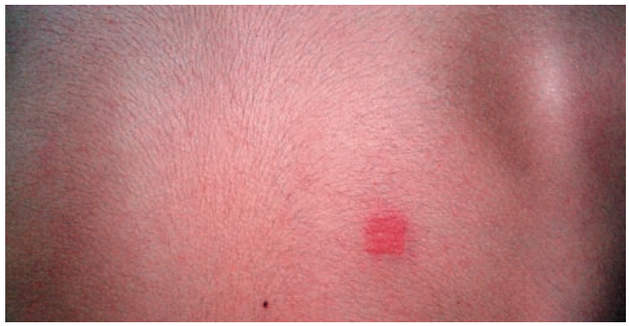


Fig. 3.62 Patch testing. Positive patch test reaction to p-tert-butylphenol formaldehyde resin in a patient with shoe dermatitis because of reactivity to the glue (see Fig. 3.71).

been shown to suppress patch-test reactivity[476] and should be avoided at the site of testing for 1 week before patch testing.

Patch tests generally should be kept in place for 48 hours, and a reading can be made after an interval of 20 to 60 minutes after removal of the patch to allow the skin to recover from the effects of pressure and occlusion (Fig. 3.62). The patch or its removal may produce mild transient erythema or a temporary blanching effect, resulting in false reactions.

Reactions are graded based on redness, induration, and presence of blistering. Unless testing for weak sensitizers (such as fabrics or cosmetics), a doubtful reaction (faint macular erythema only) is usually of no signiÞcance. A 1 plus (1+) reaction is characterized by erythema, inÞltration, and possibly papules. The addition of vesicles to this response indicates a 2 plus (2+) reaction, and a bullous reaction is read as 3 plus (3+). A second reading of the patches should be performed at 72 to 96 hours after the patches are placed. This reading distinguishes irritant from allergic reactions, because irritant reactions often resolve after patches are removed, whereas allergic reactions increase in time. Delayed reading at 5 days or beyond may be needed for certain allergens (metals such as nickel, cobalt, potassium dichromate, and gold; topical antibiotics such as neomycin and bacitracin; topical corticosteroids; PPD). In one study 66% of children had a positive reaction at 48 hours, 84% at 72 hours, and 50% between days 7 and 9; 13% only had delayed reactions to offending agents, stressing the need to include the late observation.[477]

Based on the results, families can learn more about speciÞc allergens at https://www.truetest.com/global/patientinfo.htm. The Contact Allergen Management Program (CAMP) of the American Contact Dermatitis Society provides detailed lists of products that patients are able to use through a website (https://www.contactderm.org/resources/acds-camp) and free app (https://www.contactderm.org/Þles/CAMP_App_User_Guide.pdf). It may also be advisable for patients to test a product on a limited area on the upper inner arm twice a day for 1 week (the repeat open application test [ROAT]).

Occasionally, positive reactions may have no clinical signiÞcance. In that case the reaction is termed *contact allergy* rather than ACD. Similarly, the offending material may not give rise to a positive reaction at the site of the test but may show a positive test if carried out on an area of skin closer to the point of the previously existing dermatitis. The value of patch tests is corroborative, and they should be used only as a guide in an attempt to conÞrm a suspected allergen. Scratch and intracutaneous tests are not useful in contact allergic dermatitis.

Poison Ivy (Rhus) Dermatitis

In the United States, poison ivy, poison oak, and poison sumac produce more cases of ACD than all other contactants combined.[478] The plants causing poison ivy dermatitis are included under the botanical term *Rhus* and are *Toxicodendron* species. Poison ivy and poison oak are the principal causes of *Rhus* dermatitis in the United States. Regardless of the speciÞc *Rhus* plant, the clinical appearance of the dermatitis may be identical. The *Rhus* group belongs to the family of plants known as Anacardiaceae, and cross reactions may occur. These include furniture lacquer derived from the Japanese lacquer tree, oil

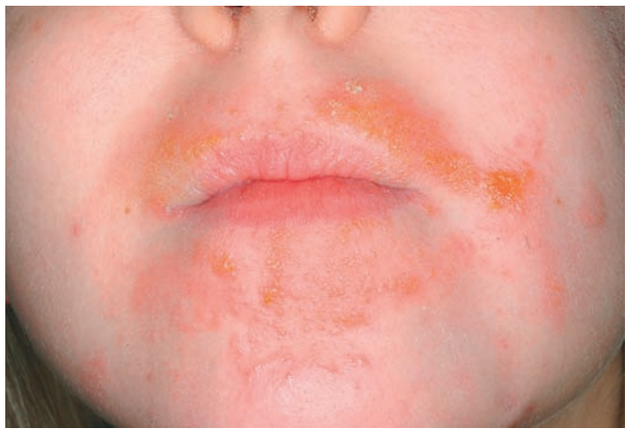


Fig. 3.63 Mango dermatitis. Individuals who react to *Rhus* family plants may demonstrate a perioral dermatitis after eating mango but only when in contact with the mango rind, not from the fruit itself.

Fig. 3.64 Poison ivy plant. A member of the *Rhus* family, showing three notched leaflets. (Courtesy Dr. Jon Dyer.)

from the shell of the cashew or Brazil nut, the fruit pulp of the gingko tree, and the marking nut tree of India, from which a black ÒinkÓused to mark apparel is produced. The ACD to this ink is termed *dhobi itch*. The rind of the mango also cross reacts, and the possibility of contact dermatitis to *Rhus* should be considered in children with perioral dermatitis after eating mango or on the hands of mango pickers[479] (Fig. 3.63).

The poison ivy plant (Fig. 3.64) characteristically shows three leaflets notched at the edge. It grows luxuriantly as a tall shrub or woody rope-like vine in vacant lots, among grasses, and on trees or fences throughout all sections of the United States except the extreme southwest. Poison sumac grows as a shrub or tree, never as a vine. It has 7 to 13 leaßets (arranged in pairs along a central stem), with a single leaßet at the end, is relatively uncommon, grows less abundantly, and is found only in woody or swampy areas primarily east of the Mississippi River. Poison oak, conversely, grows as an upright shrub, is most prominent on the West Coast, and is not a problem in the eastern United States. Although *Rhus* dermatitis is more common in the summer, the eruption may occur at any time of year by direct contact with the sensitizing allergen from the leaves, roots, or twigs of the plants.

The eruption produced by poison ivy and related plants is a delayed contact hypersensitivity reaction to an oleoresin (urushiol) of which the active sensitizing ingredient is a pentadecylcatechol. It is characterized by itching, redness, papules, vesicles, and bullae (Fig. 3.65).

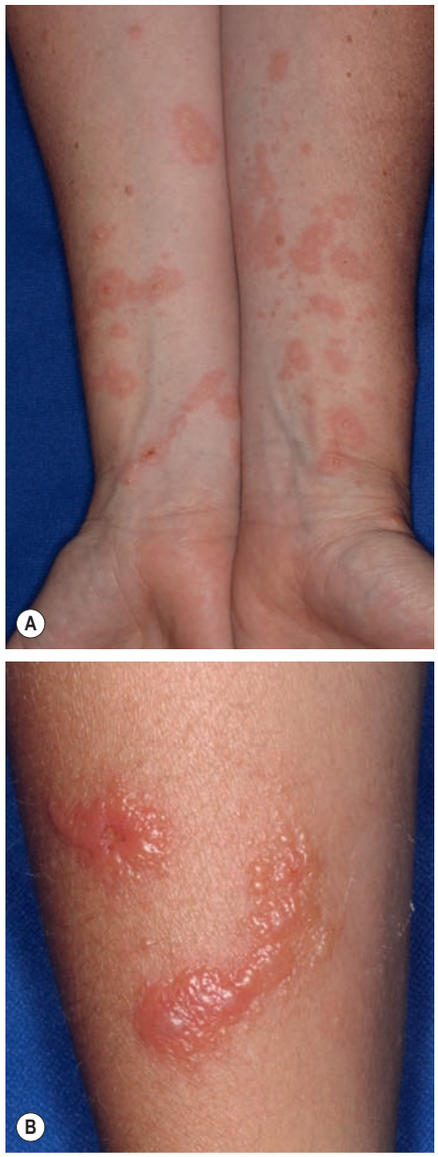


Fig. 3.65 (A) *Rhus* dermatitis with Koebner phenomenon. **(B)** A characteristic linear vesicular eruption on the forearms with poison ivy *(Rhus)* dermatitis.

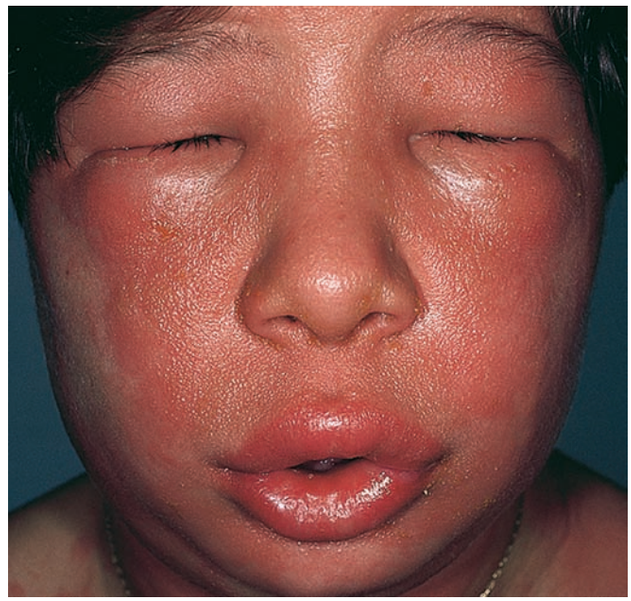


Fig. 3.66 *Rhus* dermatitis. The entire face may become swollen with *Rhus* dermatitis, especially if the patient was exposed through aerosolization. The fine vesiculation distinguishes contact dermatitis from angioedema.

Although often irregular and spotty, a linear distribution is highly characteristic because of scratching and transfer of the urushiol oleoresin (Koebner phenomenon). When contact is indirect, such as from a pet that has the oleoresin on its fur, the dermatitis is often diffuse, thus making the diagnosis more difficult unless the true nature of exposure is suspected. In the fall, when brush and leaves are burned, it must be remembered that the sensitizing oil may be vaporized and transmitted by smoke to exposed cutaneous surfaces, often presenting as a diffuse facial dermatitis with periorbital swelling (Fig. 3.66).

Rhus dermatitis usually first appears in susceptible, sensitized individuals within 1 to 3 days after contact with the sensitizing oleoresin; in highly sensitive individuals it may occur within 8 hours of exposure. Such temporal differences are probably the result of the degree of exposure, individual susceptibility, and variation in cutaneous reactivity of different body regions.

About 70% of the population of the United States would acquire *Rhus* dermatitis if exposed to the plants or the sensitizing oleoresin contained in its leaves, stems, and roots. The result is an acute eczematous eruption that, barring complications or reexposure to the offending allergen, persists for 1 to 3 weeks. Because the undiluted sap from plants of the *Toxicodendron* species turns black when exposed to dry surfaces and skin, dramatic black lacquer- or enamel-like deposits on the skin (“black spot poison ivy”) and clothing of individuals exposed to poison ivy or other urushiol-containing plants may rarely be seen.[480,481] These spots typically cannot be removed with soap and water and may precede the development of typical dermatitis.

The best prophylaxis, as with any type of ACD, is complete avoidance of the offending allergen. Patients should be instructed in how to recognize and avoid members of the poison *Rhus* group. When poison ivy is present in the garden or in children’s play areas, chemical destruction or physical removal is indicated. Heavy-duty vinyl gloves should be used if the plants are uprooted, because the urushiol is soluble in rubber and can penetrate latex gloves.[482] No topical measure is totally effective in the prevention of poison ivy dermatitis, but certain commercially available barrier preparations with quaternium-18 bentonite (organoclay) have been shown to diminish reactivity significantly (IvyBlock, StokoGard, Hollister Moisture Barrier, Hydropel).[483] Desensitization to the oleoresin of poison ivy by systemic administration of *Rhus* antigen is unreliable and should be reserved only for extremely sensitive individuals who cannot avoid repeated exposure to the antigen. Systemic reactions are not uncommon with the use of hyposensitization procedures.

In an effort to minimize the degree of dermatitis, individuals with known exposure should wash thoroughly with soap and water as rapidly as possible so that removal of the oil is accomplished, preferably within 5 to 10 minutes of exposure. If the oleoresin is not carefully removed shortly after exposure, the allergen may be transmitted by the fingers to other parts of the body (particularly the face, forearms, or male genitalia) (Fig. 3.67). However, the fluid content of vesicles and bullae is not contagious and does not produce new lesions. Thus unless the sensitizing antigen is still on the skin, the disorder is neither able to be spread on an individual nor contagious from one person to another.

Complete change of clothing is advisable, and whenever possible, contaminated shoes and clothing should be washed with soap and water or cold water mixed with alcohol to remove the urushiol. Harsh soaps and vigorous scrubbing offer no advantage over simple soaking and cool water. Thorough washing may not prevent a severe dermatitis

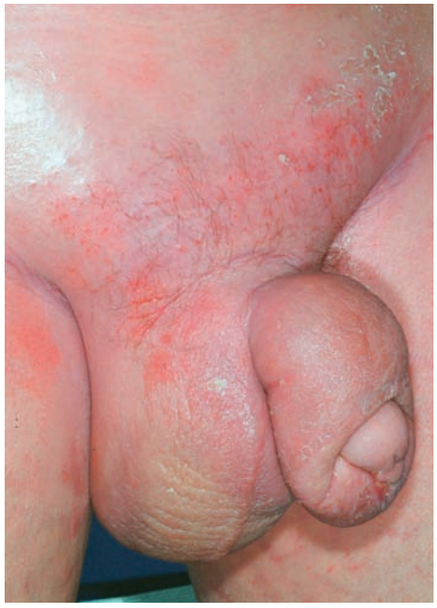


Fig. 3.67 *Rhus* dermatitis. The oleoresin may be transmitted by the fingers to other parts of the body, including the male genitalia.

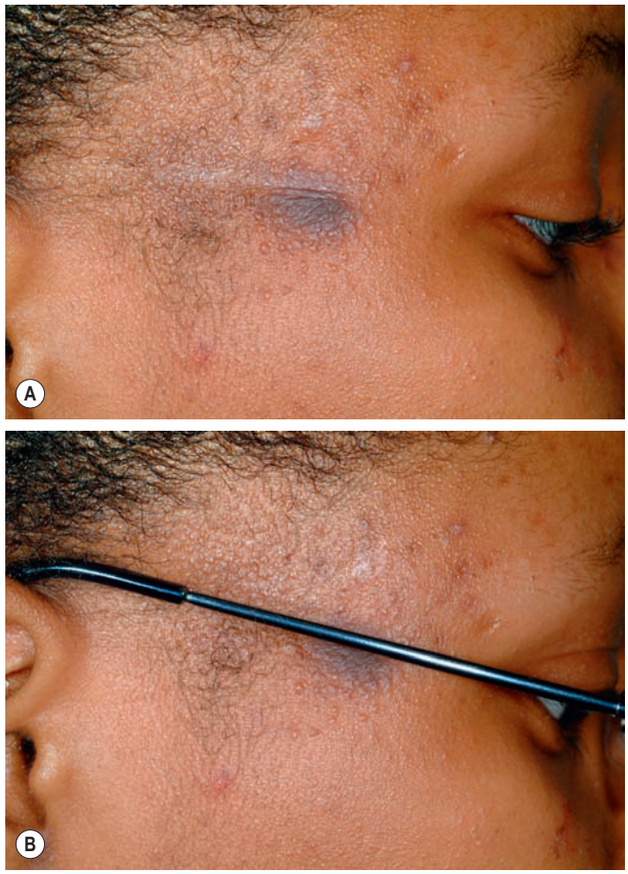


Fig. 3.68 Nickel contact dermatitis. This dermatitis **(A)** represents a reaction to nickel-containing eyeglass frames **(B)**.

in highly sensitive persons. It may, however, reduce the reaction and prevent spread of the oleoresin. When early washing is not feasible, it is worthwhile to wash at the first opportunity in an effort to remove any oleoresin remaining on the skin or clothing and thus prevent its transfer to other parts of the body.

In the management of mild *Rhus* dermatitis, treatment with an antipruritic "shake" lotion such as calamine lotion is helpful. Topical preparations containing potential sensitizers such as diphenhydramine or benzocaine should be avoided. As in other acute eczematous eruptions, cool compresses with plain tap water or Burow solution are soothing, help remove crusts, and relieve pruritus. Administration of potent topical corticosteroids and systemic use of antihistamines and antipruritic agents are helpful. Because the acutely involved areas tend to be vesicular and weeping, creams and lotion forms of topical steroids are more commonly used than occlusive ointments.

In severe, more generalized cases of *Rhus* dermatitis, short-term systemic corticosteroid treatment may be indicated. Systemic corticosteroid therapy may be initiated with dosages of 1 mg/kg per day of prednisone or its equivalent. Steroids should be tapered gradually over 2 to 3 weeks. Premature termination of systemic corticosteroids may result in a rapid rebound, with return of the dermatitis to its original intensity.

Metal and Metal Salt Dermatitis

Nickel dermatitis, the most common ACD to metal, is also by far the most common cause of contact allergy in children undergoing patch testing, with a prevalence of 10.3% to 40% in tested children worldwide.[455,468,484] Nickel may be added to other metals to increase metal strength (in chromium or cobalt) or as plating to increase attractiveness and durability (a variety of metals, including gold).

Earlobe dermatitis is a cardinal sign of nickel dermatitis. Ear piercing has repeatedly been shown to be a strong risk factor for both females[485] and males.[486] The current trend toward piercing of additional body areas in both males and females has increased the numbers of nickel-sensitive individuals. A positive family history of nickel ACD appears to be a risk factor.[466] Several studies have shown an increased risk of nickel sensitivity in girls (perhaps because of piercing).[487] Because piercing of ears or other sites is responsible for an increased tendency of sensitization to nickel and nickel products, piercing should be done with a stainless steel needle. Persons undergoing piercing should be advised to wear only stainless steel earrings or titanium earrings until the earlobes (or other sites) are completely healed, usually about 3 weeks. Although stainless steel contains up to 20% nickel, the nickel is bound tightly and usually causes no problems.

Prominent pruritic periumbilical and subumbilical papules should also trigger consideration of contact allergy to nickel from the nickel-containing buttons on pants and belt buckles and may present as recalcitrant lichenified plaques in children with AD.[488] Circular erythematous scaling patches on the midline trunk of infants may signal reactivity to the metal snaps in baby clothes, and at least 6% of the fasteners in children's clothing have been shown to release nickel ion.[489] Other potential triggers are zippers, clothing hooks, the dorsal eyelets on shoes, nickel-containing eyeglass rims (Fig. 3.68), shoe buckles, musical instruments,[490] razors,[491] gaming systems,[492] laptops,[493] tablets,[494] and cell phones and cell phone accessories.[495,496] Although the concentration of nickel in orthodontic appliances is low and has not been found to sensitize against nickel, patients who are already nickel sensitive, usually from exposure through ear piercing, rarely may show gingival reactions induced by the appliance[497]; the prevalence of reactions to orthodontic appliances is approximately 0.03%.[498] Students should be aware of the presence of nickel in seats with metal studs, which may lead to patches on the posterior thighs,[499] and metal ballet balance bars may lead to hand dermatitis. Hand dermatitis may also be associated with nickel allergy, because nickel may be present in the metal handles of scissors, keys, doorknobs, and the wheels of skateboards. Nickel coins in the United States no longer contain nickel, but small amounts are present in coins from other countries, and reactions to coin rolling or after coin ingestion by young children have been described.[500] Patch testing for nickel sensitivity can be performed, but false negatives are not uncommon, and repeated testing may be helpful. If a substance is suspected of

containing free nickel, application of a test solution of dimethylgloxime in a 10% aqueous solution of ammonia (Allerderm Ni kit) to the suspected item will usually cause the suspected metal to turn pink.

Once the presence of hypersensitivity to nickel has been established, the hypersensitivity usually lasts for years. Patients must therefore be taught how to avoid contact with nickel objects through the use of proper substitutes. If possible, wearing clothes with nickel should be avoided, and substitution of pants with elasticized waists for jeans with metal snaps and leather for metal belt buckles should be considered. Periodic coating of the offending metal with clear nail polish (including after each washing if laundered) may prevent loss of nickel, but sewing cloth over the nickel snap is not effective because sweating encourages nickel to leach through the fabric into contact with skin. In general, watches with stainless steel backs should be worn; application of an adhesive moleskin on the back of a watch may be helpful. Sterling silver or platinum jewelry is usually tolerated. Nickel-free eyeglass frames are available. The majority of inexpensive earrings contain some nickel,[501] so that individuals with the allergy should wear only surgical stainless steel earrings, ÒhypoallergenicÓ earrings with titanium (which looks like platinum), or earrings with plastic casings (Blomdahl, Simply Whispers). Vinyl gloves can be worn by patients who are sensitive to nickel to avoid hand contact with nickel. Mid- to high-potency topical steroids can be used to treat a reaction, but avoidance of nickel is required for full efÞcacy. Dietary avoidance of nickel is difÞcult but has been recommended by some authors in patients with severe nickel-induced hand ACD and those with systemic contact dermatitis who do not respond to avoidance. Foods with high nickel content include canned foods, chocolate, cocoa, soybeans, cashews, almonds, oatmeal, legumes, and several types of Þsh and shellÞsh.

Chromates are an ingredient in the manufacture of many products such as cement, mortar, leather, paints, and anticorrosives. They are used in the dye of the green felt fabric used for pool tables and the yellow-green pigment of tattoos and cosmetics. Dichromates are used to toughen the collagen in leather and allow it to resist wear, water, and changes because of heat. Most contact reactions in children that are caused by chromates manifest as shoe dermatitis (see Shoe Dermatitis section).

Cobalt blue pigment is found in glass and pottery and used in the blue and green of watercolor paints and crayons. It is inextricably linked to nickel in metal-plated objects and costume jewelry, and it can be found in cosmetics, joint replacements, and cement. Oral administration of vitamin B_{12}, which also contains cobalt, can cause intractable hand eczema, and injection may lead to dermatitis at the injection site in individuals who are sensitive to cobalt.

Allergic reactions to aluminum (Al) are probably not rare and develop most often from vaccination with Al-adsorbed vaccines, including those for diphtheria, tetanus, and pertussis; *Haemophilus influenza*; pneumococcus; hepatitis A and B; and human papillomavirus.[502,503] Children most commonly present with intensely itchy subcutaneous nodules or indurations localized to the site on the anterolateral thigh from 3 weeks to 4 years after the vaccination. Exacerbation of the itching may occur with intercurrent upper respiratory or GI tract infections, sometimes as a prodromal sign. These itchy indurated areas persist for a median duration of 4.6 years. In one study patch testing with aluminum showed reactivity in 95% of those affected, and almost 20% of these reported ACD after exposure to Al-containing deodorants, cosmetics, sunscreens, emollients, and buttons.[503] Other contactants that contain aluminum are Al-precipitated pollen extracts used for allergen-speciÞc immunotherapy, ear drops, and pigments used in tattooing. More than 90% of children with these reactive lesions had milder reactions after vaccines beyond infancy, suggesting that the value of continued vaccination outweighs the risk of avoidance of Al-adsorbed vaccines.

Shoe Dermatitis

Shoe dermatitis is an extremely common form of contact dermatitis in childhood that usually results from rubber products, especially given the increasing trend for athletic shoes. It is commonly misdiagnosed as tinea pedis, a disorder that occurs uncommonly in children before puberty. In one study, more than 50% of children with foot dermatitis showed reactivity to suspected contact allergens.[504]

Shoe dermatitis usually begins on the dorsal surface of the base of the great toe. It may remain localized or spread to involve the dorsal surfaces of the feet and other toes. The thick skin of the plantar surfaces is generally more resistant but may demonstrate dermatitis over the sole, ventral surface of the toes, instep, or even the entire plantar surface that may be confused with juvenile plantar dermatosis or psoriasis. Erythema, licheniÞcation, and, in severe cases, weeping and crusting are typical, but the interdigital spaces usually are spared. In contrast, maceration, scaling, and occasional vesiculation of the interdigital webs, particularly between the fourth and Þfth toes, are usually seen with tinea pedis. Irritant dermatitis from friction and illÞtting shoes may also sharply localize to the dorsal aspects of the toes.

Rubber components are the principal allergens[505]; these include accelerators (most commonly mercaptobenzothiazole but also thiuram, carbamate, and diphenylguanidine) and rubber antioxidants. Rubber accelerators facilitate the transformation of liquid rubber to solid. Several components of the approved patch-test kit in the United States test for rubber, including the carba mix, the black rubber mix, mercaptobenzothiazole, mercapto mix, and the thiuram mix (see Table 3.5); however, additional testing should be performed if shoe dermatitis is suspected but an agent is not found in this standard kit, because it is not fully inclusive. Rubber is a common component of the insoles of shoes and particularly of box toes. Rubber cement may be used in joining shoe uppers, outer leather, and linings.

Individuals with rubber sensitivity may also react to exposure to paciÞers (perioral); wearing latex gloves or handling rubber bands or balloons (hand dermatitis); wearing underwear, swimwear, and socks with elastic (especially if clothes are bleached; waist and inguinal areas); handling rubber handle grips (sweaty hands)[505]; wearing swim goggles (periorbital); using cosmetic applicators (face); and wearing adhesive bandages. In adolescent boys and men, penile contact dermatitis may result from wearing rubber condoms.

Neoprene is a form of rubber in which dialkyl thioureas are used to speed up vulcanization, making it tougher and more pliable for shaping. It is now widely used in sporting equipment, mouse pads and computer cases, wetsuits, athletic shoes, shin guards and other protective pads, orthopedic braces, leggings, and Halloween masks. Components of neoprene-containing items that cause ACD are diethyl thiourea (a dialkyl thiourea that is not in the T.R.U.E. test) and p-tertiary (tert)Dbutylphenol formaldehyde resin in adhesive.[507]

Less commonly, chromates in leather and adhesives (colophony and p-tert-butylphenol formaldehyde resin) can cause foot dermatitis (Fig. 3.69). p-tert-butylphenol formaldehyde resin has also recently been implicated in ACD from the foam padding of a bra.[508] The nickel in eyelets and arch supports should also be considered. Iatrogenic ACD

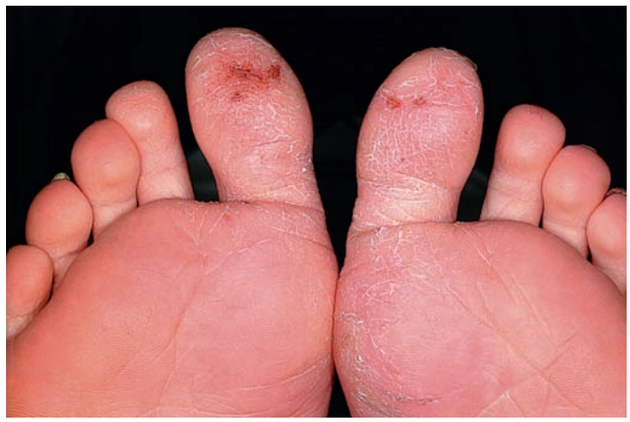


Fig. 3.69 Shoe dermatitis. The recalcitrance of this patient's dermatitis to potent topical steroids led to patch testing, which showed reactivity to p-tert-butylphenol formaldehyde resin (see Fig. 3.64), a component of the glue used in shoes. More commonly, shoe dermatitis is seen on the dorsal aspect of the feet and results from rubber products in shoes or chromates used to tan the leather.

also often occurs on the foot, particularly because of neomycin or bacitracin in topical antibiotics.[509] Hyperhidrosis and wearing of occlusive hosiery and shoes contribute to shoe-contact allergy by leaching out allergens and increasing their percutaneous penetration.

Patients with shoe sensitivity should avoid the offending allergen and control associated hyperhidrosis. Use of shoe substitutes depends on whether the reactivity is to rubber, chromates, or adhesives. Vegetable-tanned footwear is a substitute if reactivity is to chromates. Open sandals, unlined sewn leather moccasins (such as from L.L. Bean), wooden clogs, or plastic ÒjellyÓ sandals are other alternatives. In addition, polyvinyl shoes, although they increase the tendency to perspiration, commonly lack many of the potential sensitizers seen in regular shoes; Bass Weejuns loafers and vinyl tennis shoes may also be acceptable substitutes. Because the inner sole is a common source of contact sensitization, removal and replacement with cork insoles, Dr. Scholl® Air Foam pads, or Johnson® Odor-Eaters held in place with a nonrubber adhesive such as Elmer® glue are often helpful.

The management of active shoe dermatitis, as in other eczematous disorders, is aided by use of open wet compresses, topical corticosteroids, and antipruritic agents. Because hyperhidrosis is usually responsible for the ÒleachingÓ out of potential sensitizing agents, use of measures that minimize excessive perspiration of the feet is advisable. Athletic equipment can be lined with water-repellent canvas as an adjunct to the use of a protective sock or sleeve. The topical use of aluminum chloride, available as Drysol or Certain Dri, or tannic acid soaks (two teabags in 1 quart of water) once or twice weekly, often assist in the control of hyperhidrosis. Noncaking agents such as Zeasorb powder dusted freely into shoes and hosiery not only tend to lessen perspiration but also may act as a mechanical barrier, thus limiting contact with potential allergens and irritants. When painful fissures are present, soaking the foot in water for 20 minutes at bedtime followed by the careful application of superglue or liquid adhesive into the fissured areas, the use of topical corticosteroids and emollient creams, and occlusion at night with plastic wrap or small plastic bags will hasten resolution and lessen discomfort. Barrier socks (Microair), which have three layers of fabric that provide a physical barrier and are breathable, have been helpful in decreasing reactions if exposure cannot be avoided.[510] Individuals with rubber allergy should wear vinyl rather than rubber gloves and avoid bleaching clothes with elastic and using rubber swim goggles, rubber headphones, and latex condoms.

Dermatitis to Cosmetics and Topical Medications

The most common cosmetic agents causing ACD are lipsticks, antiperspirants, hair dyes with PPD, substances in commercial and home permanent wave formulations, lanolins, acrylics, nail lacquers, benzalkonium and ascorbic acid in contact-lens solutions, fragrances (perfumes), sunscreen components (particularly benzophenone and increasingly octocrylene), and a number of preservatives used in cosmetics and shampoos. These allergens are the most common triggers of ACD of the hands.[511] Because early use of cosmetics abets this problem, it is recommended that cosmetics be avoided in young children. Even ÒtoyÓ cosmetics contain fragrance, particularly cinnamic aldehyde.[512] In many instances the eyelids are affected not by cosmetics applied to the lids and lashes but by preparations applied to the scalp, face, and nails. Exposure to peppermint oil most commonly leads to perioral dermatitis.[513] Peppermint oil is found in cosmeceuticals, personal hygiene products (mouthwashes, toothpastes, and bath preparation), topical medications (cooling sensation), and food.

ACD is increasingly blamed on preservatives and vehicle components.[514] MCI/MI (Kathon CG)[515] and MI alone[515] are used as preservatives in baby shampoos, soaps, wet wipes, and protective creams. The dermatitis usually manifests on the face, perianal/buttock area, or hands and resists topical and oral antibiotics and corticosteroids. One study found that MCI/MI ranked third in positive patch-testing results in pediatric patients.[516,517] Lesions from MCI/MI on the buttock may be confused with baboon syndrome, which is characterized by well-defined symmetric erythema on the buttocks and sometimes on the upper thighs and axillae and usually is related to oral drug ingestion.[518] Recent studies found that testing to higher concentrations of MCI/MI as well as to MI alone is necessary to detect ACD to MCI or MI.[519] However, the T.R.U.E. test identifies only the MCI/MI mix at lower concentration.

Another common cause of fingertip and facial dermatitis is CAPB, a surfactant contained in many no-tears shampoos and soaps, contact-lens solutions, and moist baby and facial wipes. CAPB reactivity has been found in 11.3% children who have undergone patch testing.[468,520]

Formaldehyde and formaldehyde releasers (such as quaternium-15, diazolidinyl or imidazolidinyl urea, bromonitropropanediol/bronopol, and dimethylol dimethyl hydantoin)[514] are other preservatives that may trigger contact allergy. A reaction to tosylamide/formaldehyde resin in nail polish is seen largely in female patients who paint their nails[521] but has been described in boys, including from application to the nails as a deterrent to nail biting.[522] Dermatitis tends to occur on the eyelids, cheeks, lips, chin, and neck, rather than on the nails themselves. Although the incidence of lanolin sensitivity from emollients is low, lanolin and its derivatives may be present under many different names (e.g., wool wax, wool grease, and wool fat). Lanolin sensitivity should be suspected in children with AD who tolerate application of petrolatum but not the application of lanolin-containing emollients, such as Aquaphor or Eucerin.

In the United States, parabens (compounds containing p-hydroxybenzoic acid) are often added in low concentrations to creams, lotions, and cosmetics in an attempt to retard microbial growth; although possible allergens, they are much weaker than other preservatives such as MCI/MI, CAPB, and formaldehyde/formaldehyde releasers and, in fact, were named the nonallergen of the year in 2019 by the American Contact Dermatitis Society.[523] Thimerosal is an organic mercurial compound used as a preservative. It has largely been removed from vaccines but can be found in cosmetics, eye drops, and contact-lens solutions. Although positive patch testing to thimerosal may occur, reactivity is unlikely to be clinically relevant, and rates of sensitization will likely decline with the removal of thimerosal from many vaccines.[524] Although still in the T.R.U.E. test kit, the NACDG has removed thimerosal from their standard testing trays because of its low clinical relevance.

More than 5000 different fragrances are in use today, and the ingredient ÒfragranceÓ on a label represents a mixture of many. Reactivity to fragrance has been shown to increase with age.[525] Use of perfumes in adolescent girls has been associated with the Òatomizer sign,Ó the presence of primary dermatitis at the Adam® apple where the perfume is sprayed.[526] Deodorants can be triggers for ACD in the axillary vault and generally cause an eczematous dermatitis (see Metal and Metal Salt Dermatitis section); inclusion of sandalwood and ylang ylang oils in some deodorants encourages sensitization through shaved axillae. Antiperspirants containing zirconium may produce allergic granulomatous reactions. If near the axillary area but not in the vault, disperse dye in clothing is the most likely cause of the reactivity (see Clothing Dermatitis section). Even baby washes and shampoos have fragrance as a component. ÒUnscentedÓ or Òfragrance-freeÓ means that the product has no perceptible odor but does not necessarily mean devoid of fragrance chemicals; it may just reflect the addition of masking agents. Furthermore, manufacturers are not required in the United States to list specific fragrances and often do not list essential oils and fragrances used for reasons other than aroma (e.g., preservatives, bisabolol, citrus oil). Testing to both fragrance mix and balsam of Peru captures 70% to 80% of fragrance allergies. True fragrance-free products are available.[527]

The most common allergy-containing fragrances are cinnamic alcohol and cinnamic aldehyde, which are among the eight components of the fragrance mix used in contact allergy testing. Cinnamic alcohol and cinnamic aldehyde are components of chewing gums, toothpaste, mouthwash, flavored lip balms, chewable vitamins,[528] detergents, soaps, and deodorants.[529] Other fragrances are used in perfumes, aftershaves, colognes, and even food flavorings. Reactions to fragrance mix were noted in 18% of 500 children in a study in the United Kingdom.[456]

Balsam of Peru (*Myroxylon pereirae* tree extract) is an oleoresin that may contain some of the fragrances in the fragrance mix as well as a range of other components (such as citrus peel, tea tree oil, benzoic acid, and others). Individuals who react to balsam of Peru may react to beeswax, colophony, various spices, turpentine, and coumarin. Balsam of Peru is found in many body washes, shampoos, and diaper area topical products. Balsam of Peru cross reacts with other balsam derivatives, such as balsam of pine, which is found in fluocinolone oil.[530] Its presence as a flavoring in citrus peel and spices (e.g., cinnamon, cloves, vanilla, nutmeg, paprika, and curry) has led to systemic contact dermatitis reactions to citrus products, spices, pickles, chocolate,

Table 3.6 Classification of Topical Corticosteroids Based on Chemical Structure and Cross Reactivity

Group A	Group B	Group C	Group D1	Group D2
Hydrocortisone acetate	Amcinonide	Desoximethasone	Alclometasone	Difluoprednate
Methylprednisolone	Budesonide*	Dexamethasone	Beclomethasone	Hydrocortisone 17-butyrate*
Prednisolone	Desonide	Diflucortolone	Betamethasone dipropionate	Prednicarbate
Tixocortol-21-pivalate*	Fluocinolone	Fluocortolone	Betamethasone 17-valerate	
	Fluocinonide	Halometasone	Clobetasol	
	Halcinonide		Diflorasone	
	Triamcinolone		Fluticasone	
			Mometasone	

*Used to test reactivity.

wine, and colas[531]; avoidance of ketchup in affected children can lead to marked clearance of widespread, recalcitrant dermatitis.[532] Balsam of Peru also cross reacts with a chemical in Mastisol, often used to increase adhesive adherence

A variety of topical prescription and over-the-counter formulations are capable of producing contact and (at times) systemic contact reactions. Of these, ethylenediamine, benzocaine and its derivatives, topical antibiotics, and topical preparations with diphenhydramine are the most common. Topical application of diphenhydramine (such as in Caladryl) is generally frowned on because it reportedly could cause sensitization and lead to a generalized reaction after systemic administration of diphenhydramine, but occurrence is exceedingly rare. In addition, application of over-the-counter topical antibiotics may cause contact dermatitis and may lead to worsening of cutaneous inflammation despite appropriate use. Neomycin sulfate has long been considered the most allergenic of the topical antibiotics, but bacitracin allergy now exceeds it in prevalence in some studies, and anaphylactic reactions to topical application of bacitracin have been described[533]; both are ingredients in "triple antibiotic" formulations. Although neomycin and bacitracin are not chemically related, both bacitracin and neomycin cosensitization may occur concurrently when topical antibiotics with both are applied. Fusidic acid is an antibiotic used topically outside the United States that can cause both ACD and anaphylaxis after topical application.[534] Recently, ACD to potassium peroxymonosulfate, used as a chemical shock treatment for hot tubs and swimming pools to clear the water, has been described.[535]

Ethylenediamine, a compound stabilizer seen in various topical creams, including with nystatin cream, cross reacts with certain antihistamines, among them hydroxyzine and promethazine hydrochloride. Ingestion of a cross-reacting oral antihistamine in an ethylenediamine-sensitive individual can cause generalized dermatitis[536]; systemic contact dermatitis may also occur from administration of hydroxyzine but without reactivity to ethylenediamine.

The trend in adolescents of hair streaking and dyeing and henna tattoos has increased exposure to dyes containing PPD. In addition to typical contact allergic dermatitis, these reactions to PPD may resemble erythema multiforme or vesicular erythema multiforme.[537] Because of the tendency to use PPD in the mixture to darken and increase the precision of design of the temporary henna tattoo, children may show ACD to PPD at any site of henna tattooing.[452,538] Henna itself is rarely a sensitizer. Concentrations of PPD as high as 17.5% have been found in henna-tattoo preparations despite the limit of 6% PPD allowed in hair dyes. Once sensitized to PPD after a henna tattoo, children not only have a lifelong potential reactivity to permanent oxidative hair dye[539] but also may show systemic contact dermatitis to components that cross react with PPD such as hydrochlorothiazide, sulfonamide medications, and ester anesthetics such as benzocaine.[540] PPD may be a component of fur dyes, dark-colored cosmetics, inks, rubber products, and photographic supplies. PPD reactions in children may also occur because of "connubial dermatitis," in which a child is sensitized through contact with the product on a parent.[463]

ACD from topical corticosteroids has been increasing in incidence and should be considered when patients with dermatitis are worsening despite the application of topical steroids.[541] Sensitization can also occur from ophthalmic solutions and aerosolized inhaled corticosteroids.[542] Reactions to topical steroids can be anywhere, but typically those from ophthalmic solutions involve the conjunctivae, eyelids, and periorbital areas, whereas ACD to inhaled steroids is usually on the face, sometimes with extension. Generalized eruptions may occur after systemic exposure to a cross-reacting steroid. Five groups of corticosteroids have been classified based on their chemical structures (A, B, C, D1, and D2) (Table 3.6). Sensitization to group A steroids (in over-the-counter hydrocortisone and oral prednisone) is highest (overall 5.72%).[543] Topical steroids can be screened by ROAT on the forearm. Tixocortol pivalate, budesonide, and hydrocortisone 17-butyrate are used to test for allergy to topical corticosteroids, although the combination of tixocortol pivalate and budesonide detect almost 90% of the patients with corticosteroid allergies. Positive reactions to topical steroids may not be detectable until 5 days or more after patching. The majority of individuals who test positive to topical steroids have other positive patch tests as well, and it should be remembered that ACD may result from the excipient (e.g., preservative or penetration enhancer) or even the nickel from the tube, rather than the steroid itself.

Adhesive Tape Dermatitis

Although most cutaneous reactions related to the wearing of adhesive tape are of a mechanical rather than contact sensitivity type, allergic reactions may be caused by the rubber compounds (rubber accelerators or antioxidants) that have been incorporated into the adhesive or the vinyl backing of the adhesive (Fig. 3.70). Dermicel (Johnson &

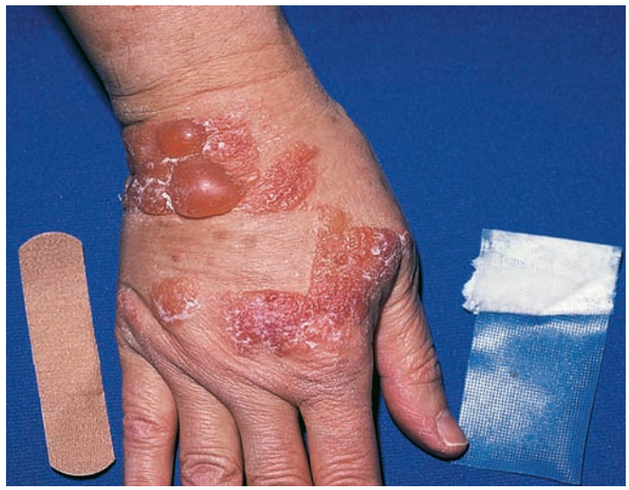


Fig. 3.70 Tape contact dermatitis. Note that this patient did not react to the cloth Band-Aid *(left)* but rather to the larger tape *(right)*.

Johnson), Steri-Strips, or Micropore surgical tape (3M Company), nonrubber acrylate, and spray-on bandages are helpful for those individuals allergic to or irritated by ordinary adhesive tapes. Nevertheless, acrylates in plastics are increasingly becoming an emerging allergen and can reach the skin without direct contact.

Clothing Dermatitis

Although nonspeciPc irritation from fabrics, rubber, dyes, and cleaning solutions is not uncommon, ACD caused by true sensitization to fabrics is occasionally seen in childhood. Permanent press and crease-resistant fabrics have been responsible for many cases of contact dermatitis because of the use of formaldehydes and formaldehyde-releasing preservatives. Of textiles, blended cottons, corduroy, silk, and rayon have the highest concentrations of formaldehyde, whereas polyester has the least. In a recent survey of 65 children suspected of having contact dermatitis, 7.5% reacted to formaldehyde and 3.8% to each of the listed formaldehyde-releasing preservatives.[468] This type of dermatitis is more likely to occur in individuals whose clothes are tight Ptting and close to the skin. The inner thighs, axillary lines, and popliteal fossae are particularly susceptible.

Dermatitis attributable to dyes in wearing apparel such as school and athletic uniforms is increased from clothing dyed black or dark blue (because the concentration of dyes in dark clothing is much higher than that of dyes in light-colored clothing, and dark colors tend to bleed more readily than dyes of lighter hue). Disperse dyes may be used in patch testing, but the garment can also be directly applied for patch testing. Children may also react to the epoxy resin in the adhesive holding a knee patch onto jeans and elastic or rubber waist bands in underwear in which the rubber components are leached out after exposure to bleach.

Compositae Dermatitis

Compositae is one of the largest plant families (10% of the worldÕs Sowering plants) and includes among its members chrysanthemum, ragweed, artichoke, sunSower, lettuce, spinach, chamomile, gingko, feverfew, parthenium, and dandelions. Contact allergy to compositae is well recognized in Sorists, gardeners, and farmers but only occasionally occurs in children.[544] Bisabolol, a compositae derivative, is a component of moisturizers and has been implicated in pediatric ACD.[545]

The complete list of 545 references for this chapter is available online at http://expertconsult.inkling.com.

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