CHAPTER 11

Atopic Dermatitis and Allergic Contact Dermatitis

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CHAPTER OUTLINE

SUMMARY OF IMPORTANT CONCEPTS

- Atopic dermatitis is the most common chronic skin disease of young children, with lifetime prevalence in US schoolchildren of up to 17%.
- Abnormal skin barrier differentiation and immune response genes play key roles in atopic dermatitis.
- Colonization and infection by microbial organisms (e.g., *Staphylococcus aureus*, herpes simplex virus) in atopic dermatitis patients reflect its complex skin pathophysiology.
- Treatment for most patients with chronic atopic dermatitis includes avoidance of irritants and allergens, hydration and moisturizers to maintain a healthy epidermis, antimicrobial therapy for acute infections, and topical anti-inflammatory agents

(e.g., corticosteroids, calcineurin inhibitors). Systemic immunomodulatory agents should be reserved for patients with recalcitrant disease.

- Because non-lesional skin in atopic dermatitis patients is not normal with respect to skin barrier and immune abnormalities, proactive (maintenance) therapy may be appropriate for a subgroup of patients with relapsing disease.

INTRODUCTION

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease usually associated with respiratory allergy.[1] In the 1930s, Hill and Sulzberger[2] suggested the name 'atopic dermatitis' to describe both the weeping eczema of early childhood and the chronic xerosis and lichenified lesions more typical of older patients. Before that time, however, a number of other terms were used to describe this disease, with the earliest illustrations consistent with AD dating back to the late 1700s and early 1800s (Fig. 11-1).[3] Of note, the term *atopic dermatitis* recognized the close relationship among AD, asthma, and allergic rhinitis. In support of this observation, in the largest cross-sectional study of a cohort of 2270 children with physician-confirmed AD, Kapoor and colleagues[4] showed that almost 66% had symptoms of at least one additional form of atopy (particularly asthma or allergic rhinitis) by the third year of life. Although significant progress has been made in the understanding of AD, its cause is still unknown, and much remains to be learned about the complex interrelationship of genetic, environmental, immunologic, and epidermal factors in this disease.[1,5]

HISTORICAL PERSPECTIVE

Descriptions of illness consistent with AD can be found dating back to the ancient Roman Empire. In the 1800s, clinical descriptions of skin disorders by Willan and others included terms such as *strophulus confertus*, *lichen agrius*, *porrigo larvalis*, and *eczema rubrum*, whose images are consistent with the diagnosis of AD on retrospective review. Besnier's *diathetic prurigo* established an association between pruritic skin disease and respiratory as well as gastrointestinal symptoms. The discovery of the concept of allergy in the early 1900s was followed by descriptions of 'atopy' in the 1920s, which in turn eventually led to introduction of the term 'atopic dermatitis' in the 1930s.[2] The role of allergens in AD was demonstrated by Tuft in the 1940s, whilst the role of *Staphylococcus aureus* was shown in the 1970s. The 1980s saw important insights into immune abnormalities associated with the disease, including recognition of the role of IgE

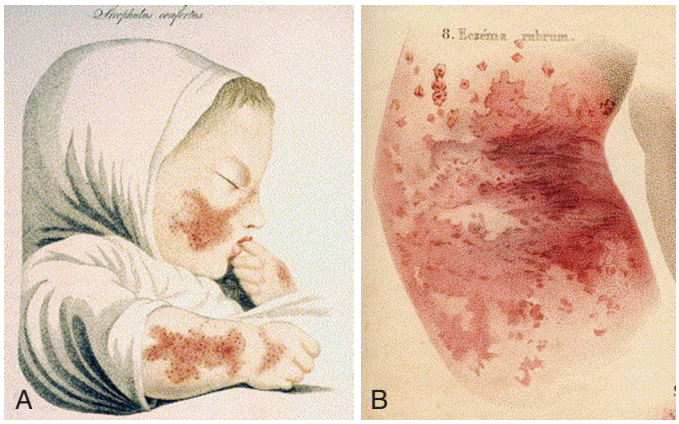

Figure 11-1 Early historical drawings of atopic dermatitis. **A.** Strophulus confertus, 1796; **B.** Eczema rubrum, 1835. *(From Wallach D, Coste J, Tilles G, Taïeb A. The first images of atopic dermatitis: an attempt at retrospective diagnosis in dermatology. J Am Acad Dermatol 2005;53:684–689.)*

molecules on epidermal Langerhans cells. In the 1990s, Leung and colleagues demonstrated a role for Th2 cytokines and staphylococcal toxins as novel allergens in AD as well as important immunologic distinctions between uninvolved, acutely involved, and chronically involved skin at the lesional level. In addition, the concept of T cell homing to the skin via a unique skin-selective receptor, cutaneous lymphocyte-associated antigen, was described in AD. The following decade started with the FDA's approval in 2000 of tacrolimus ointment, the first topical calcineurin inhibitor indicated for AD, described as "*a new milestone in the management of AD*." The publication of a landmark study in 2006 established a strong association between loss-of-function mutations in the gene encoding filaggrin, a skin barrier protein and risk for AD. Of note, the authors also found that mutations in the filaggrin gene were associated with increased risk for asthma in patients with AD, suggesting a mechanism for the atopic march. Further investigation into uninvolved skin in AD pointed to broad terminal differentiation abnormalities along with previously described immune abnormalities. These studies provided a rationale for a paradigm shift in treating AD patients with a relapsing course by changing from reactive to proactive management. Studies addressing both skin barrier and immune abnormalities, utilizing a molecular signature for AD provide a rationale for the next generation of biologic therapies in this disease.

EPIDEMIOLOGY

A number of studies suggest an increasing prevalence of AD. In Denmark, Schultz Larsen[6] demonstrated a cumulative incidence rate (up to 7 years) of 12% for twins born between 1975 and 1979 versus 3% for twins born from 1960 to 1964. A 1992 cross-sectional questionnaire confirmed this increased prevalence with a frequency of AD of 15.6% in 3000 children age 7 years from Denmark, Germany, and Sweden.[7] Questionnaire data from US schoolchildren age 5 to 9 years found a lifetime prevalence of AD up to 17%.[8] More recent data derived from the 2003 National Survey of Children's Health found prevalence ranging by state from 8.7% to 18.1% in a sample of 102 353 children age 17 years and younger.[9] A Japanese study used skin examinations rather than questionnaires to ascertain the prevalence of childhood and adolescent AD.[10] More than 7000 patients were examined, and AD was documented in 24% of those age 5 to 6 years; 19% of those 7 to 9 years; 15% of those 10 to 12 years; 14% of those 13 to 15; and 11% of those age 16 to 18 years. Importantly, the prevalence of AD in 9- to 12-year-old children was twice that in children of similar ages examined 20 years earlier, and for 18-year-old adolescents it was five times higher. A subsequent study in 23 719 children aged 6 to 7 and 11 to 12 years, examined by dermatologists in eight prefectures of Japan randomly selected from urban and rural districts, found a point prevalence of AD of 11.2% (7.4–15.0%).[11] Of the patients, 74% were classified with mild; 24% with moderate; 1.6% with severe; and 0.3% with more severe AD. Prevalence in the younger cohort was slightly higher than in the older patients (11.8% vs 10.5%; $p < 0.01$). No apparent difference was seen in prevalence between urban and rural districts or between boys and girls.

Increased exposure to pollutants and indoor allergens (especially house-dust mites) and a decline in breastfeeding, along with a greater awareness of AD, have been suggested as reasons for the increased frequency of AD.[12] In a prospective study, Zeiger and associates[13,14] found that restricting the pregnant mother's diet during the third trimester and lactation, and the child's diet during the first 2 years of life, resulted in decreased prevalence of AD in the prophylaxis group compared with a control group at age 12 months but not at 24 months. Follow-up through 7 years of age showed no difference between the prophylaxis and control groups for AD or respiratory allergy.[14] In a large study of an ethnically and socially diverse group of children in suburban Birmingham, England, Kay and coworkers[15] found that breastfeeding did not affect the lifetime AD prevalence rate of 20%. A study of prevalence of childhood eczema found a correlation with increased socioeconomic class that did not result from heightened parental awareness.[16] The National Survey of Children's Health analysis by Shaw and

associates[9] also found increased prevalence of eczema to be related to metropolitan living, along with black race and higher education level.

The effects of genetic and environmental factors on allergic diseases were studied in two Japanese cities with differing climates.[17] The prevalence of allergic diseases and AD in the city with a temperate climate was significantly higher than in the one with a subtropical climate, even after controlling for genetic and environmental factors. In both cities, children from atopic families had a significantly higher risk of contracting respiratory allergies and AD. In a global survey of the prevalence of asthma, allergic rhinoconjunctivitis, and AD, 463 801 children age 13 to 14 years from 155 centers in 56 countries participated.[18] The highest prevalence of AD was reported from scattered centers, including sites in Scandinavia and Africa, that were not among centers with the highest prevalence of asthma. On the other hand, the lowest prevalence rates for AD occurred in centers with the lowest prevalence of asthma and allergic rhinoconjunctivitis. Thus, the ultimate presentation of an atopic disease may depend on a complex interaction of environmental exposures with end-organ response in a genetically predisposed individual.

Updated data from the International Study of Asthma and Allergies in Childhood (ISAAC phase III) on 385 853 participants age 6 to 7 years from 143 centers in 60 countries showed that the prevalence of current AD ranged from 0.9% in India to 22.5% in Ecuador, with new data showing high values in Asia and Latin America.[19] Prevalence in 663 256 participants age 13 to 14 years from 230 centers in 96 countries ranged from 0.2% in China to 24.6% in Columbia, with the highest occurrence in Africa and Latin America. These data emphasize the importance of AD as a global health problem in both developed and developing countries.

PATHOGENESIS AND ETIOLOGY

Genetics

The genetics of atopic disease is complex and an area of active research.[20] A number of genes are likely involved in the development of AD, but skin barrier/epidermal differentiation genes[21] and immune response/host defense genes have been proposed as playing a key role. An important advance in understanding the contribution of skin barrier abnormalities was recognizing loss-of-function mutations of the gene encoding the epidermal barrier protein filaggrin as a major predisposing factor for AD.[22] Patients with *FLG* gene mutations have early-onset, severe, and persistent AD,[23] although most appear to outgrow their disease, just more slowly than those without *FLG* mutations.[24] Importantly, AD patients with *FLG* mutations are at increased risk for development of asthma, as well as food and inhalant allergies[22] (see 'Role of the Abnormal Epidermal Barrier,' below).

Studies of gene and protein expression of the skin barrier proteins loricrin and involucrin showed that both were significantly decreased in involved and uninvolved skin of AD patients.[25] Candidate-gene approaches have implicated variants in the *SPINK5* gene, which is expressed in the uppermost epidermis, where its product, LEKTI-1, inhibits two serine proteases (stratum corneum tryptic and chymotryptic enzymes) involved in desquamation and inflammation.[5] Thus, an imbalance of protease versus protease inhibitor activity may contribute to skin barrier breakdown and staphylococcal colonization in AD. These observations establish a key role for impaired skin barrier function in AD pathogenesis, allowing increased transepidermal water loss and, importantly, increased entry of allergens, antigens, and chemicals from the environment, resulting in skin inflammatory responses (Fig. 11-2).

Atopic Diathesis

Most patients with AD have a genetic predisposition to develop an IgE response to common environmental allergens. Abnormal IgE responses are associated with cellular abnormalities resulting in overproduction of helper T type 2 (Th2)-type cytokines, which also contribute to the eosinophilia seen in these diseases. Early onset of AD is associated

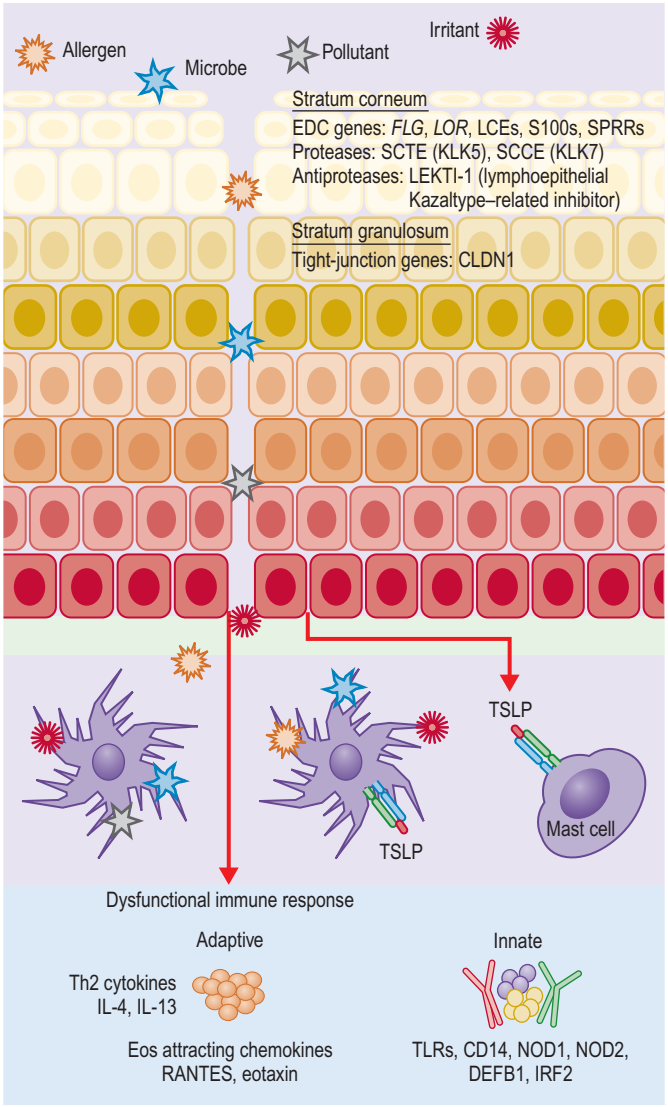

Figure 11-2 Epidermal barrier abnormalities and immune dysregulation. SCCE, stratum corneum chymotryptic enzyme; SCTE, stratum corneum tryptic enzyme; TLRs, Toll-like receptors; TSLP, thymic stromal lymphopoietin. *(From Barnes KC. An update on the genetics of atopic dermatitis: scratching the surface in 2009. J Allergy Clin Immunol 2010;125:16–29.)*

with an increased risk for respiratory allergy. The highest incidence of asthma at a given age has been observed in children with onset of AD before 3 months, in those with severe AD and a family history of asthma. An association of increased risk for asthma and/or rhinoconjunctivitis with early onset of AD has been confirmed.[26] Respiratory allergy occurred in 50% of children who had onset of AD during the first 3 months of life and two or more atopic family members, compared with 12% of children who had onset of AD after 3 months of age and no atopic family members.

In a prospective study of 94 children with AD observed through 7 years of age, only 14 had experienced no signs or symptoms of asthma or allergic rhinoconjunctivitis.[27] In addition, children with AD have more severe asthma than asthmatic children without AD, suggesting that epidermal allergen sensitization may predispose to more severe and persistent respiratory disease through effects on the systemic allergic response. In support of this hypothesis, mouse studies have shown that epicutaneous sensitization with protein antigen can elicit a localized dermatitis, along with elevated serum IgE, airway eosinophilia, and hyperresponsiveness to methacholine.[28] Importantly, epidemiologic studies in AD patients with *FLG* mutations have also shown a strong association with

asthma and allergies (as discussed previously). In addition, in a murine model of filaggrin deficiency, cutaneous sensitization leads to systemic allergic responses.[29]

Patients with AD react to both allergic and non-specific triggers, similarly to patients with asthma and allergic rhinitis. Skin hyperreactivity to irritants such as sodium lauryl sulfate (SLS) has been shown in patients with both active and inactive AD, as well as patients with allergic respiratory disease even with no skin involvement, compared with non-atopic subjects.[30] An abnormal intrinsic hyperreactivity of inflammatory cells in atopic individuals may predispose them to a lower threshold of irritant responsiveness. Confirming and extending these (individuals) observations, Tabata and associates[31] showed that the stratum corneum abnormalities in non-involved AD skin were associated with increased transepidermal water loss, even 7 days after application of SLS.[31] Of note, atopy can be transferred through bone marrow transplantation.[32] These observations suggest that the cutaneous abnormality in AD results from a complex interaction of resident and infiltrating cells.

Furthermore, a study of bronchial and cutaneous reactivity in asthmatic patients with and without AD found a latent predisposition for bronchial asthma and implicated circulating activated eosinophils as the common effector cells.[33] Because the ability of eosinophils to reach their target organ depends partly on eosinophil-specific chemotactic factors, increased expression of eotaxin and monocyte chemotactic protein-4 (MCP-4), structurally homologous eosinophil chemoattractants acting through a common CCR3 receptor, has been reported in the respiratory mucosa of both asthma patients[34] and AD patients.[35] Also, increased numbers of IgE^+ Langerhans cells have been shown in both active AD and active asthma versus inactive AD and inactive asthma, suggesting systemic regulation of active allergic disease, further aggravated by local inflammation in atopic skin lesions.[36]

Natural History

AD typically manifests in early childhood, with onset before 5 years of age in approximately 90% of patients. In adults with new-onset dermatitis, especially without a history of childhood eczema, asthma, or allergic rhinitis, other diseases need to be considered (Table 11-1).

Although Vickers's 20-year follow-up[37] suggested that 84% of children outgrow their AD by adolescence, more recent data present less optimistic outcomes. In one study, AD

TABLE 11-1 Differential Diagnosis in Patients with Atopic Dermatitis

Differential category	Diagnostic examples
Congenital disorders	Netherton syndrome
Chronic dermatoses	Seborrheic dermatitis Contact dermatitis (allergic or irritant) Nummular eczema Lichen simplex chronicus
Infections and infestations	Scabies Human immunodeficiency virus–associated dermatitis
Malignancy	Cutaneous T cell lymphoma (mycosis fungoides/Sézary syndrome)
Immunodeficiencies	Wiskott–Aldrich syndrome Severe combined immunodeficiency Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome Hyper-IgE syndrome *DOCK8* mutation associated immunodeficiency
Metabolic disorders	Zinc deficiency Pyridoxine (vitamin B_6) and niacin deficiency Multiple carboxylase deficiency Phenylketonuria
Proliferative disorders	Letterer–Siwe disease

had disappeared in only 18% of children observed from infancy until age 11 to 13 years, although it had become less severe in 65%.[38] In another study, 72% of patients diagnosed during the first 2 years of life continued to have AD 20 years later.[39] In a prospective study from Finland, 77–91% of adolescent patients treated for moderate to severe AD had persistent or frequently relapsing dermatitis as adults, although only 6% had severe disease.[40] In addition, more than half the adolescents treated for mild dermatitis experienced a relapse of disease as adults. Often, adults whose childhood AD has been in remission for a number of years present with hand dermatitis, especially if daily activities require repeated hand wetting. In a prospective study of children with AD observed through age 7 years, Gustafsson and associates[27] found that, although most had milder eczema by 7 years, only approximately one third had no evidence of disease activity.

The Multicenter Allergy Study, a German birth cohort, followed 1314 children from birth to age 7 years with physical examinations and parental interviews on atopic symptoms and diagnoses, along with determination of specific IgE levels.[41] The cumulative prevalence of AD in the first 2 years of life was 21.5%. Of these children with early AD, 43.2% were in complete remission by age 3 years; 38.3% had an intermittent pattern of disease; and 18.7% had symptoms of AD every year. Severity and atopic sensitization were major determinants of prognosis. Of note, the insights into the genetics of AD previously discussed provide new information regarding risk factors for persistent AD into adulthood.[23]

Role of the Abnormal Epidermal Barrier

Atopic dermatitis is associated with abnormalities in skin barrier function that include increased transepidermal water loss, increased levels of endogenous proteolytic enzymes, and reduced ceramide levels. Use of soaps can increase skin pH, increasing activity of endogenous proteases and leading to breakdown of epidermal barrier function.[5] The epidermal barrier may be further damaged by exogenous proteases from house-dust mites and *S. aureus*. This is worsened by the lack of endogenous protease inhibitors in the skin of patients with AD. These epidermal changes likely contribute to increased allergen absorption into the skin and microbial colonization. As previously discussed, mutations in the *FLG* gene, located in the epidermal differentiation complex on chromosome 1q21, have been shown to result in complete or partial decrease of expression of a key epidermal protein, filament-aggregating protein (filaggrin), involved in formation of the epidermal barrier.[21] In addition, Th2 cytokines such as interleukins 4 and 13 (IL-4, IL-13), which are upregulated in AD, were shown to downregulate *FLG* expression.[42] More recently, a distinct subpopulation of IL-22-producing 'Th22' $CD4^+$ and $CD8^+$ cells has been reported in the skin of AD patients, and IL-22-regulated genes include those implicated in epidermal barrier abnormalities in AD such as *FLG*, as well as the proteins loricrin and involucrin.[43]

The growing number of mutations reported includes many unique for Caucasians of European ancestry and others for Asian populations.[22] Importantly, *FLG* mutations were a major risk factor for eczema-associated asthma. Importantly, because epicutaneous sensitization to allergens results in a greater immune response than sensitization via the airway,[28] decreased epidermal barrier function could act as a site for allergen sensitization and predispose such children to the development of respiratory allergy later in life.[44] Meta-analyses support the association of *FLG* mutations with increased risk for both asthma[45] and allergies.[46]

De Benedetto and colleagues[47] pointed to a role of a second barrier defect in AD. Tight junctions (TJs) located directly below the stratum corneum regulate the selective permeability of the paracellular pathway. Reduced expression of the tight-junction proteins claudin-1 and claudin-23 were observed only in patients with AD, validated at the messenger RNA (mRNA) and protein levels. Claudin-1 expression inversely correlated with Th2 biomarkers. CLDN1 haplotype-tagging SNPs were associated with AD. These data suggest that an impairment in TJs contributes to the barrier dysfunction and immune dysregulation observed in AD patients, which may be mediated in part by reduction in claudin-1 (Fig. 11-2).

In a novel approach, Broccardo and associates[48] used a non-invasive, semiquantitative profiling method to identify proteins involved in the pathogenesis of AD. Proteins related to the skin barrier (filaggrin-2, corneodesmosin, desmoglein-1, desmocollin-1, transglutaminase-3) and generation of natural moisturizing factor (arginase-1, caspase-14, γ-glutamylcyclotransferase) were expressed at significantly lower levels in lesional versus non-lesional sites of AD patients. Epidermal fatty acid-binding protein was expressed at significantly higher levels in patients with MRSA. The lower expression of skin barrier proteins and enzymes involved in the generation of natural moisturizing factor could further exacerbate barrier defects and perpetuate water loss from the skin. The greater expression of epidermal fatty acid-binding protein, especially in patients colonized with MRSA, might perpetuate the inflammatory response through eicosanoid signaling.

CLINICAL FEATURES (PHENOTYPE)

Atopic dermatitis has no pathognomonic skin lesions or unique laboratory parameters. Therefore, the diagnosis is based on the presence of major and associated clinical features (Box 11-1).[49] Attempts to standardize signs and symptoms of AD include severity scoring of atopic dermatitis (SCORAD) and the eczema area and severity index (EASI).[50,51] The principal features include severe pruritus, a chronically relapsing course, typical morphology and distribution of the skin lesions, and a history of atopic disease. The presence of pruritus is critical to the diagnosis of AD, and patients with AD have a reduced threshold for pruritus.

Acute AD is characterized by intensely pruritic, erythematous papules associated with excoriations, vesiculations, and serous exudate. Subacute AD is characterized by erythematous, excoriated, scaling papules, whereas chronic AD is characterized by thickened skin with accentuated markings (lichenification) and fibrotic papules. Patients with chronic AD may have all three types of lesions. In addition, patients usually have dry skin. Significant differences can be observed in pH, capacitance, and transepidermal water loss between AD lesions and uninvolved skin in the same patient and on skin of normal controls.

During infancy, AD involves primarily the face, scalp, and extensor surfaces of the extremities. The diaper area is usually spared; if involved, it may be secondarily infected with *Candida* species, in which case the dermatitis does not spare the inguinal folds. In contrast, infragluteal involvement is a common distribution in children. In older patients with longstanding disease, the flexural folds of the extremities are the predominant location of lesions. In the Copenhagen Prospective Study on Asthma in Childhood, arm

Box 11-1 Clinical Features of Atopic Dermatitis

MAJOR FEATURES

- Pruritus
- Facial and extensor involvement in infants and children
- Flexural lichenification in adults
- Chronic or relapsing dermatitis
- Personal or family history of atopic disease

MINOR FEATURES

- Xerosis
- Cutaneous infections
- Non-specific dermatitis of hands or feet
- Ichthyosis, palmar hyperlinearity, keratosis pilaris
- Pityriasis alba
- Nipple eczema
- White dermatographism and delayed blanch response
- Anterior subcapsular cataracts
- Elevated serum IgE levels
- Positive immediate-type allergy skin tests

(Modified from Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol (Stockh) 1980;92:44–47.)

and joint involvement carried the highest predictive value for the development of AD at age 3 years.[52] Localization of AD to the eyelids may be an isolated manifestation but should be differentiated from allergic contact dermatitis.

Complicating Features

Ocular Problems

Increased numbers of IgE-bearing Langerhans cells are found in the conjunctival epithelium of patients with AD. These cells can capture aeroallergens and present them to infiltrating T cells, thus contributing to ocular inflammation. Ocular complications associated with AD can result in significant morbidity.

Atopic keratoconjunctivitis is always bilateral, and symptoms include itching, burning, tearing, and copious mucoid discharge.[53] It is frequently associated with eyelid dermatitis and chronic blepharitis and may result in visual impairment from corneal scarring. Keratoconus is a conical deformity of the cornea that is thought to result from persistent rubbing of the eyes in patients with AD and allergic rhinitis. Anterior subcapsular cataracts may develop during adolescence or early adult life.

Hand Dermatitis

Patients with AD often have non-specific hand dermatitis that is frequently irritating and aggravated by repeated wetting, especially in the occupational setting. A history of past or present AD at least doubles the effects of irritant exposure and doubles the risk in occupations where hand eczema is a common problem.

Infections

Patients with AD have an increased susceptibility to infection or colonization with a variety of organisms.[54] These include viral infections with herpes simplex virus (HSV), molluscum contagiosum, and human papillomavirus (HPV). Important insights into our understanding of the unique susceptibility that AD patients have to eczema herpeticum (EH) and eczema vaccinatum (a potentially lethal complication of smallpox vaccine) include the demonstration of an acquired defect in the cutaneous antimicrobial peptide response.[55] Beck and colleagues[56] showed that AD patients with EH had more severe disease based on scoring systems, body surface area affected, and biomarkers (e.g., circulating eosinophil counts, serum IgE, TARC, CTACK), than AD patients without a history of EH. AD patients with EH also had more cutaneous infections with *Staphylococcus aureus* or molluscum contagiosum virus and were also more likely to have a history of asthma and food and inhalant allergies. Leung and associates[57] showed that AD patients with eczema herpeticum have reduced interferon-γ (IFN-γ) production, and that IFN-γ and receptor (IFN-γR1) single-nucleotide polymorphisms (SNPs) are significantly associated with AD and EH and may contribute to an impaired immune response to HSV. In addition, genetic variants in interferon regulatory factor 2 were also shown to be associated with AD and EH and may contribute to abnormal immune responses to HSV.[58]

Superimposed dermatophytosis may cause AD to flare. The opportunistic yeast *Malassezia sympodialis* (formerly *Pityrosporum ovale*) has also been associated with a predominantly head and neck distribution of AD and reported to occur in both extrinsic and intrinsic subtypes of AD.[59]

A number of studies have elucidated the importance of *S. aureus* in AD.[54] Preferential adherence of *S. aureus* may be related to expression of adhesins such as fibronectin and fibrinogen in inflamed skin.[60] *S. aureus* can be cultured from the skin of more than 90% of patients with AD, compared with only 5% of normal subjects.[61] The higher rate of *S. aureus* colonization in AD lesions compared with lesions from other skin disorders may also be associated with colonization of the nares, with the hands serving as the vector of transmission.[62] Patients without obvious superinfection may have a better response to combined anti-staphylococcal and topical corticosteroid therapy than to corticosteroids alone.[63] Recurrent pustulosis has become a significant problem for a

number of patients, especially with the emergence of methicillin-resistant *S. aureus* (MRSA) as an important pathogen in AD.[64]

PATIENT EVALUATION, DIAGNOSIS, AND DIFFERENTIAL DIAGNOSIS

A number of diseases may be confused with AD (Table 11-1). In infants, immunodeficiency, including immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome, need to be considered. IPEX is a rare disorder associated with dermatitis, enteropathy, type 1 diabetes, thyroiditis, hemolytic anemia, and thrombocytopenia.[65] IPEX results from mutations of *FOXP3*, a gene located on the X chromosome that encodes the DNA-binding forkhead box P3 protein required for development of regulatory T cells.

Wiskott–Aldrich syndrome is an X-linked recessive disorder characterized by an eczematous rash, associated with thrombocytopenia, along with variable abnormalities in humoral and cellular immunity and severe bacterial infections. Hyper-IgE syndrome (HIE) with mutations in the gene encoding signal transducer and activator of transcription 3 (*STAT3*) is a multisystem autosomal dominant disorder characterized by recurrent deep-seated bacterial infections, including cutaneous cold abscesses and pneumonias caused by *S. aureus*.[66] Patients with mutations in the gene encoding dedicator of cytokinesis 8 protein (*DOCK8*) have a unique combined primary immunodeficiency that accounts for most cases of autosomal recessive HIE.[67] These patients have an eczematous dermatitis with recurrent viral skin infections but lack the coarse facies of autosomal dominant HIE.

Scabies can present as a pruritic skin disease. However, distribution in the genital and axillary areas, the presence of linear lesions, and the finding of mites, ova, and scybala in epithelial debris from skin scrapings help distinguish scabies from AD. An adult who has eczematous dermatitis with no history of childhood eczema and without other atopic features may have contact dermatitis, but more importantly, cutaneous T cell lymphoma needs to be ruled out. Ideally, biopsies should be obtained from three separate sites to increase the yield in identifying abnormal Sézary cells. In addition, eczematous rash suggestive of AD can be seen in patients with human immunodeficiency virus (HIV) infection.

Contact dermatitis should be considered in patients whose AD does not respond to appropriate therapy.[68] It is caused by the interaction of substances with the skin and includes allergic and irritant contact dermatitis, photoallergic contact dermatitis, phototoxic dermatitis, contact urticaria, and protein contact dermatitis. Allergic contact dermatitis, however, complicating AD may appear as an acute flare of the underlying disease rather than the more typical vesiculobullous eruption following direct contact with the injurious substance. People with an atopic diathesis are more likely to experience irritant contact dermatitis, especially in the workplace. Proper diagnosis depends on confirmation of a suspected allergen with patch testing.

Psychosocial Implications

Patients with AD may have high levels of anxiety and problems dealing with anger and hostility.[69] Although not a cause, these emotions can exacerbate AD. Patients often respond to stress or frustration with itching and scratching.[70] Stimulation of the central nervous system may intensify cutaneous vasomotor and sweat responses and contribute to the itch–scratch cycle. In some patients, scratching is associated with significant secondary gain or with a strong component of habit. Severe disease can have a significant impact on patients, leading to problems with social interactions and self-esteem. Importantly, sleep disturbance is common in this chronic disease and significantly impacts the quality of life of patients and family members.[71]

Role of Allergens

Although elevated serum IgE levels can be demonstrated in 80–85% of patients with AD, particularly those seen in tertiary care/specialist centers, and a similar number have

immediate skin test response or positive in-vitro tests to food and inhalant allergens, the relationship between the course of AD and implicated allergens has been difficult to establish. Nevertheless, well-controlled studies suggest that allergens can impact the course of this disease.[72]

Foods

May[73] first recognized that patients with AD and positive food allergen skin tests could have negative food challenges to the implicated allergen, distinguishing between symptomatic and asymptomatic hypersensitivity. Thus, triggers for clinical disease cannot be predicted simply by performing allergy testing. However, double-blind, placebo-controlled food challenges have demonstrated that food allergens can cause exacerbations in a subset of patients with AD.[74] Approximately 33% of infants and young children with AD will show clinically relevant reactivity to a food allergen.[75]

Although lesions induced by single positive challenges are usually transient, repeated challenges, more typical of real-life exposure, can result in eczematous lesions. Food-specific T cells have been cloned from lesional skin and peripheral blood of patients with AD.[76,77] Furthermore, elimination of food allergens results in amelioration of skin disease and a decrease in spontaneous basophil histamine release.[78]

Aeroallergens

The evidence supporting a role for aeroallergens in AD includes the finding of both allergen-specific IgE antibodies and allergen-specific T cells.[79] Exacerbation of AD can occur with exposure to allergens such as house-dust mites, animal danders, and pollens. In the 1940s, Tuft[80] demonstrated that introduction of aeroallergens intranasally could exacerbate AD. Subsequently, in a double-blind, randomized, placebo-controlled trial (RCT), a subgroup of patients with AD who underwent bronchoprovocation with a standardized house-dust mite extract developed unequivocal cutaneous lesions after inhalation of dust mite.[81] All the patients with dust mite–induced dermatitis had a history of asthma, and in eight of these nine patients, the skin reaction was preceded by an early bronchial reaction. Therefore, the respiratory route may be important in the induction and exacerbation of AD. Direct contact with inhalant allergens can also result in eczematous skin eruptions.[82] Using the atopy patch test, Langeveld–Wildschut and coworkers[83] showed that positive reactions to house-dust mites were associated with IgE^+ Langerhans cells in the epidermis of AD patients.

In addition, the severity of AD has been correlated with the degree of sensitization to aeroallergens.[84] Most importantly, environmental control measures aimed at reducing dust mite allergen have been shown to result in clinical improvement in AD patients.[85,86] These studies suggest that inhalation or contact with aeroallergens may be involved in the pathogenesis of AD.

Microbial Agents

In addition to their role as infectious agents, both the lipophilic yeast *Malassezia sympodialis*[59] and the superficial dermatophyte *Trichophyton rubrum* have been associated with elevated specific-IgE levels. Patients with AD predominantly of the head and neck, compared with a group without this distribution and with a group of normal controls, more often demonstrated IgE testing, and specific histamine release to *M. sympodialis*. These findings are of clinical significance because patients improve after antifungal therapy.

Leung and colleagues[87] showed that exotoxins secreted by *S. aureus* are superantigens that can result in persistent inflammation or exacerbations of AD. More than half of the AD patients studied had *S. aureus* cultured from their skin; the organisms secreted primarily enterotoxins A and B and toxic shock syndrome toxin-1. In addition, almost half of the patients had specific IgE antibodies directed against the staphylococcal toxins found on their skin. AD patients are unique in that they can be colonized by *S. aureus* bacteria that secrete more than one superantigen compared with patients with other superantigen-mediated disease such as toxic shock syndrome.[64] Basophils from patients

with antitoxin IgE released histamine on exposure to the relevant toxin but not in response to toxins to which they had no specific IgE. Other investigators have confirmed these observations.[88,89] In addition, analysis of the peripheral blood skin-homing (CLA^+) T cells of superantigen-positive patients, as well as their skin lesions, revealed that they had undergone expansion of the T cell receptor (TCR) variable-domain β-chain (Vβ), consistent with superantigenic stimulation.[90,91] A correlation also has been found between the presence of IgE against superantigens and severity of AD.[88] Furthermore, superantigens have an additive effect with conventional allergens in inducing cutaneous inflammation.[92] Superantigens can also augment allergen-specific IgE synthesis,[93] subvert T regulatory (Treg) cell function,[94] and induce corticosteroid resistance,[95] suggesting several mechanisms by which superantigens could aggravate the severity of AD. In addition, staphylococcal enterotoxin B (SEB) applied to the skin induced erythema and induration, with the infiltrating T cells selectively expanded in response to the specific superantigen.[96,97]

Autoantigens

Several groups have suggested a role for autoantigens in chronic AD. Valenta and associates[98] reported that the majority of sera from patients with severe AD contain IgE antibodies directed against human proteins. One of these IgE-reactive autoantigens, a 55-kD cytoplasmic protein in skin keratinocytes, has been cloned from a human epithelial complementary DNA (cDNA) expression library and designated Hom s 1.[99] Although the autoallergens characterized to date have mainly been intracellular proteins, they have been detected in IgE immune complexes of AD sera, suggesting that release of these autoallergens from damaged tissues could trigger IgE or T cell-mediated responses. In another study, 30% of sera from patients with AD had both IgG and IgE autoantibodies that reacted with an autoantigen called dense fine speckled 70 (DFS70).[100]

These data suggest that skin inflammation in AD, especially in severe cases, could be maintained by endogenous human antigens. Because these autoantigens are primarily nuclear or microsomal in origin, damage to the skin by infectious organisms or scratching could release intracellular antigens that in turn could elicit and perpetuate IgE and T cell responses in AD. Of interest, human manganese superoxide dismutase (MnSOD) may play a role as an autoallergen in a subset of patients with AD.[101] By molecular mimicry leading to cross-reactivity, such sensitization might be induced primarily by exposure to MnSOD of the skin-colonizing yeast *M. sympodialis*.

Immunology

A number of immunoregulatory abnormalities have been described in AD (Box 11-2).[102] B cells from patients with AD synthesize high levels of IgE. T cells from these patients produce increased amounts of IL-4 and express abnormally high levels of IL-4 receptor. Peripheral blood mononuclear cells (PBMCs) isolated from patients with AD have a decreased capacity to make IFN-γ, which is inversely correlated with serum IgE levels.

Box 11-2 Immunoregulatory Abnormalities in Atopic Dermatitis

- Increased synthesis of IgE
- Increased levels of specific IgE to multiple allergens, including foods, aeroallergens, microorganisms, and enterotoxins
- Increased expression of CD23 on B cells and monocytes
- Increased surface expression of FcεRI on antigen-presenting cells in the skin
- Increased levels of cutaneous T cell-attracting chemokine (CTACK) and thymus- and activation-regulated chemokine (TARC)
- Increased secretion of interleukin-4 (IL-4), IL-5, and IL-13 by T helper type 2 (Th2) cells
- Decreased secretion of interferon-γ by Th1 cells
- Decreased $CD4^+/CD25^+$ regulatory T (Treg) cell immunosuppressive activity after superantigen stimulation
- Decreased secretion of antimicrobial peptides by keratinocytes
- Increased levels of monocyte cyclic adenosine monophosphate phosphodiesterase, with increased IL-10 and prostaglandin E_2.

Among differences noted between the intrinsic and extrinsic forms of AD, skin-derived T cells from extrinsic AD interacted with B cells to support IgE synthesis, whereas T cells from the intrinsic form of AD did not.[103]

Studies have shown an increased frequency of both circulating[104,105] and lesional allergen-specific Th2 cells secreting IL-4, IL-5, and IL-13 in patients with AD.[103,106] Furthermore, an increased frequency of circulating skin-homing (CLA^+) type 2 cytokine-producing cells and decreased frequency of CLA^+ type 1 cytokine-producing cells have been reported in the peripheral blood of AD patients.[107] In addition to acting as an IgE isotype-specific switch, IL-4 also inhibits the production of IFN-γ and downregulates the differentiation of Th1 cells.[108] The importance of Th2 cytokines in driving AD skin inflammation is strongly supported by the observation that a humanized monoclonal antibody that blocks the action of IL-4 and IL-13 was found to reduce the skin severity of AD.[109]

Immunopathologic Features

Routine histologic examination of clinically normal-appearing skin in AD reveals mild epidermal hyperplasia and a sparse, predominantly lymphocytic infiltrate in the dermis.[102] Acute eczematous lesions are characterized by both intercellular edema of the epidermis (spongiosis) and intracellular edema. A sparse lymphocytic infiltrate may be observed in the epidermis, whereas a marked perivenular infiltrate consisting of lymphocytes and some monocytes with rare eosinophils, basophils, and neutrophils is seen in the dermis. In chronic lichenified lesions, the epidermis has prominent hyperkeratosis with increased numbers of epidermal Langerhans cells and predominantly monocytes/macrophages in the dermal infiltrate.

Immunohistochemical staining of acute and chronic skin lesions in AD shows that the lymphocytes are predominantly CD3, CD4, and CD45RO memory T cells; that is, the lymphocytes previously encountered antigen (Fig. 11-3).[1] These cells also express CD25 and human leukocyte antigen (HLA)-DR on their surface, indicative of intralesional activation. In addition, almost all the T cells infiltrating into atopic skin lesions express high levels of the skin lymphocyte-homing receptor cutaneous lymphocyte antigen (CLA).

The role of keratinocytes in skin inflammation in AD has been increasingly recognized.[1] Keratinocytes are an important source of thymic stromal lymphopoietin (TSLP), which activates dendritic cells to prime naive T cells to produce IL-4 and IL-13 (Th2 cell differentiation). Mice genetically engineered to overexpress TSLP in the skin develop AD-like skin inflammation.[110] Recently, *S. aureus* membrane-derived lipopeptides were shown to induce TSLP in keratinocytes through the Toll-like receptor 2 (TLR2)-TLR6 pathway.[111]

Besides producing proinflammatory cytokines, keratinocytes also play a vital role in the cutaneous innate immune responses by secreting antimicrobial peptides, including human β-defensins and β-cathelicidins, in response to microbial insult or tissue injury. Their keratinocytes produce reduced amounts of antimicrobial peptides, which may predispose AD patients to their frequent colonization and infection by *S. aureus*, viruses, and fungi.[112] Vitamin D has been found to be involved in the regulation of antimicrobial peptides in keratinocytes,[113] and the treatment with oral vitamin D in AD patients supports this hypothesis.[114] Patients with AD receiving oral vitamin D supplementation showed prevention of winter time exacerbation of eczema.[115]

Cytokine Expression

Cytokine expression in AD lesions reflects the nature of the underlying inflammation (Fig 11-4). Hamid and associates[116] used in situ hybridization to study IL-4, IL-5, and IFN-γ mRNA expression in acute and chronic skin lesions as well as uninvolved skin of patients with AD. Biopsies from uninvolved atopic skin showed a significant increase in the number of cells expressing IL-4 mRNA, but not IL-5 or IFN-γ mRNA. Both acute and chronic lesions had significantly greater numbers of cells positive for IL-4 and IL-5 than did uninvolved or normal skin. Neither acutely involved nor uninvolved atopic

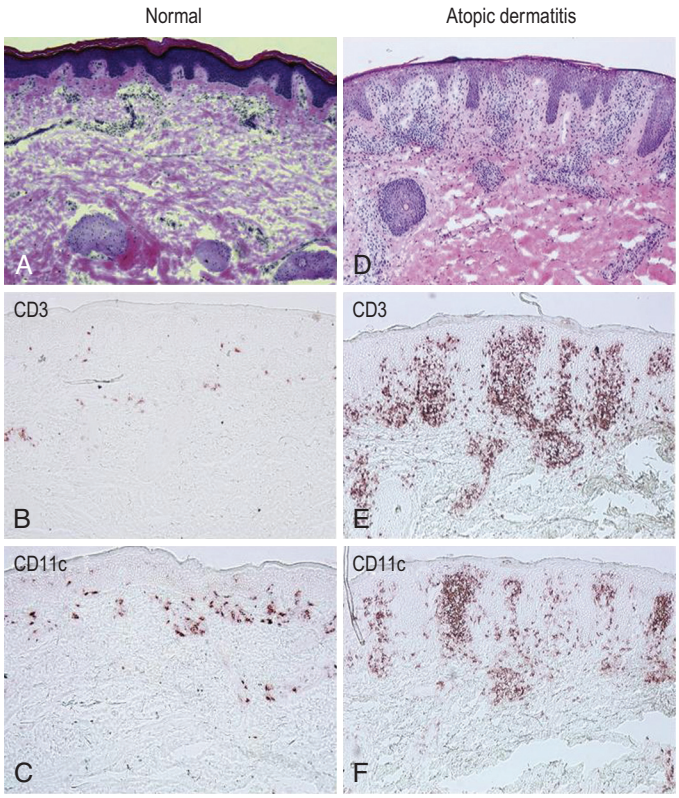

Figure 11-3 Immunohistology of atopic dermatitis versus normal skin showing epidermal hyperplasia with T cells (CD3) and dendritic cells (CD11c) in the superficial dermis. *(From Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis. Part I. Clinical and pathologic concepts. J Allergy Clin Immunol 2011;127:1110–1118.)*

skin showed significant numbers of IFN-γ mRNA-expressing cells. In contrast, chronic AD skin lesions had significantly fewer IL-4 mRNA-expressing cells and significantly more IL-5 mRNA-expressing cells than acute lesions. T cells made up the majority of IL-5-expressing cells in both acute and chronic lesions. Activated eosinophils were found in significantly greater numbers in chronic than in acute lesions. These data suggest that although both acute and chronic lesions in AD are associated with increased IL-4 and IL-5 gene activation, acute skin inflammation is associated with predominantly IL-4 expression, whereas chronic inflammation is associated with IL-5 expression and eosinophil infiltration.

Interleukin-13 expression was also found to be higher in acute AD lesions than in chronic AD or psoriatic lesions.[117] These data suggest that IL-13 may be involved in the pathogenesis of AD and further support the hypothesis that acute inflammation in AD is mediated by Th2-type cytokines. Chronic lesions had increased numbers of IL-12 mRNA-positive cells compared with acute or uninvolved skin. IL-12 is a potent inducer of IFN-γ synthesis, and consistent with this observation, increased IFN-γ expression has been reported in chronic AD lesions.[118] At a clonal level, T cells from AD patients with cow's milk allergy showed significantly greater production of IL-4, whereas IFN-γ production was greater in the milk-tolerant patients.[119] IL-5 and IL-13 cytokine production strongly correlated with IL-4 production.

Pruritus is a hallmark of AD, and the underlying processes involved are complex.[120] Mice that overexpress the T cell–derived cytokine IL-31 develop intense pruritus and dermatitis, and patients with AD have CLA^+ T cells that produce higher levels of IL-31.[121] In patients with AD as well as allergic contact dermatitis (ACD, another pruritic dermatosis), expression of IL-31 is associated with expression of IL-4 and IL-13, which are Th2 cytokines that characterize the atopic phenotype.[122] In addition, *S. aureus* superantigen rapidly induces IL-31 expression in atopic individuals, and because patients

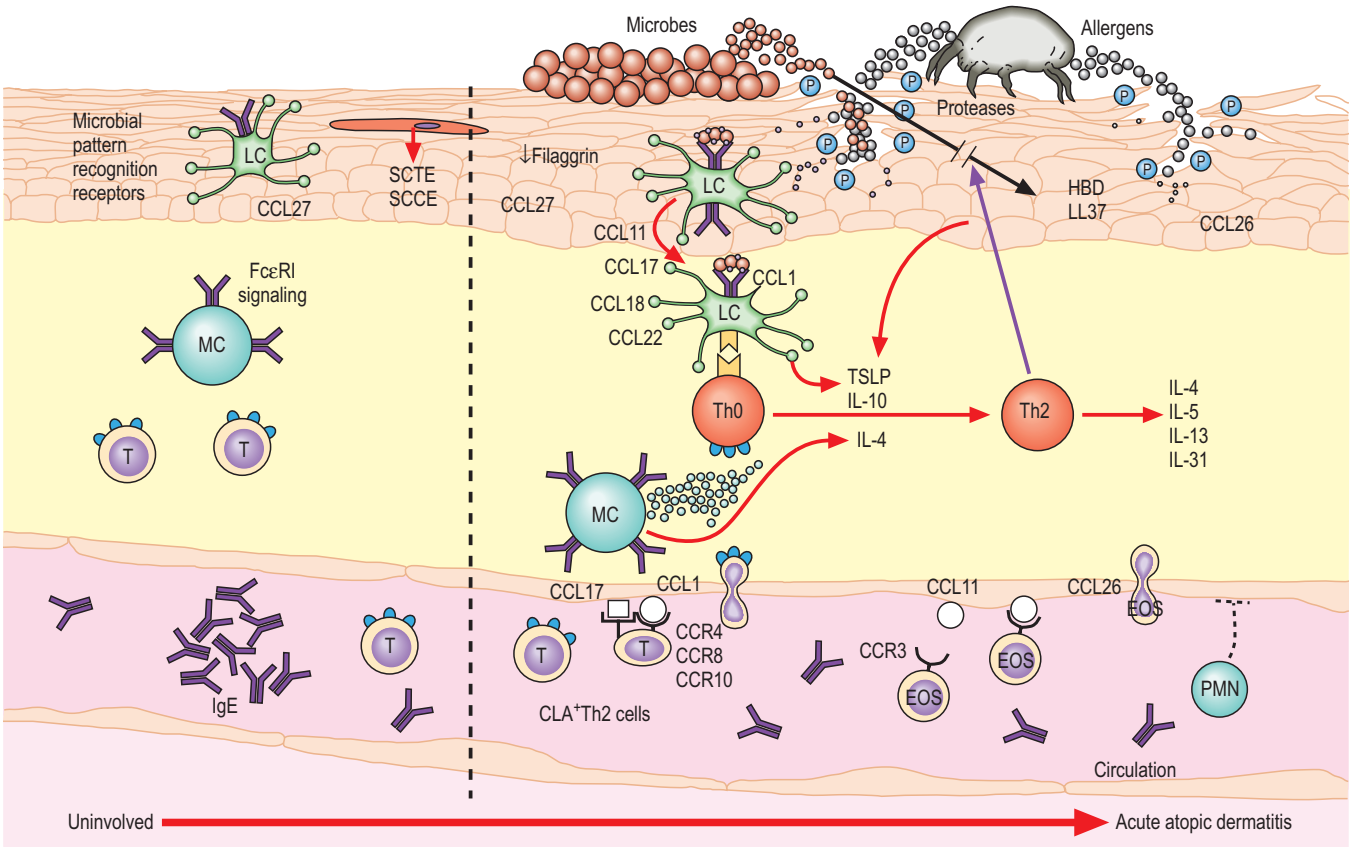

Figure 11-4 Immunologic abnormalities in the progression of atopic dermatitis. MC, mast cell; PMN, polymorphonuclear neutrophil; T, T lymphocyte; Th, helper T cell. *(Reproduced from J Allergy Clin Immunol 2006;118:cover.)*

with AD are heavily colonized with toxin-producing *S. aureus*, this can further contribute to their pruritus.[123] Calcineurin inhibitors and other agents that target T cells are effective at reducing pruritus in AD patients, and new insights into the role of IL-31 in AD may reveal new targets for anti-pruritic therapy.

Increasingly, as previously discussed, the keratinocyte-derived cytokine TSLP has been recognized as the 'master switch' for allergic inflammation.[124] In AD the TSLP-induced Th2 cytokine milieu can participate in a vicious cycle impacting the skin barrier and microbial colonization.[111] Genetic variants in TSLP have been shown to be associated with AD and eczema herpeticum.[125,126]

Role of IgE in Cutaneous Inflammation

In AD patients, IgE may play an important role in allergen-induced, cell-mediated reactions involving Th2-type cells that are distinct from conventional delayed-type hypersensitivity reactions mediated by Th1-type cells.[127] IgE-dependent biphasic reactions are frequently associated with clinically significant allergic reactions and may contribute to the inflammatory process of AD. Immediate-type reactions related to mediator release by mast cells bearing allergen-specific IgE may result in the pruritus and erythema that occur after exposure to relevant allergens. IgE-dependent late-phase reactions can then lead to more persistent symptoms. The T cell infiltrate in cutaneous allergen-induced late-phase reactions has increased mRNA for IL-3, IL-4, IL-5, and GM-CSF, but not for IFN-γ. These cells are therefore similar to the Th2-type cells found in AD lesions. In addition, the cutaneous late-phase reaction is associated with a pattern of cell adhesion molecule (CAM) expression similar to that in AD. Therefore, a sustained IgE-dependent late-phase reaction may be part of the chronic inflammatory process in AD patients.

Furthermore, epidermal LCs in AD skin express IgE on their cell surface and are significantly more efficient than IgE-negative LCs at presenting allergen to T cells.[128] In addition, LCs from atopic individuals have a much higher level of FcεRI expression.[129] Efficient allergen capture and presentation to Th2 cells in atopic skin may be an important mechanism for sustaining local T cell activation.

Skin-Directed Th2-Like Cell Response

A number of studies have demonstrated important similarities between the allergic inflammation of asthma and AD. Common features include local infiltration of Th2-type cells in response to allergens, development of specific IgE to allergens, a chronic inflammatory process, and organ-specific hyperreactivity. In both diseases, IL-4- and IL-5-secreting memory Th2-type cells have a central role in the induction of local IgE responses and recruitment of eosinophils.[116] The recognition of T cell heterogeneity based on expression of tissue-selective homing receptors suggests that an individual's propensity for specific allergic disease may be a function of end-organ targeting by effector T cells. In this respect, T cells migrating to the skin express CLA, whereas most memory/effector T cells isolated from asthmatic airways do not.

In a study of patients with milk-induced AD, casein-reactive T cells expressed significantly higher levels of CLA than did *Candida albicans*–reactive T cells from these patients or casein-reactive T cells from patients with milk-induced enterocolitis or eosinophilic gastroenteritis.[130] As further evidence for selective end-organ targeting by T cell subsets in allergic inflammation, data show that dust mite–specific T cell proliferation in mite-sensitized patients with AD was localized to the CLA-expressing fraction of T cells.[131] In contrast, T cells isolated from mite-allergic asthmatic patients that proliferated on exposure to the relevant allergen were CLA^-. Furthermore, CLA-expressing T cells isolated from patients with AD, but not from normal controls, showed evidence of activation (HLA-DR expression) and also spontaneously produced IL-4 but not IFN-γ. This suggests that T cell effector function in AD is closely linked to CLA expression.

TREATMENT

Conventional Therapy

Current understanding of the pathophysiology of AD supports the concept that assessing the role of allergens, infectious agents, irritants, physical environment, and emotional stressors is as important as initiating therapy with first-line agents. The acute and chronic aspects of AD need to be considered when designing an individualized treatment plan. Patients should understand that therapy is not curative, but that avoidance of exacerbating factors together with proper daily skin care can control symptoms and improve the long-term outcome. Management of patients with AD has been comprehensively reviewed (Fig. 11-5).[132–134]

Irritants

Patients with AD have a lowered threshold of irritant responsiveness. Therefore, recognition and avoidance of irritants are integral to successful management of this disease. Irritants include detergents, soaps, chemicals, pollutants, and abrasive materials, as well as extremes of temperature and humidity. Cleansers with minimal defatting activity and a neutral pH should be used rather than soaps. A number of mild cleansers are available in sensitive skin formulations. New clothing should be laundered before it is worn, to reduce the content of formaldehyde and other chemicals. Residual laundry detergent in clothing may be irritating, and although changing to a milder detergent can be helpful, using liquid rather than powder detergent and adding an extra rinse cycle are more beneficial. Occlusive clothing should be avoided, and cotton or cotton blends should be used.

Ideally, the temperature in the home and work environments should be temperate to minimize sweating. Swimming is usually well tolerated; however, because swimming

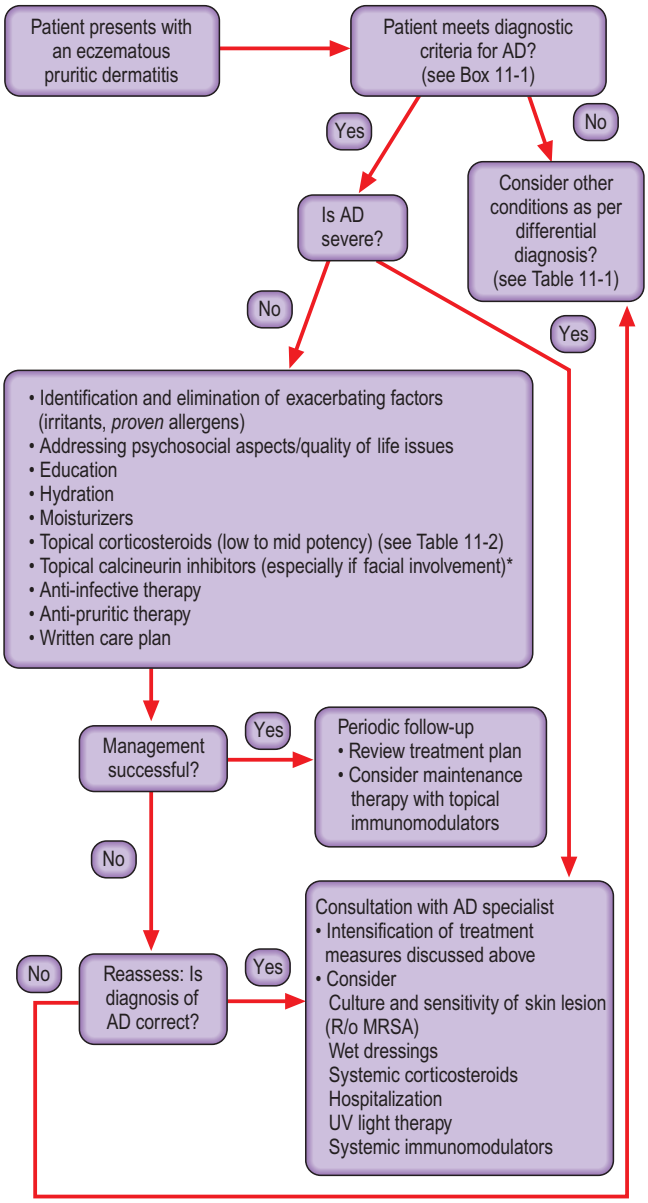

Figure 11-5 Approach to the patient with atopic dermatitis (AD). R/o MRSA, rule out methicillin-resistant *Staphylococcus aureus*; UV, ultraviolet. **Per boxed warning*: second-line, intermittent therapy for patients ≥2 years of age.

pools are treated with chlorine or bromine, it is important for patients to shower and use a mild soap immediately afterward, to remove these potentially irritating chemicals, and then to apply moisturizers or occlusives. Although sunlight may be beneficial to some patients with AD, non-sensitizing sunscreens should be used to avoid sunburn. Products developed for use on the face are often best tolerated by patients with AD. Prolonged sun exposure can cause evaporative losses, overheating, and sweating, which can be irritating.

Allergens

Identification of allergens involves taking a careful history and doing selective immediate-hypersensitivity skin tests or in-vitro tests when appropriate. Negative skin tests with proper controls have a high predictive value for ruling out a suspected allergen. Positive skin tests have a lower correlation with clinical symptoms in suspected food

allergen-induced AD and should be confirmed with double-blind, placebo-controlled food challenge, unless the patient has a history of anaphylaxis to the suspected food. In children who have undergone such a challenge, milk, egg, peanut, soy, wheat, and fish account for approximately 90% of the food allergens found to exacerbate AD. More importantly, avoidance of foods implicated in controlled challenges results in clinical improvement.[74,78]

Extensive elimination diets, which may be both extremely burdensome and at times nutritionally unsound, are almost never warranted, because even patients with multiple positive allergy tests are rarely clinically sensitive to more than three foods on challenge. Specific IgE concentrations in response to four food allergens measured by the Phadia ImmunoCAP assay—*egg*, 7 kU_A/L (2 kU_A/L age ≤2 years); *milk*, 15 kU_A/L (5 kU_A/L age ≤2 years); *peanut*, 14 kU_A/L; and *fish*, 20 kU_A/L—have been shown to be associated with a >95% probability of clinical reaction.

However, these levels do not identify the type or severity of reaction.[135] The atopy patch test has revealed sensitization in some patients with AD but remains an investigational tool.[136]

Environmental control measures aimed at reducing dust mite load may improve AD in patients who demonstrate specific IgE to dust mite allergen.[85] These measures include using dust mite–proof encasings on pillows, mattresses, and box springs; washing linens in hot water weekly; removing bedroom carpeting; and decreasing indoor humidity levels. Adult AD patients not sensitized to house-dust mite benefited from allergy-proof covers as much as sensitized patients, suggesting that impermeable covers may reduce exposure to other allergens, irritants, or infectious organisms.[137]

Psychosocial Factors

Recognizing and addressing sleep disturbance problems in both patients and caregivers are critical in a chronic, relapsing disease such as AD.[71] Counseling is often helpful in dealing with the frustrations associated with AD. Relaxation, behavioral modification, and biofeedback may all be of benefit, especially for patients with habitual scratching.[69]

Patient Education

Learning about the chronic nature of AD, exacerbating factors, and appropriate treatment options is important for both patients and caregivers.[138] In addition, patients and their families should be counseled about the natural history and prognosis and receive appropriate vocational counseling. The International Study of Life with Atopic Eczema (ISOLATE) found that patients and caregivers often delay initiation of treatment for AD flares and have concerns about their prescribed medications.[139] Clinicians should provide patients and their families with detailed written skin care recommendations and should review this information on follow-up. Educational materials may be obtained from the National Eczema Association (www.nationaleczema.org), a not-for-profit, patient-oriented organization. In addition, written information and a DVD on skin care are available from the Office of Professional Education, National Jewish Health (http://www.nationaljewish.org/professionals/education/pro-ed/overview).

Hydration

Atopic dry skin shows enhanced transepidermal water loss and reduced water-binding capacity. Patients may also have decreased ceramide levels in their skin, resulting in reduced water-binding capacity, higher transepidermal water loss, and decreased water content.[35,140] Therefore, skin hydration is an essential component of therapy. The best way to re-establish the skin's barrier function is to soak the affected area or bathe for approximately 10 min in warm (not lukewarm) water and then apply an occlusive agent to retain the absorbed water. Substances such as oatmeal or baking soda added to the bathwater may feel soothing to certain patients but do not affect water absorption. Hydration of the face or neck can be achieved by applying a wet facecloth or towel to the involved area. A wet washcloth may be more readily accepted if holes are cut out

for the eyes and mouth, allowing the patient to remain functional. Hand or foot dermatitis can be treated by soaking the limb in a basin. Baths may need to be taken several times a day during flares of AD, whereas showers may be adequate for patients with mild disease. It is essential to use an occlusive preparation within a few minutes after hydrating the skin to prevent evaporation, which is damaging to the epidermis. Patients and their families need to understand proper hydration techniques.

Bathing may also remove allergens from the skin surface and reduce colonization by *S. aureus*. Bleach baths with dilute sodium hypochlorite have been recommended to reduce skin infections (¼ to ½ cup of household bleach per full tub of water), but this approach may lead to skin irritation and should be used with caution. In a small, controlled study of diluted bleach baths, Huang and associates[141] showed that patients who received both dilute bleach baths and intranasal mupirocin treatment had significantly greater mean reductions from baseline in EASI scores than the placebo group at 1- and 3-month visits. However, patients remained colonized by *S. aureus*.

Moisturizers and Occlusives

The use of an effective emollient, especially when combined with hydration therapy, helps to restore and preserve the stratum corneum barrier and can decrease the need for topical corticosteroids.[142] Moisturizers are available as lotions, creams, and ointments. Lotions contain more water than creams and may be more drying because of an evaporative effect. Both lotions and creams can cause skin irritation secondary to added preservatives and fragrances. Because moisturizers usually need to be applied several times daily on a long-term basis, they should be obtained in 1-pound (0.45 kg) jars if available. Vegetable-oil shortening (e.g., Crisco) can be used if an inexpensive moisturizer is needed. Petroleum jelly (e.g., Vaseline) is an effective occlusive when used to seal in water after bathing.

Alpha-hydroxy acids affect keratinization through corneocyte cohesion and stratum corneum formation and increase dermal mucopolysaccharides and collagen formation. Assessment of 12% ammonium lactate emulsion by clinical criteria and by non-invasive methods showed a significant increase in electrical capacitance, skin surface lipids, dermal extensibility and firmness, and improvement in the skin barrier function and skin surface topography in all patients.[143] Ammonium lactate mitigated the epidermal and dermal atrophy associated with topical corticosteroid use.[144]

In contrast to changes in sphingolipid metabolism caused by aging, the enzyme SM deacylase is highly expressed in the epidermis of AD patients and competes with sphingomyelinase or β-glucocerebrosidase for the common substrate SM or glucosylceramide.[145] This in turn leads to ceramide deficiency of the stratum corneum in AD. Whereas an equimolar ratio of ceramides, cholesterol, and either the essential fatty acid linoleic acid or the non-essential palmitic or stearic fatty acids allows normal repair of damaged human skin, further acceleration of barrier repair occurs as the ratio of any of these ingredients is increased up to three-fold.[146] Non-steroidal creams (e.g., Atopiclair, EpiCeram, MimyX) marketed as 'medical devices' have unique formulations and have not been compared; although not regulated by the US Food and Drug Administration (FDA), these creams do require a prescription.[147]

Corticosteroids

Corticosteroids reduce inflammation and pruritus and are effective for both the acute and chronic components of AD. They affect multiple resident and infiltrating cells primarily through suppression of inflammatory genes, reducing inflammation and pruritus. Topical corticosteroids are available in a wide variety of formulations, ranging from extremely high-potency (group 1) to low-potency (group 7) preparations (Table 11-2). The vehicle in which the product is formulated can alter the potency of the corticosteroid and move it up or down in this classification. Generic formulations of topical corticosteroids are required to have the same active ingredient and the same concentration as the original product. However, many generics do not have the same vehicle formulation, and the bioequivalence of the product can vary significantly.

TABLE 11-2 Select Topical Corticosteroid Preparations*

Group	Preparations
1	Clobetasol propionate (Temovate) 0.05% ointment/cream Betamethasone dipropionate (Diprolene) 0.05% ointment/cream
2	Mometasone furoate (Elocon) 0.1% ointment Halcinonide (Halog) 0.1% cream Fluocinonide (Lidex) 0.05% ointment/cream Desoximetasone (Topicort) 0.25% ointment/cream
3	Fluticasone propionate (Cutivate) 0.005% ointment Halcinonide (Halog) 0.1% ointment Betamethasone valerate (Valisone) 0.1% ointment
4	Mometasone furoate (Elocon) 0.1% cream Triamcinolone acetonide (Kenalog) 0.1% ointment/cream Fluocinolone acetonide (Synalar) 0.025% ointment
5	Fluocinolone acetonide (Synalar) 0.025% cream Hydrocortisone valerate (Westcort) 0.2% ointment
6	Desonide (DesOwen) 0.05% ointment/cream/lotion/gel Alclometasone dipropionate (Aclovate) 0.05% ointment/cream
7	Hydrocortisone (Hytone) 2.5% and 1% ointment/cream

*Representative corticosteroids are listed by group from 1 (superpotent) through 7 (least potent).
(Modified from Stoughton RB. Vasoconstrictor assay-specific applications. In: Maibach HI, Surber C, eds. Topical corticosteroids. Basel, Switzerland: Karger; 1992:42–53.)

Choice of a particular product depends on the severity and distribution of skin lesions. In general, an effective topical corticosteroid of the lowest potency should be used. However, choosing a preparation that is too weak may result in persistent or worsening AD. Resistant lesions may respond to a potent topical corticosteroid under occlusion, although this needs to be used cautiously to prevent irreversible atrophic changes. When treating pediatric patients, clinicians should be aware of age-appropriate indications (e.g., fluticasone 0.05% cream, up to 28 days in children age ≥3 months; fluticasone lotion, ≥12 months of age; mometasone cream/ointment, ≥2 years of age).

With appropriately used low- to medium-potency topical corticosteroids, side effects are infrequent. Thinning of the skin with telangiectasias, bruising, hypopigmentation, acne, striae, and secondary infections may occur. The face, particularly the eyelids, and the intertriginous areas are especially sensitive to these adverse effects, and only low-potency preparations should be used routinely on these areas. Perioral dermatitis, characterized by erythema, scaling, and follicular papules and pustules that occur around the mouth, in the alar creases, and sometimes on the upper lateral eyelids, can occur with the use of topical corticosteroids on the face. 'Steroid addiction' describes an adverse effect primarily of the face of adult women treated with topical corticosteroids, who complain of a burning sensation. Patients improve with total discontinuation of the corticosteroid therapy.[148] High-potency topical corticosteroids must be used cautiously, especially under occlusion, because they may lead to significant atrophic changes and systemic side effects.

Topical corticosteroids are available in a variety of bases, including ointments, creams, lotions, solutions, gels, sprays, oil, and even tape (Table 11-2). Therefore, no need exists to compound these medications. Ointments are most occlusive and as a rule provide better delivery of the medication while preventing evaporative losses. In addition, ointments spread more evenly than other creams or solutions. In a humid environment, creams may be better tolerated than ointments because the increased occlusion can cause itching or even folliculitis. In general, however, creams and lotions, although easier to spread, are less effective and can contribute to skin dryness and irritation. Solutions can be used on the scalp and hirsute areas, although the alcohol content can be irritating, especially if used on inflamed or open lesions, and additives used to formulate the different bases can cause sensitization. Furthermore, allergic contact

dermatitis to the corticosteroid molecule is being recognized with increasing frequency.[149] This diagnosis is often difficult to establish clinically because it can present as acute or chronic eczema. Patch testing has been done primarily with tixocortol pivalate and budesonide. Expanded testing has been associated with both false-positive and false-negative reactions.

An inadequate prescription size often contributes to suboptimally controlled AD, especially when patients have widespread, chronic disease. Approximately 30 g of medication is needed to cover the entire body of an average adult. The *fingertip unit* (FTU) has been proposed as a measure for applying topical corticosteroids and has been studied in children with AD.[150] This is the amount of topical medication that extends from the tip to the first joint on the palmar aspect of the index finger. It takes approximately 1 FTU to cover the hand or groin; 2 FTUs for the face or foot; 3 FTUs for an arm; 6 FTUs for the leg; and 14 FTUs for the trunk. Patients need to be instructed in the proper use of topical corticosteroids.

Application of an emollient immediately before or over a topical corticosteroid preparation may decrease the effectiveness of the corticosteroid. Patients often assume that the potency of their prescribed corticosteroid is based solely on the percentage noted after the compound name (e.g., they believe that hydrocortisone 2.5% is more potent than clobetasol 0.05%) and therefore may apply the preparations incorrectly. In addition, patients are often given a high-potency corticosteroid and told to discontinue it after a time without being given a lower-potency corticosteroid; this can result in rebound flaring of the AD, similar to that often seen with oral corticosteroid therapy for AD. A stepwise care approach with a midrange or high-potency preparation (although usually not to face, axillae, or groin) followed by low-potency preparations may be more successful.

Once-daily treatment may help with patient adherence to the regimen and has been effective for fluticasone propionate, a molecule with an increased binding affinity for the corticosteroid receptor.[151] Topical mometasone has been studied in children with AD and is also approved for once-daily use.[152] Topical corticosteroids usually have been discontinued after the inflammation resolves, while hydration and moisturizers are continued. An important concept to recognize is that normal-appearing skin in AD shows evidence of immunologic dysregulation,[116] and more recently, skin barrier abnormalities have been demonstrated in non-lesional skin.[153] These data provide a rationale for the use of topical corticosteroids as 'proactive' or maintenance therapy.[154]

In several studies with fluticasone, after control of AD with a once-daily regimen was achieved, long-term control could be maintained with twice-weekly applications of the topical corticosteroid to areas that had previously been involved but now appeared normal. This approach has resulted in fewer relapses and less need for topical corticosteroids than has 'reactive' eczema therapy.

In addition to their anti-inflammatory properties, topical corticosteroids can decrease *S. aureus* colonization in patients with AD. In a double-blind, randomized, 1-week trial of desonide compared with a vehicle in children with AD, clinical scores improved and *S. aureus* density significantly decreased within the desonide group but not in the vehicle group.[155]

A number of AD patients may not show clinical improvement with topical corticosteroids, perhaps the result of superinfection complication or inadequate drug potency. In addition, allergen-induced immune activation can alter the T cell response to glucocorticoids by inducing cytokine-dependent abnormalities in glucocorticoid receptor-binding affinity.[156] PBMCs from patients with chronic AD have reduced glucocorticoid receptor-binding affinity, which can be sustained with the combination of IL-2 and IL-4 in-vitro. In addition, corticosteroid unresponsiveness may contribute to treatment failure in some patients.[131] Endogenous cortisol levels have been found to control the magnitude of cutaneous allergic inflammatory responses, suggesting that an impaired response to corticosteroids could contribute to chronic AD.[157] Alternatively, Blotta and associates[158] suggested that chronic corticosteroid therapy can have deleterious but insidious immunologic effects in allergic patients. These results are based on in-vitro data that may not

recreate the complex milieu in allergic inflammation. A much more common reason for failure of corticosteroid therapy is non-adherence to the treatment regimen. Patients or parents often expect a quick and permanent resolution of the AD and become disillusioned by the lack of cure with current therapy. A significant number of patients and caregivers also admit to non-adherence to prescribed topical corticosteroid therapy because of fear of using this class of medications.[139,159] These findings emphasize the need for both education and alternative therapies.

Systemic corticosteroids, including oral prednisone, should be avoided in the management of a chronic, relapsing disorder such as AD.[133] Often, patients or parents demand immediate improvement of the disease and find systemic corticosteroids more convenient to use than topical therapy. However, the dramatic improvement observed with systemic corticosteroids may be associated with an equally dramatic flaring of AD after discontinuation. If a short course of *oral* corticosteroids is given, topical skin care should be intensified during the taper to suppress rebound flaring of AD.

Topical Calcineurin Inhibitors

The approval of the topical calcineurin inhibitors (TCIs) tacrolimus ointment 0.03% and 0.1% and pimecrolimus cream 1% represented a milestone in AD management.[160] Both non-steroidal drugs have proved effective, with a good safety profile for treatment up to 4 years with tacrolimus ointment[161] and up to 2 years with pimecrolimus cream.[162] A fairly common side effect with TCIs is a transient burning sensation of the skin, although a few patients may complain of more prolonged burning or stinging. TCIs are not associated with skin atrophy and thus are particularly useful on the face and intertriginous regions. TCIs may be particularly useful in the treatment of steroid-insensitive patients.[163] Ongoing surveillance and recent reports have shown no trend for increased frequency of viral superinfections, especially eczema herpeticum, and no problems with response to childhood vaccinations.[164]

Currently, tacrolimus ointment 0.03% is approved for intermittent treatment of moderate to severe AD in children 2 years and older; tacrolimus ointment 0.1% for intermittent treatment of moderate to severe AD in adults; and pimecrolimus cream 1% for intermittent therapy of patients 2 years and older with mild to moderate AD.

Although there is no evidence of a causal link between cancer and TCIs, the FDA has issued a boxed warning for tacrolimus ointment 0.03% and 0.1% (Protopic, Astellas) and pimecrolimus cream 1% (Elidel, Novartis) because of a lack of long-term safety data (see US package inserts for Protopic, Astellas; and Elidel, Novartis). Further, the new labeling states that these drugs are recommended as second-line treatments and that their use in children under the age of 2 years is currently not recommended. Long-term safety studies with TCIs in patients with AD, including infants and children, are ongoing. A joint task force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology reviewed the available data and concluded that the risk : benefit ratios of tacrolimus ointment 0.03% and 0.1% and pimecrolimus cream 1% are similar to those of most conventional therapies for the treatment of chronic relapsing eczema.[165] In addition, a nested case–control study of a large database ($n = 293\,253$) did not find an increased risk of lymphoma in AD patients treated with TCIs.[166]

Ongoing studies with TCIs have shown that pimecrolimus cream 1% is well tolerated and effective in infants 3 to 23 months of age with AD.[167,168] Given the chronic and relapsing nature of AD, the question of whether TCI therapy for early signs or symptoms of disease could influence long-term outcomes was addressed in clinical trials up to 1 year in duration with pimecrolimus cream 1%.[169] The primary efficacy parameter was the incidence of flares and need for topical corticosteroid rescue. In the infant study, 64% of the pimecrolimus group versus 35% of the vehicle group did not require topical corticosteroids during the study.[168] Subgroup analysis showed significantly fewer flares in the pimecrolimus-treated children of all degrees of clinical severity, including severe AD. These studies suggest that earlier use of a TCI can lead to better long-term disease control with fewer flares and significantly less need for topical corticosteroid rescue

therapy. Similar to the proactive use of topical corticosteroids, several studies of tacrolimus ointment in both adults and children have shown efficacy with this approach.[154] Proactive therapy with tacrolimus ointment has been approved for use in Europe for up to 12 months in patients 2 years or older.

Tar Preparations

Crude coal tar extracts have anti-inflammatory properties that are not as pronounced as those of topical corticosteroids. Nevertheless, in a study using the atopy patch test, tar performed similar to a topical corticosteroid in its ability to inhibit the influx of proinflammatory cells and in the expression of cell adhesion molecules (CAMs) in response to epicutaneous allergen challenge.[170] Tar preparations used with topical corticosteroids in chronic AD may reduce the need for more potent corticosteroid preparations. Tar shampoos are often beneficial for scalp involvement. The use of tar preparations on acutely inflamed skin should be avoided because it may result in skin irritation. Other than dryness or irritation, side effects associated with tar products are rare but include photosensitivity reactions and a pustular folliculitis.

Wet Dressings

Wet-wrap dressings reduce pruritus and inflammation, act as a barrier to trauma associated with scratching, and improve penetration of topical corticosteroids.[133] In addition, wet-wrap therapy can aid with epidermal barrier recovery that persists even after wrap therapy is discontinued.[171] In one study, children with severe AD showed significant clinical improvement after 1 week of treatment using tubular bandages applied over diluted topical corticosteroids.[172] No significant differences were demonstrated among several dilutions of a midpotency corticosteroid, suggesting that clinical benefit can be achieved with this approach in more severely affected patients even with the use of lower-potency corticosteroids. Although long-term studies with wet-wrap therapy are lacking, most of the improvement in the latter study occurred during the first week. An alternative approach employs clothing, using wet pajamas or long underwear, with dry pajamas or a sweatsuit on top.[133] Hands and feet can be covered by wet tube socks under dry tube socks. Alternatively, the face, trunk, or extremities can be covered by wet gauze then dry gauze and secured in place with an elastic bandage or pieces of tube socks. Dressings may be removed when dry or may be rewetted. Dressings are often best tolerated at bedtime.

Overuse of wet-wrap dressings can result in chilling, maceration of the skin, or, infrequently, secondary infection. Because this approach can be labor intensive, it is best reserved for acute exacerbations of AD, along with selective use in areas of resistant dermatitis. The package inserts recommend that TCIs not be used under any occlusive dressing.

Anti-Infective Therapy

Systemic antibiotics may be necessary to treat AD when a secondary infection with *S. aureus* is present.[133] Therapy with semisynthetic penicillins or first- or second- generation cephalosporins for 7 to 10 days is usually effective. Erythromycin-resistant organisms are fairly common, making macrolides less useful alternatives. Unfortunately, recolonization after a course of antistaphylococcal therapy occurs rapidly.[173] Maintenance antibiotic therapy should be avoided, however, because it may result in colonization by methicillin-resistant organisms. The topical antistaphylococcal antibiotic mupirocin (Bactroban), applied three times daily to affected areas for 7 to 10 days, may be effective for treating localized areas of involvement. Twice-daily treatment for 5 days with a nasal preparation of mupirocin may reduce nasal carriage of *S. aureus*, which may result in clinical benefit in AD patients. Although effective in reducing bacterial skin flora, antibacterial cleansers can cause significant skin irritation. However, a double-blind, placebo-controlled study found that daily bathing with an antimicrobial soap containing 1.5% triclocarban resulted in reductions in *S. aureus* colonization and

significantly greater clinical improvement than with the placebo soap[174] (see earlier discussion of bleach baths).

Patients with disseminated eczema herpeticum, also called Kaposi varicelliform eruption, usually require treatment with systemic acyclovir.[54] Recurrent cutaneous herpetic infections can be controlled with daily prophylactic oral acyclovir. Superficial dermatophytosis and *M. sympodialis* infections can be treated with topical (or rarely with systemic) antifungal drugs.[54]

Anti-pruritic Agents

Pruritus is the most common and usually the worst-tolerated symptom of AD. Even partial reduction of pruritus can significantly improve quality of life for patients with severe AD. The participation of histamine in the pruritus of AD has been questioned, and a dermal microdialysis study of mast cell degranulation concluded that mediators other than histamine cause pruritus.[175] Neuropeptides or cytokines may be important mediators because centrally acting agents such as opioid receptor antagonists have been effective against the itch of AD.[176] Use of cyclosporin A, which results in decreased transcription of several proinflammatory cytokines, leads to rapid improvement in pruritus for many AD patients.[177]

Systemic antihistamines and anxiolytics may be most useful through their tranquilizing and sedative effects and can be used primarily in the evening to avoid daytime drowsiness. The tricyclic antidepressant doxepin, which has both histamine H_1 and H_2 receptor-binding affinity as well as a long half-life, may be given as a single 10- to 50-mg dose in the evening in adults. If nocturnal pruritus remains severe, short-term use of a sedative to allow adequate rest may be appropriate. Although reportedly ineffective in treating the pruritus associated with AD, second-generation antihistamines have shown modest clinical benefit in at least some AD patients.[178]

Treatment of AD with topical antihistamines and topical anesthetics should be avoided because of potential sensitization. Although in a 1-week study, topical 5% doxepin cream resulted in significant reduction of pruritus and no sensitization,[179] re-challenge with the drug after the 7-day course of therapy was not evaluated. Later case reports have documented reactions to topical doxepin.[180]

Recalcitrant Disease Hospitalization

Patients with AD who are erythrodermic or who appear toxic may need to be hospitalized. Hospitalization may also be appropriate for patients with severe disseminated AD resistant to first-line therapy. Often, removing the patient from environmental allergens or stressors, together with intense education and assurance of compliance with therapy, results in marked clinical improvement. In this setting, the patient can also undergo appropriately controlled provocative challenges to help identify potential triggering factors. This can be done in a day hospital model.[133]

Cyclosporin A

The benefit of oral cyclosporin A in severe AD in adults has been demonstrated in placebo-controlled studies.[181,182] A 1-year study of cyclosporin A (5 mg/kg per day) in a pediatric population using either intermittent or continuous treatment showed no significant differences between these two approaches with respect to efficacy or safety parameters, and a subset of patients remained in remission after treatment was stopped.[183] In addition, children as young as 22 months responded to low-dose (2.5 mg/kg per day) cyclosporin A.[184] A meta-analysis of 15 studies that included 602 patients with AD found that cyclosporin A consistently decreased disease severity in all studies.[185]

Short-term oral cyclosporin A therapy can result in increased serum urea, creatinine, and bilirubin concentrations, but these values normalize after treatment is discontinued. Because of the concern for progressive or irreversible nephrotoxicity with extended treatment, few patients receiving maintenance therapy have been evaluated. In one study, patients with severe AD treated with oral cyclosporin A, 5 mg/kg per day for 6 weeks, were monitored until relapse, then treated with a second 6-week course.[186]

Although this regimen did not result in lasting remission for most patients, a subset appeared to receive extended clinical benefit. In another prospective, open multicenter study, 100 adults with severe AD were treated for up to 48 weeks.[187] For the first 8 weeks, cyclosporin A was administered at 2.5 mg/kg per day, then adjusted according to clinical response. Cyclosporin A produced rapid and highly significant improvements in all indices of disease activity, including signs and symptoms, body surface area, pruritus, and sleep disturbance.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF), a purine biosynthesis inhibitor, has been used for inflammatory skin disorders. The drug has been well tolerated, although herpes retinitis has been reported. An observer-blinded RCT compared enteric-coated MMF (1440 mg) with cyclosporin A (5 mg/kg) as long-term treatment in 55 adult patients with severe AD.[188] During maintenance phase, disease activity was comparable in both study arms. Side effects in both groups were mild and transient. After study medication withdrawal, disease activity of the cyclosporin A patients significantly increased compared with MMF patients. In a retrospective analysis of 14 AD children treated with MMF as systemic monotherapy, four achieved complete clearance, four had >90% improvement, five had 60–90% improvement, and one failed to respond.[189] Initial responses occurred within 8 weeks (mean 4 weeks) with maximal effects attained after 8 to 12 weeks (mean 9 weeks) at MMF doses of 40 to 50 mg/kg per day in younger children and 30 to 40 mg/kg per day in adolescents. MMF was well-tolerated in all patients, with no infectious complications or laboratory abnormalities.

Azathioprine

Azathioprine is a systemic immunosuppressive agent affecting purine nucleotide synthesis and metabolism shown to be effective for dermatologic diseases such as severe recalcitrant AD.[134] A systematic review of patients with refractory AD showed an overall decrease in disease severity after active treatment with azathioprine.[190]

Azathioprine has a number of side effects, including myelosuppression, hepatotoxicity, gastrointestinal disturbances, increased susceptibility to infections, and risk of skin cancer. The drug is metabolized by the enzyme thiopurine methyltransferase; TPMT deficiency should be excluded before starting oral immunosuppressive therapy with azathioprine. The recommended dosage of azathioprine for dermatologic indications is 1 to 3 mg/kg daily but should be adjusted based on TPMT levels, and routine screening blood tests should be performed. The onset of action is usually slow, and benefit may not be apparent for several months after starting treatment.

Methotrexate

Methotrexate, a folic acid antagonist that interferes with purine and pyrimidine synthesis, has been effective in moderate to severe AD. In an open-label dose-ranging study (median dose 15 mg/week), disease activity decreased by 52% from baseline after 24 weeks.[191] A group of patients had continued improvement more than 12 weeks after discontinuing therapy. In a retrospective study, 75% of patients treated with weekly doses of 7.5 to 25 mg of methotrexate intramuscularly had clinical improvement of >70% after 3 months of therapy.[192] In another retrospective study of methotrexate (10–25 mg) given weekly (8–12 weeks), 80% of patients with moderate to severe AD had a mean decrease in AD severity score (SCORAD) of 44%.[193] A randomized assessor-blinded trial in patients with severe AD found methotrexate (10–22.5 mg/week) to be comparable in clinical efficacy to azathioprine (1.5–2.5 mg/kg per day) after 12 weeks of treatment.[190]

Symptom improvement in responders can be seen as early as 2 weeks and up to 3 months after initiating therapy, and patients not responding to 15 mg of methotrexate weekly after 3 months are unlikely to improve with further dose escalation.[191] Nausea and liver enzyme elevation are the most common adverse events, resulting in transient or complete discontinuation of methotrexate therapy.

Phototherapy and Photochemotherapy

Ultraviolet (UV) light therapy can be a useful treatment for chronic recalcitrant AD, but should be done under the supervision of an experienced dermatologist. The most common phototherapy modalities are narrowband UVB, broadband UVB, and UVA1.[194–196] Short-term adverse effects from phototherapy may include erythema, skin pain, pruritus, and pigmentation. Potential long-term adverse effects include premature skin aging and cutaneous malignancies.

In an open trial in patients with moderate to severe chronic AD, all patients had a ≥50% reduction in SCORAD with narrowband UVB phototherapy three times weekly for up to 12 weeks.[197] Gene expression and immunohistochemistry studies of both lesional and non-lesional skin showed that Th2, Th22, and Th1 immune pathways were suppressed and measures of epidermal hyperplasia and differentiation normalized. Clinical improvement was associated with decrease in Th2/Th22 associated cytokines and chemokines and importantly, normalized expression of epidermal barrier proteins. A retrospective review of children with severe eczema who had undergone narrowband UVB found that of those who completed more than 10 exposures, complete clearance, or minimal residual activity was achieved in 40%; good improvement in 23%; and moderate improvement in 26%.[198] Overall, the treatment was well tolerated, and the median length of remission was 3 months. A prospective analysis of narrowband UVB phototherapy found that it was an effective and well-tolerated treatment modality in children.[199] A systematic review of phototherapy in AD found that UVA1 should be used to control acute flares of AD, whereas UVB modalities, especially narrowband, should be used for management of chronic AD.[200] However, a 6-week course of medium-dose UVA1 and narrowband UVB in a double-blind crossover RCT showed no significant difference between treatments with respect to clinical scores, pruritus score, or health-related quality of life.[201] In a randomized, investigator-blinded, half-sided comparison study between narrowband UVB and medium-dose UVA1 in adults with AD, both modalities significantly decreased clinical severity and dermal cellular infiltrate.[202] Importantly, UVB phototherapy has been shown to significantly decrease levels of toxin producing *S. aureus* on the skin of pediatric AD patients.[203]

Photochemotherapy with oral methoxypsoralen therapy followed by UVA (PUVA) may be indicated in patients with severe AD, although studies comparing it with other modes of phototherapy are limited. In one randomized observer-blinded crossover trial, PUVA was shown to provide better short-term and long-term response than medium-dose UVA1 in patients with severe AD.[204] Short-term adverse effects may include erythema, pruritus, and pigmentation, whereas long-term adverse effects include premature skin aging and cutaneous malignancies. Topical psoralens combined with UVA may be equally effective. PUVA therapy in children with severe AD and growth suppression has resulted in accelerated growth.[205] However, the long-term risk of cutaneous malignancies has usually precluded treatment of children with PUVA.

Allergen Immunotherapy

Uncontrolled trials have suggested that desensitization to specific allergens may improve AD. In a double-blind controlled trial of desensitization with tyrosine-adsorbed *Dermatophagoides pteronyssinus* (house-dust mite) extract (Der p 1), children with AD and immediate hypersensitivity to *D. pteronyssinus* failed to demonstrate any clinical benefit from desensitization compared with placebo after an 8-month course of treatment.[206] In a second phase, children to whom *D. pteronyssinus* extract was initially administered were randomly assigned to continue on active treatment or placebo for an additional 6 months. The clinical scores suggested that extended desensitization was more effective than placebo, but the numbers were too small to permit confident conclusions. A high placebo effect may have concealed any additional therapeutic effect from active treatment. In a systematic review of immunotherapy for AD that included four comparable placebo-controlled studies involving a small number of patients, statistical analysis

showed significant improvement in symptoms in patients with AD who received subcutaneous immunotherapy.[207]

A multicenter 1-year RCT of dust mite–pecific immunotherapy in sensitized AD patients showed a dose-dependent effect on disease symptoms.[208] An open-label study of patients with dust mite allergy and AD treated with subcutaneous dust mite allergoid demonstrated serologic and immunologic changes consistent with tolerance, in addition to significant reductions in objective and subjective SCORAD.[209] One double-blind, placebo-controlled study of children with AD treated with dust mite sublingual immunotherapy reported a significant difference from baseline values in visual analog scores, SCORAD, and medication use in the mild to moderate severity group, whereas patients with severe disease had only a marginal benefit.[210] Based on a review of available studies, the most recent practice parameter states that some data indicate immunotherapy can be effective for patients with AD when it is associated with aeroallergen sensitivity.[211]

Experimental and Unproven Therapies

Intravenous Immune Globulin

Because chronic inflammation and T cell activation appear to play a critical role in the pathogenesis of AD, high-dose intravenous immune globulin (IVIG) could have immunomodulatory effects in this disease. IVIG could also interact directly with infectious organisms or toxins involved in the pathogenesis of AD. IVIG has been shown to contain high concentrations of staphylococcal toxin-specific antibodies that inhibit the in-vitro activation of T cells by staphylococcal toxins.[212] The mechanism of inhibition by IVIG was direct blocking of toxin binding to, or presentation by, antigen-presenting cells. In addition, IVIG has been shown to reduce IL-4 protein expression in AD patients.[213]

Treatment of severe refractory AD with IVIG has yielded conflicting results. Studies have not been controlled and have involved small numbers of patients. In a study of nine patients with severe AD treated with IVIG (Venoglobulin-I, Alpha Therapeutic), 2 g/kg monthly for seven infusions, skin disease improved slightly in six patients, but their average daily prednisone dosage did not change significantly.[214] Mean serum IgE levels did not decrease significantly during IVIG therapy, and in-vitro IgE production by PBMCs after IL-4 and anti-CD40 stimulation was not significantly reduced. In contrast, a review of 32 AD patients treated with high-dose IVIG found clinical improvement in 61% of the patients.[215] Adults were less likely to respond (48%) than children (90%), and duration of response was also more prolonged in children.

Adjunctive therapy in adults was more effective than monotherapy (59% vs 0%), whereas monotherapy was effective in 90% of children. In a randomized placebo-controlled study, 48 children with moderate to severe AD were treated with three injections of 2.0 g/kg IVIG or placebo at 1-month intervals.[216] Assessments were conducted after each injection and at 3 and 6 months after completion of treatment. The disease severity index was significantly decreased at 3 months after treatment compared with baseline. However, improvement declined by 6 months after therapy.

Additional controlled studies are needed to answer the question of IVIG efficacy in a more definitive manner.

Omalizumab

Case reports and small case series in AD patients treated with omalizumab have shown both clinical benefit and lack of improvement.[217–223] Belloni and associates[222] could find no specific markers to identify responders to omalizumab. A prospective analysis assessed efficacy of omalizumab in 21 patients age 14 to 64 years with moderate to severe persistent allergic asthma and concomitant AD.[224] AD severity was assessed at 0, 1, 3, 6, and 9 months by Investigator Global Assessment; pretreatment serum IgE levels ranged from 18.2–8396 IU/mL (mean 1521 IU/mL). All 21 patients showed clinical and

statistically significant improvement of their skin disease. However, a placebo-controlled trial of omalizumab given for 16 weeks to 20 patients with AD showed no significant clinical benefit.[225]

Recombinant Human Interferon-γ

Interferon-γ suppresses IgE synthesis and inhibits Th2 cell function. Treatment with subcutaneous recombinant human interferon-γ (rhIFN-γ) results in reduced clinical severity and decreased total circulating eosinophil counts in patients with AD.[226] Clinical improvement has also been shown to correlate with reduction in white blood cell, eosinophil, and lymphocyte counts and normalization of the CD4/CD8 ratio among large lymphocytes. Patients may show continued improvement several months after discontinuation of therapy. Two open, long-term studies showed clinical efficacy in AD patients receiving 50 μg/m^2 of rhIFN-γ daily or every other day for at least 22 months.[227,228] These studies demonstrated that patients with AD can be treated on a long-term basis with rhIFN-γ without deterioration of their disease or significant adverse effects. This is noteworthy because IFN-γ has proinflammatory effects in some clinical settings. Importantly, effective dosing with rhIFN-γ is associated with a decrease in eosinophil counts, suggesting that rhIFN-γ acts primarily on the allergic inflammatory response, as opposed to IgE synthesis. Therefore, a subset of patients treated with rhIFN-γ might respond to individualized titration of their treatment dose.[229]

Probiotics

Lactobacilli and *bifidobacteria* are gut microorganisms hypothesized to educate the neonatal immune system by converting the Th2-biased prenatal responses into balanced immune responses. Lactobacilli have been shown to prime monocyte-derived DCs to drive the development of T regulatory cells.[230] These Tregs produced increased levels of IL-10 and were capable of inhibiting the proliferation of bystander T cells in an IL-10-dependent manner. The mechanism was shown to be binding of the C-type lectin dendritic cell (DC)-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN). Blocking antibodies to DC-SIGN inhibited the induction of the Tregs by these probiotic bacteria, stressing that ligation of DC-SIGN can actively prime DCs to induce Tregs and might explain their beneficial effect in AD.

Clinical trials in patients with AD have had varying results, and in addition, these supplements are currently not FDA regulated.[231–233] Administration of probiotics to pregnant women and subsequently to at-risk newborns to prevent AD or even to treat established AD was addressed in a review of therapeutic attempts to shift the presumed Th2 response early in life to a Th1 response.[234] Although one meta-analysis suggested a modest role for probiotics in children with moderately severe disease in reducing SCORAD,[235] another found that current evidence is more convincing for the efficacy of probiotics in the prevention rather than treatment of pediatric AD.[236] Furthermore, a study designed to reproduce earlier beneficial effects of probiotics in AD patients found that supplementation with *Lactobacillus* GG during pregnancy and early infancy neither reduced the incidence of AD nor altered the severity of AD in affected children, but was associated with an increased rate of recurrent episodes of wheezing bronchitis.[237]

A Cochrane review concluded that probiotics are not an effective treatment for AD in children, and that probiotic treatment carries a small risk of adverse events.[238] Salfeld and Kopp[239] pointed to flaws in the methodology of some analyses and the heterogeneity of treatment protocols, concluding that selection of the most beneficial probiotic strain or strains, use of probiotics with or without prebiotics, and timing of supplementation, along with optimal dose and delivery, remain to be determined. More recently, a meta-analysis of RCTs through 2011 that attempted to overcome some of the limitations of prior reviews found a reduction of approximately 20% in the incidence of AD and IgE-associated AD in infants and children with probiotic use.[240] Although these results are encouraging, probiotics for the prevention of AD remain investigational.

Rituximab

Rituximab, a chimeric anti-CD20 mAb developed for treatment of B cell malignancies was given to six patients with severe AD in an open trial.[241] Patients received two intravenous infusions of rituximab (1000 mg) 2 weeks apart, with all patients showing clinical improvement within 4 to 8 weeks. Histology of skin biopsies showed significant improvement in spongiosis and acanthosis, and dermal T cell and B cell infiltrates also decreased. Whereas circulating B cells were below detectable levels, lesional B cells were reduced by approximately 50%. Expression of IL-5 and IL- 13 was also reduced after rituximab therapy. Although total serum IgE levels were reduced, allergen-specific IgE levels were not affected.

Dupilumab

Dupilumab®, a humanized anti-IL-4 receptor alpha mAb that blocks the action of IL-4 and IL-13, was recently reported to cause rapid reduction in clinical severity of AD and reduce pruritus in these patients.[109] Assessment of AD skin biopsies revealed that the abnormal molecular signatures characteristic of AD were reversed after treatment with dupilumab.[242]

Other Investigational Agents

Experimental and unproven therapies for AD include antifungals, traditional Chinese herbal therapy, essential fatty acids, and leukotriene receptor antagonists.

CONCLUSIONS

Although the diagnosis of AD continues to be based on the recognition of characteristic signs and symptoms, significant advances have been made in understanding the role of epidermal barrier defects and immune abnormalities in this increasingly prevalent disease. These studies have identified new mutations of key stratum corneum proteins and a deficiency in antimicrobial peptide synthesis by keratinocytes contributing to skin colonization and infection in AD. Other studies have revealed a multifunctional role for IgE in atopic skin inflammation. Furthermore, Th2-type cells with skin-homing capability, newly discovered Th22 cells, Langerhans cells, other dendritic cells, keratinocytes, mast cells, and eosinophils all contribute to the complex inflammatory process in AD. These observations have provided the rationale for development of immunomodulatory and anti-inflammatory agents in the treatment of chronic AD.[243] Identification of a specific biochemical or genetic marker could not only improve diagnostic capabilities but also lead to more specific strategies for studying the epidemiology and genetics of AD. Undoubtedly, the new insights into pathogenesis of AD will lead to more specific therapeutic agents and, perhaps eventually, to prevention of this disease.

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Key references are preceded by an asterisk.