

Atopic Dermatitis Is a Barrier Issue, Not an Allergy Issue



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KEYWORDS

- Atopic dermatitis • Eczema • Atopic march • Food allergy • Allergic rhinitis
- Asthma

KEY POINTS

- Atopic dermatitis is a chronic, relapsing, and pruritic disease that typically presents in early childhood and is the result of impaired epithelial barrier function and immunodysregulation.
- Allergen sensitization through the skin is likely an important initial step in the development of other allergic diseases in patients with atopic dermatitis.
- Although children with atopic dermatitis are more likely to produce specific Immunoglobulin E to both food and environmental allergens, there is conflicting evidence that allergen avoidance in these patients improves disease severity.
- The most effective treatments of atopic dermatitis are aimed at repairing and protecting the skin barrier and decreasing inflammation.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing, and pruritic illness that affects up to 10% to 20% of children in developed countries and is associated with significant morbidity and decreased quality of life.¹ Within the United States, population studies have shown a national prevalence of 10.7% of children younger than 18 years, with a growing pool of evidence that the prevalence is increasing worldwide.²

Although the general term “eczema” was initially used to describe the condition, the correlation between eczema and other atopic conditions led to Wise and Sulzberger coining the term AD in 1933.³ More recently, longitudinal studies have demonstrated that the presence of AD increases the risk of developing food allergy, allergic rhinitis, and asthma later in life.⁴ This progression from AD to the manifestation of food allergy, allergic rhinitis, and asthma is often referred to the atopic march of childhood.

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Although the exact cause of AD is not completely understood, it is thought to be the result of a complex interaction of genetic and environmental factors that ultimately leads to impaired epidermal barrier function and immune dysregulation. Because sensitization to environmental proteins often occurs as a result of a more porous skin barrier, it is a common misconception that allergy is at the root of the disease. In contrast, AD tends to be the initial manifestation of the atopic march, and sensitization through the skin is likely an important initial step in the development of other allergic diseases that have been associated with AD.⁵

This article reviews the clinical presentation, pathophysiology, and genetic factors associated with AD, briefly discusses proposed therapeutic strategies aimed at barrier repair, and describes the associations between AD and other allergic diseases.

CLINICAL PRESENTATION OF ATOPIC DERMATITIS

Clinical Features and Diagnosis

The characteristic features of AD are dry skin and severe pruritus. Although the clinical presentation can be variable, the disease typically begins in early childhood with a large proportion of cases going into remission during later childhood. Garmhausen and colleagues⁶ analyzed more than 700 patients with AD and described 5 distinct subgroups based on symptom onset, disease course, and laboratory features. These investigators found that about one-third of all patients with AD had a disease history that began in early childhood and persisted until adulthood, and also noted that patients with early-onset AD were more likely to have other concomitant atopic conditions. Others have described 3 main age-related stages: infantile (up to age 2 years), childhood (ages 2–12 years), and adult.⁷ The morphology of AD lesions varies with age. Infants tend to have red, crusted, and weeping patches located primarily on cheeks and extensor surfaces. Lesions become more papular in older children, localizing to flexural surfaces and often forming thickened, lichenified plaques. In adulthood, the disease can take on more of a relapsing and remitting course with flexures and hands continuing to be problem areas.⁷

Diagnosis is based on clinical history and the presence of characteristic eczematous lesions. Hanifin and Rajka⁸ developed the initial diagnostic standard for AD in 1980, describing 4 major criteria and nearly 2 dozen minor criteria encompassing characteristics of the disease. Some of the minor criteria have been questioned since the initial publication because they are thought to not be specific to AD.⁷ To remedy this, the United Kingdom Working Party attempted to refine the original Hanifin and Rajka criteria; however, their revision was not easily applied to young children.⁹ In 2003, the American Academy of Dermatology (AAD) again revised the Hanifin and Rajka criteria to make it inclusive of all ages.¹⁰ The AAD criteria are the most widely used in the United States and use essential characteristics of AD, important patient features, and less specific associated skin findings.

Natural History

AD follows a chronic or chronic-relapsing course over months to years, and the natural history of the disease is variable based on age of presentation and other clinical features. Although most patients will have resolution of AD by late childhood, in a proportion of cases the disease will persist into adulthood. Kim and colleagues¹¹ performed a meta-analysis of more than 45 studies including more than 110,000 subjects, and found that 80% of childhood AD did not persist past 8 years of age and a small percentage (less than 5%) persisted by more than 20 years after diagnosis. Another large longitudinal cohort study of more than 7000 patients showed that AD symptoms may

persist longer than originally believed, as it was not until 20 years of age that 50% of patients reported at least one lifetime 6-month symptom-free and treatment-free period.¹² Peters and colleagues¹³ performed a large prospective cohort study in Germany and found that genetic factors, early allergen sensitization, and a high-risk work environment were significant predictors of disease persistence through late adolescence.

PATHOPHYSIOLOGY OF ATOPIC DERMATITIS

Although food and environmental allergies are commonly implicated in the pathogenesis of AD, it is now well known that the disease is the result of skin barrier dysfunction and inappropriate immune response to skin antigens.¹⁴

Normal Skin Structure

The skin, specifically the epidermis, acts as a physical and immunologic protective barrier against the outside world. The epidermis is made up of keratinized stratified squamous epithelium in 4 main cell layers: the stratum basale, the stratum spinosum, the stratum granulosum, and the outermost layer, the stratum corneum.¹⁵ The stratum corneum (made up of structural proteins, tight-junction proteins, ceramides, fatty acids, and cholesterol) is responsible for the primary barrier function of the epidermis. The stratum corneum itself is organized into 2 compartments, the corneocytes and the extracellular matrix, which prevent water loss and protect against microbial pathogens.¹⁶ The structural makeup of the stratum corneum and the molecular organization of its multiple lipid bilayers creates the epidermis' permeable barrier. Absorption across the epidermis is primarily intercellular, through the lipid bilayer, and thus lipophilic molecules penetrate across the skin more readily than hydrophilic compounds.¹⁷ Additional diffusion across the epidermis is accomplished paracellularly through tight-junction proteins that provide adhesive functions between keratinocytes.¹⁴

Structural Changes that Occur in Atopic Dermatitis

The main epithelial structural changes in AD that are thought to be responsible for disease pathogenesis include keratinocyte dysfunction and altered lipid composition, which lead to increased permeability of the stratum corneum and increased transepidermal water loss (**Box 1**).

Defects in terminal differentiation of keratinocytes have been identified in patients with AD through comparisons between skin lesions in patients with psoriasis, AD, and normal human skin. Ong and colleagues¹⁸ compared skin biopsy specimens from patients with psoriasis, AD, and healthy controls and found that patients with AD had a deficiency in the expression of antimicrobial peptides (cathelicidins and β -defensins). This has been suggested as a contributing factor for the superimposed skin infections that are frequently seen in patients with AD. In addition, elevations in proteases have been described in acute flares of AD, which have been associated with impaired barrier function and reduced skin capacitance.¹⁹

Changes in the intercellular lipid composition and structure of the stratum corneum can also contribute to the increased skin permeability seen in AD. Ishikawa and colleagues²⁰ found that total levels of ceramides were significantly lower in the affected sites of patients with AD compared with normal skin sites in healthy individuals. Janssens and colleagues²¹ found that ceramide chain length and lipid organization were directly correlated with the skin barrier defects in patients with AD, even in nonlesional skin.

Box 1**Pathogenic changes that lead to epithelial barrier dysfunction and immunodysregulation in atopic dermatitis***Epidermal Changes*

- Defective terminal differentiation of keratinocytes
- Structural changes within the stratum corneum
- Increases in protease production
- Decreased amounts of ceramides with altered lipid composition
- Increased transepidermal water loss

Immunologic Changes

- Mechanical trauma–induced TSLP, IL-33, and IL-25 production
- Marked production of Th2 and Th22 cytokines
- Increased production of IL-31, leading to itch
- Abnormal signaling in pattern recognition receptor pathways
- Decreased production of antimicrobial peptides (defensins, cathelicidins)

Microbiome Changes

- Decreased bacterial diversity
- Increased colonization with toxin-producing strains of *S aureus*

Impairment of the stratum corneum results in an increase in transepidermal water loss (TEWL) or a decrease in water-holding ability (capacitance). Studies have shown significantly higher TEWL and lower capacitance in the lesional skin of patients with AD compared with normal controls.²² Other studies have demonstrated similar findings of compromised skin barrier function and increased TEWL even in nonlesional skin of patients with AD.²³

Immunologic Changes that Occur in Atopic Dermatitis

In addition to the dysfunction of the epidermal barrier in AD, research into the pathogenesis of AD has highlighted the role of immunologic pathways in cutaneous inflammation and barrier dysfunction (see **Box 1**).

Hyperinflammatory state of atopic dermatitis

In patients with AD, disruption of the skin barrier is associated with the release of proinflammatory cytokines that promote chemoattractants and adhesional molecules to recruit T cells to cutaneous sites. In response to mechanical trauma, epithelial cells release thymic stromal lymphopoietin (TSLP), interleukin (IL)-33, and IL-25.^{24–26} This is associated with an increase in type 2 innate lymphoid cells (ILC2s) that drive the production of IL-5 and IL-13 and ultimately lead to T helper 2 (Th2) cell differentiation and inflammation. In addition to the inflammatory response produced by barrier disruption, others have reported on the increased expression of Th2, Th22, and Th1 cells in nonlesional skin of patients with AD compared with healthy subjects.²¹ This finding suggests that systemic immune activation plays a role in the pathogenesis of eczema.

Immunologic changes in atopic dermatitis contribute to barrier dysfunction

In patients with AD, there is marked activation of Th2 and Th22 axes, causing profound increases in IL-4, IL-5, IL-13, IL-31, and IL-22.²⁷ These cytokines play a significant role

in the pathogenesis of AD. IL-4 and IL-13 have been shown to affect keratinocyte differentiation, leading to a decreased expression of genes that are important for barrier function.²⁸ IL-22 acts synergistically with IL-17 to increase inflammation and contribute to barrier abnormalities.²⁹ IL-31 is thought to be responsible for the pathognomonic itch in eczema, and overexpression of IL-31 mRNA has been described in both lesional and nonlesional skin of patients with AD.³⁰ Subsequent scratching further disrupts the skin barrier, and the “itch-scratch” response has been shown in mouse models to enhance both Th1- and Th2-mediated inflammation.³¹ Because of their role in the pathogenesis of AD, IL-4, IL-13, and IL-31 have subsequently become the targets of treatment with biological therapies.

Skin Microbiome Changes that Occur in Atopic Dermatitis

There is evidence that changes in the skin microbiome in patients with AD contribute to epithelial barrier dysfunction and exacerbate underlying immunodysregulation. Kong and colleagues³² reported that skin bacterial diversity was decreased in AD compared with healthy controls. Patients with AD showed a greater proportion of *Staphylococcus* species (especially *Staphylococcus aureus*) during disease flares, with the presence of *S aureus* also being linked to increased disease severity. Other studies have identified *S aureus* colonization in greater than 90% of eczema lesions.³³ It is thought that the Th2 inflammation seen in AD facilitates *S aureus* binding by down-regulating keratinocyte production of antimicrobial peptides.³⁴ It has been shown that *S aureus* toxin production can lead to exacerbations in AD by causing regulatory T cell dysfunction and promoting inflammation.³⁵ Additionally *S aureus* can produce an extracellular protease, which has been suggested to disrupt the epidermal barrier.³⁶

GENETIC CAUSES OF ATOPIC DERMATITIS

Studies of twin populations have historically demonstrated the heritability of AD.^{37,38} Multiple genetic factors have been identified to be associated with the development of AD, with most genes playing a role in skin barrier integrity.

Genes Important for Skin Structure

Several of the genes that have been associated with the development of AD are located on chromosome 1q21 in an area termed the epidermal differentiation complex (EDC).³⁹ These genes code for proteins that are important for epithelial keratinocytes to produce the tough, cornified envelope of the epidermis that is integral for the barrier function. The strongest known genetic risk factors for AD are loss-of-function (LOF) mutations in the filaggrin gene (*FLG*), which is located in the EDC.⁴⁰ *FLG* provides instructions for making the large protein called profilaggrin. Profilaggrin is ultimately cleaved to produce filaggrin, which is one of the final proteins necessary for the process of cornification. LOF mutations in *FLG* were first identified during studies investigating ichthyosis vulgaris, a disorder of keratinization and epidermal dysfunction.⁴¹ Later studies have consistently demonstrated that LOF variants in filaggrin were also associated with AD.⁴² The discovery of decreased filaggrin expression in patients with AD contributed significantly to the understanding of the pathogenesis of eczema. *FLG2* and *SPRR3* are 2 other genes located within the EDC that have been implicated in AD, both of which code for proteins that are important for the structure of the cornified envelope.⁴³

Other genes not located within the EDC identified in patients with AD include *SPINK5*,⁴⁴ *CLDN1*,⁴⁵ and *TMEM79*.⁴⁶ All of these genes code for proteins that are important for epidermal homeostasis and barrier function.

THERAPEUTIC STRATEGIES OF BARRIER REPAIR IN ATOPIC DERMATITIS

Primary Prevention

There is evidence to support the proposal that the application of emollients early in life leads to a decreased incidence of AD. Because the stratum corneum is more permeable in infants younger than 1 year, it had been hypothesized that early emollient use could prevent AD in infants at risk for disease.⁴⁷ Horimukai and colleagues⁴⁸ performed the first randomized controlled trial of emollient use during the first months of life and found that approximately 32% fewer neonates developed AD in the treatment group. Although allergic sensitization was associated with eczematous skin, the study did not find a statistically significant effect of emollient use on the prevention of allergic sensitization as measured by allergen-specific immunoglobulin E (IgE). Simpson and colleagues⁴⁷ performed a randomized controlled trial evaluating emollient use in neonates at high risk for AD in the United States and United Kingdom. The investigators found that infants who used daily, full-body emollients had a relative risk reduction of 50% for incidence of AD at 6 months. Lowe and colleagues⁴⁹ evaluated emollient use in an Australian population of neonates and found that prophylactic emollient use for the first 6 months of life was associated with a trend toward reduced incidence of AD and food sensitization at both 6 and 12 months of age, although this study's results did not reach statistical significance.

Secondary and Tertiary Prevention

Cleansing and moisturization are the mainstay of treatment in AD, and current recommendations are for a short bath or shower followed immediately by the application of emollient moisturizer when the skin is still slightly wet.⁵⁰ This approach promotes improved hydration of the skin, whereas bathing alone without moisturization may result in decreased skin hydration. Adding diluted bleach to bathwater or other antiseptic cleansers provides antibacterial activity that can help in the management of AD given the increased colonization with *S aureus* and other pathogens.⁵¹

Emollients have remained a mainstay for the treatment of AD, providing a lipid-rich moisturizer that compensates for the lipid and ceramide deficiencies in AD skin.⁵⁰ In addition, studies have shown that aggressive emollient use as maintenance and prevention therapy in AD can reduce the number of prescriptions for topical corticosteroids and other medications in severe disease.⁵² There is no single emollient that has emerged as the ideal maintenance therapy, and previous randomized controlled trials have shown similar efficacy for over-the-counter petroleum-based emollients and prescription barrier creams for monotherapy in AD.⁵³

For more intensive moisture replacement, wet-wrap therapy can be used alone or in conjunction with topical steroids. This approach involves the application of a layer of wet cotton garments over topical treatment, and has been shown to improve AD severity and reduce the need for systemic immunosuppressive therapies.⁵⁴

ASSOCIATION BETWEEN ATOPIC DERMATITIS AND ALLERGIC DISEASE

General Overview of the Atopic March and IgE-Mediated Disease

As previously discussed, the atopic march describes the typical progression of allergic diseases in childhood, with AD presenting early and food allergy, allergic rhinitis, and asthma presenting later. Proposed molecular mechanisms for the atopic march suggest that skin sensitization after allergen exposure induces local inflammation with Th2 cells that subsequently migrate through the blood to other sites including the respiratory mucosa of the lungs and nasal passages. Mouse models have shown that epicutaneous exposure to food protein antigens (such as ovalbumin and peanut protein)

leads to Th2-mediated skin inflammation and a systemic immune response.⁵⁵ Using data from a cohort of preschool children with peanut allergy, Lack and colleagues⁵⁶ identified that the use of creams containing peanut oil during the first 6 months of life was significantly associated with increased risk for peanut allergy. Other studies have detected increased TEWL in the neonatal period in infants who later developed food allergy, further suggesting a link between skin barrier impairment and sensitization to food allergens.⁵⁷

In studying the impact of AD on the manifestation of other allergic diseases, it is important to differentiate between sensitization, defined as the detection of IgE antibodies to a specific allergen through either serum or skin-prick testing (SPT), and the presence of clinical allergic disease. Many studies use environmental and food sensitization as an analog of allergic disease; however, the presence of allergen sensitization does not perfectly correlate with the presence of true allergy.

Atopic Dermatitis, Asthma, and Allergic Rhinitis

Atopic dermatitis is a risk factor for asthma and allergic rhinitis

Multiple birth cohort studies have described an association between early eczema and subsequent development of asthma. Horwood and colleagues⁵⁸ first identified early eczema as a risk factor for the development of asthma in a cohort of New Zealand children in their 1984 study. Subsequent cohort studies have also shown that early eczema was associated with increased risk of wheezing and asthma later in childhood.^{59–61}

Studies of the German Multicenter Atopy Study cohort identified a significant association between AD and wheeze at age 7 years, but reported that most of these children also had documented wheezing in early childhood, which the authors argue is suggestive of a comanifesting disease process.⁶² However, the Melbourne Atopic Cohort Study (MACS) showed that even after controlling for sensitization and early wheeze, AD was still significantly associated with an increased risk of asthma in boys.⁶³ More recently, data from the Canadian Healthy Infant Longitudinal Development Study found that AD without allergic sensitization was not associated with an increased risk of asthma.⁴ The investigators argue that the combination of AD and allergic sensitization had interactive effects on asthma and food allergy risk. Additional studies of the MACS cohort have demonstrated that early-onset severe AD is most strongly associated with development of asthma and hay fever later in childhood.⁶⁴

Environmental allergen avoidance strategies have shown limited improvement of atopic dermatitis

Despite the association between aeroallergens and AD, there is limited evidence to suggest that avoidance strategies improve AD severity. In several prospective, randomized controlled studies of avoidance strategies for house dust mite, there were no differences in sensitization to dust mite or incidence of AD when compared with those without avoidance strategies.^{65–67} In fact, in 2 studies AD was more prevalent in the treatment group (ie, those using mattress covers to prevent dust mite exposure) compared with the control group.^{67,68} In a Cochrane review including 7 studies of more than 300 children and adults with AD, the authors found mixed evidence regarding treatment response to dust mite avoidance in patients with AD.⁶⁹

Atopic Dermatitis and Food Allergy

Atopic dermatitis increases the risk of food sensitization and allergy

There is evidence to support the notion that AD increases the risk of food sensitization. In the MACS, involving more than 600 infants, the presence of AD before 6 months of

age increased the risk of developing a new positive SPT result at 1 year.⁷⁰ In addition, early-onset persistent AD has been associated with allergic sensitization to food allergens within the first 2 years of life.⁷¹ In a large Australian cohort study, up to 50% of patients with early-onset and severe AD had developed challenge-proven food allergy by 12 months of age, and overall infants with AD were approximately 5 times more likely to develop food allergy in comparison with infants without AD.⁷²

As previously described, LOF mutations in *FLG* are an important part of the pathogenesis of skin barrier disruption in AD. Some studies have also reported an increased risk of food allergy in patients with LOF mutations in *FLG*.^{73,74} However, others have shown that *FLG* mutations do not increase the risk of food allergy over and above that of food sensitization.⁷⁵

Elimination diets in eczema have shown no prolonged benefit

Despite the association between early-onset severe AD and the prevalence of food allergy, it is noteworthy that studies evaluating elimination or exclusion diets as treatment of AD have not shown prolonged benefit.⁷⁶ An early study of avoidance of milk and egg in children with AD showed some improvement in pruritus and sleeplessness,⁷⁷ although a different study of milk- and egg-exclusion diets showed no significant benefit.⁷⁸ Whereas 2 studies showed a significant clinical improvement in SCORAD index for eczema severity in patients with cow's milk allergy/intolerance and AD after milk elimination,^{79,80} pooled data in a comprehensive review including these studies found no difference in AD severity at 2 to 3 months or 6 to 8 months.⁷⁶ One study of children with egg sensitivity and AD did show some improvement in eczema severity score after egg elimination.⁸¹ However, trials of elemental diets in adults and children with AD have not demonstrated improvement in AD symptoms or severity.^{82,83} Lastly, a trial of a limited, few-foods diet in which all foods were excluded except for 5 to 8 failed to show benefit in AD symptoms or severity.⁸⁴

Prolonged food avoidance may lead to immediate IgE-mediated reactions

With the growing evidence to support early introduction to prevent food allergy and the limited evidence to support elimination diets for the treatment of AD, it is important to be aware of the risks associated with elimination diets. There have been multiple case reports of patients on elimination diets for AD who previously tolerated the eliminated food developing acute allergic reactions after accidental ingestion or reintroduction of the food.^{85–87} Furthermore, a retrospective chart review performed by Chang and colleagues⁸⁸ found that 19% of patients who had eliminated food for treatment of AD developed new, immediate allergic reactions after reintroduction to the food.

SUMMARY

AD is a chronic, relapsing disease that typically manifests in early childhood and improves with age in most individuals. It is the result of genetic and environmental factors that lead to impaired epidermal barrier function, increased TEWL, and immune dysregulation. Primary prevention strategies of replenishing epithelial water loss and maintaining the skin barrier early in life with daily emollient application have shown success. In patients with established AD, the most effective treatments are aimed at repairing and protecting the skin barrier and decreasing inflammation.

Many studies have demonstrated that AD is the start of an atopic march that leads to the development of other allergic diseases later in life, likely as a result of antigen exposure through a more porous and inflamed skin barrier. Although children with AD are more likely to produce specific IgE to both food and environmental allergens, there is conflicting evidence that allergen avoidance in these patients significantly

improves disease severity. Furthermore, food-elimination diets in patients with AD may increase the risk of developing immediate, life-threatening reactions to the removed food. Given these findings, it is important to educate and counsel parents of children with AD about the disease pathogenesis, proven treatment strategies, and the limited benefit and even potential harm associated with strict allergen avoidance.

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