

Update on Epidemiology, Diagnosis, and Disease Course of Atopic Dermatitis

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■ Abstract

Studies of the prevalence of atopic dermatitis (AD) have provided insights into associated environmental risk factors, demonstrating the complex interactions between the presence of filaggrin (*FLG*) gene defects and environment. Among other important findings is that elevated transepidermal water loss (TEWL) in newborns is a strong predictor of AD, regardless of *FLG* status. Recently recognized predictors of disease course and severity include onset of AD signs and symptoms before 12 months of age and the presence of an *FLG* mutation and concomitant immunoglobulin E sensitization early in life.

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Atopic dermatitis; eczema; filaggrin; food allergy; peanut allergy; obesity; skin infection

Within the past 5 to 10 years, the results of research regarding the epidemiology, diagnosis, and course of atopic dermatitis (AD) have led to new insights in understanding this disease. In turn, these new insights have provided the necessary background for developing novel prevention and management strategies.

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Environmental Risk Factors for AD—Insights from Disease Prevalence Studies

AD is estimated to affect between 15% and 20% of children in developed countries.¹ The evidence on adult AD prevalence is less robust, with estimates ranging from 1% to 10%, depending on how AD is defined in the various studies considered. Pediatric AD prevalence appears to be increasing in developing countries, with a maximum prevalence of 20% to 30% in some populations.² The reasons for the increasing prevalence of pediatric AD are unclear, but large-scale studies suggest that several environmental factors may be responsible.

The first systematic, international investigation of AD prevalence from regions outside of Northern Europe came from the International Study of Asthma and Allergies in Childhood (ISAAC) in 1999.³ In ISAAC, Williams and colleagues noted wide variations in AD symptom prevalence between and within countries with similar ethnic groups, an observation that led the authors to suggest that disease expression might depend largely on environmental factors.³

The Urban/Rural Gradient

A number of studies from various countries and regions have noted the increase in AD among populations worldwide, and regional studies have suggested and supported the notion of an urban/rural gradient in AD disease prevalence. Schram and colleagues⁴ performed a systematic analysis of 26 of these studies to determine whether an urban/rural gradient could be established, and concluded that “there is some evidence” of a higher risk for AD in urban versus rural regions.

More recently, Wang et al⁵ noted that the increase in AD among Taiwanese infants overall increased from 6.7% in 2005 to 7.9% in 2007; in Taipei, the 40th most populous urban area in the world, the prevalence of AD among 6- to 7-year-old children significantly increased over a period of about 13 years, from 23.9% in 1994, to 26.3% in 2002, and to 29.8% in 2007. These authors observed that genetic variability in the population could not have changed within this time frame and proposed that “environmental factors are likely to be responsible for the rise” in AD prevalence.

In another example, a cross-sectional study of preschool children from Shanghai, China showed an overall AD prevalence of 8.3%, with a significantly higher prevalence in the core urban area (10.2%) than in the regions farthest from the urban area (4.6%).⁶

The specific factors that may explain these increases in AD prevalence, as well as the differences between prevalence in urban and rural areas, have not yet been established. Some studies suggest that exposure to microbes found in agricultural environments protect the developing immune system from T helper cell type 2 (T_H2) overactivity.^{7,8} McFadden and colleagues⁹ argue that early life low-dose chemical exposures via epithelial and epidermal surfaces promote T_H2 responses.

Thyssen and colleagues¹⁰ suggest a lack of ultraviolet (UV) radiation exposure may be an additional factor contributing to the rise in AD prevalence, given the beneficial effect of UV radiation on epidermal functioning and inflammation.

More recently, Kathuria and Silverberg¹¹ studied the correlation between small-particle air pollution, climate, and childhood eczema in a US population database of children 17 years of age and younger. The investigators considered measurements of air pollutants and ozone levels from the 2006-2007 US Environmental Protection Agency report and measurements of humidity, ultraviolet radiation index, outdoor air temperatures, and precipitation levels from the National Climatic Data Center. These investigators found a number of statistical associations between these various factors and AD, but further study is required to verify and further characterize these findings.

Interactions Between Genetics and Environment

Patients who carry a flaggrin loss-of-function (*FLG* null) mutation have been shown to have a greater than threefold increased risk for developing AD,^{12,13} and both rare and common *FLG* null mutations of various types have been identified in patients with AD worldwide. *FLG* mutations cause a loss of *FLG* protein of at least 50%, leading to multiple biophysical defections in skin barrier function, including elevated pH, a disorganized stratum corneum, reduced lipid content, and increased transepidermal water loss (TEWL).¹⁴

However, not all children with an *FLG* defect develop AD, and cohort studies are beginning to elucidate the complex interactions between environment and *FLG* status. For example, cat ownership enhances the detrimental effects of *FLG* mutations, whereas dog ownership may be protective.^{15,16} Another cohort study confirmed the importance of *FLG* in predicting AD, but showed skin barrier dysfunction early in life (that

is, elevated TEWL at 2 days and 2 months of age) was the strongest predictor of AD development, independent of *FLG* status.¹⁷ These data suggest environmental factors affecting the skin barrier, together with a person's genetic profile, help determine the risk for developing AD. A similar study in a cohort of Japanese infants also demonstrated that early TEWL is a strong and independent predictor of AD.¹⁸

Disease Presentation

Morphology

Morphologically, AD presents with the classic signs of erythema, papulation, lichenification, excoriation, oozing, and crusting. This classic presentation can vary in patients with skin of color. For example, in darker skin types, lichenification can resemble flat-topped lichenoid papules, and follicular accentuation and hyper- and hypopigmentation are common. In addition, a grayish-white discoloration (sometimes referred to as “ashy” skin) is a manifestation of xerosis and, possibly, ichthyosis vulgaris.

AD Configuration

In the classic configuration, AD presents as poorly demarcated papules and plaques; however, AD also may have a well-demarcated nummular configuration, resembling nummular dermatitis. True nummular dermatitis, unrelated to atopic disease, is uncommon in children.¹⁹

Age-Specific AD Distribution Patterns

In children, AD usually begins in the face, moves to the extensors, and becomes more accentuated over time in the antecubital and popliteal fossae (**Figure**). In adults, the face is commonly involved, and periocular disease is common. It is unclear at this time whether different patterns of distribution reflect differences in pathophysiology or prognosis, and/or whether different patterns warrant a different therapeutic approach.

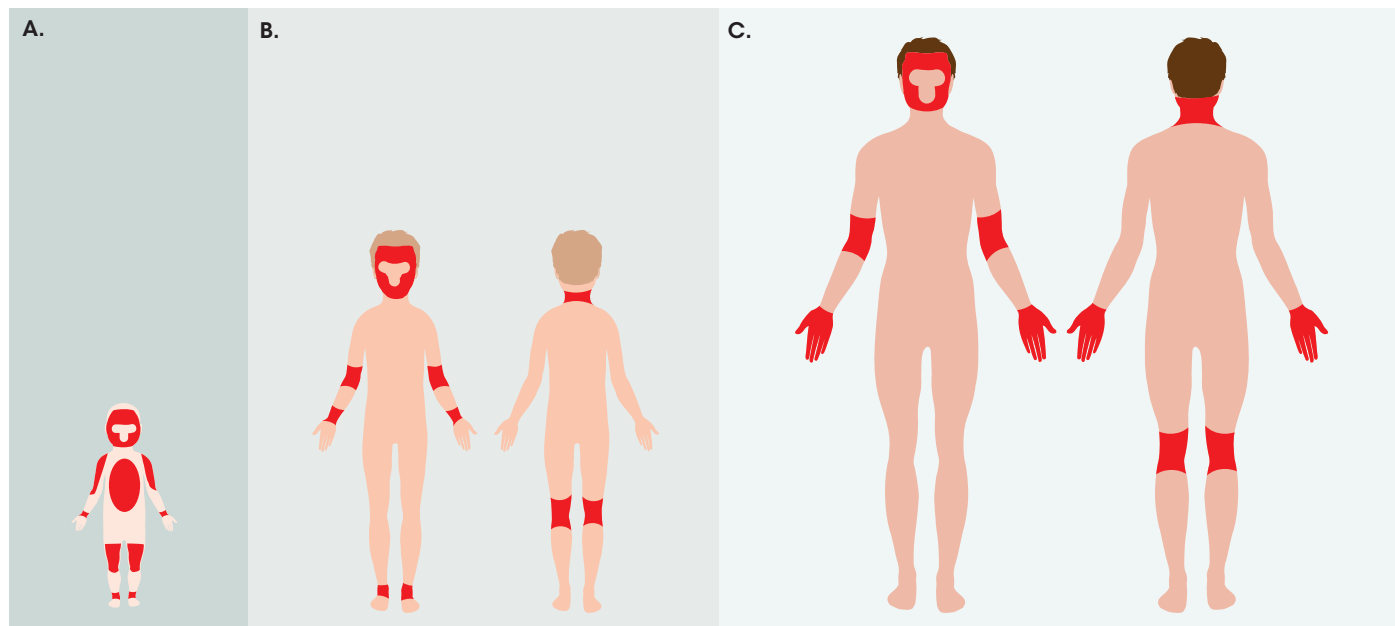


FIGURE Atopic Dermatitis: Age-Related Patterns of Involvement.

A. In babies less than 2 years of age, the signs of atopic dermatitis (AD) first appear on the scalp, forehead, and face (typically, the cheeks), then on the extensor surfaces of the extremities. **B.** In older children, AD is more accentuated in the flexural folds: the nape of the neck, the antecubital popliteal fossae, and the wrists and ankles. **C.** In adults, the pattern of distribution commonly includes the face, often with periocular involvement, the hands, and the flexural areas of the neck, arms, and legs.

Recently, Werfel and colleagues²⁰ described a subtype of AD in adults that is characterized by a worsening of dermatitis provoked by environmental allergens. These authors reported that exposure to pollen was associated with exacerbation of eczema in the head and neck areas. To date, no clinical trials have identified any specific therapeutic approach for this subset of patients that varies from the strategies currently in routine use. Some weak evidence suggests that oral antifungal agents could be helpful in a subset of adult patients with predominant head and neck involvement, as *Malassezia* has been hypothesized to play a role in this presentation.²¹

Clues to Consider a Differential Diagnosis

The differential diagnosis of AD is well known to pediatric and dermatology health care providers (**Table**). This list is important to consider in patients with a lesion morphology or distribution that is not typical for AD, in patients who do not respond to treatment, in those with a history of significant infections, and in cases of failure to thrive.

Disease Severity

In the majority of children, AD is mild; according to data from population-based surveys, up to one-third of parents report moderate to severe signs and symptoms in their children with

AD. The severity of AD in older children and adults has long been thought to be greater than that in young children, but data to support this view are lacking.

The factors that determine disease severity are unclear, but existing data indicate that early age of onset—that is, onset of signs and symptoms before 12 months of age—is a relatively strong predictor of severe AD.²² Other important predictors that have become recognized are the presence of an *FLG* mutation and concomitant immunoglobulin E (IgE) sensitization early in life.

Disease Course

Although most large birth cohort studies reveal that the majority of children with AD do not have disease persisting into adulthood, the true relapsing and remitting course of the disease is difficult to capture accurately in large studies. At least a subset of individuals in cohort studies whose disease “remits” likely have a persistent atopic tendency which, later in life, manifests intermittently with signs and symptoms. This group includes adults who are defined as having “sensitive skin,” but because they may not have had active eczematous signs and symptoms, they are not diagnosed with adult AD.

Recently, Margolis and colleagues²³ found that symptoms of AD actually may persist longer than previously thought. Their analysis of a registry of children with mild to moderate diseases showed that 50% of patients continued with symptoms of AD until 20 years of age.

Comorbidities

The course of AD is not defined solely by the inflammatory skin disease but also includes a high likelihood of associated comorbidities. Several comorbidities for AD are traditionally recognized, including the so-called allergic comorbidities—allergic asthma, allergic rhinitis, and food allergy. Children with AD have at least a twofold increased risk for these comorbidities.²⁴ The risk for developing comorbidities—and the severity of those associated conditions—appears to correlate directly with the severity of the skin disease.²⁴

Emerging Views on Food Allergy in Patients With AD

Food allergies are the most common allergies in children with AD, most commonly involving cow’s milk, chicken eggs, peanuts, wheat, soy, nuts, and fish.^{25,26} In a large, retrospective population-based study in the United States, the prevalence of food allergy has been reported to be slightly greater than 15% in patients with AD.^{24,27} In moderate-to-severe childhood AD, the incidence of food allergy is approximately 35%.²⁸ Previous guidelines for preventing food allergy recommended avoidance of antigenic foods in high-risk populations. However, epidemiologic studies from Lack’s group²⁹ found a lower level of peanut allergy in populations who had early exposure to peanuts.

An important advance in understanding the development of peanut allergy, specifically, in patients with AD came from the Learning Early About Peanut Allergy (LEAP) study, a randomized controlled trial of the early introduction of peanuts in children at high risk for developing food allergy.³⁰ Young children with either an egg allergy or severe AD comprised the population identified for LEAP. In this study, children were randomized to one of two groups: peanut consumption at 4 to 11 months of age or peanut avoidance. (Children who had demonstrated skin prick wheal sizes greater than 4 mm were excluded from enrollment.) At 5 years

TABLE Differential Diagnosis of Atopic Dermatitis

Autosomal recessive hyperimmunoglobulin E syndrome (AR-HIES)
Benign cephalic histiocytosis
Contact dermatitis (irritant or allergic; consider bathing products, moisturizers)
Cutaneous T-cell lymphoma
Immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome
Langerhans cell histiocytosis
Netherton syndrome (severe erythroderma, failure to thrive)
Nummular dermatitis
Psoriasis (rash in napkin distribution, which is not typical for atopic dermatitis)
Pediatric herpes simplex virus infection
Scabies (papular and nodular, affecting palm and sole)
Seborrheic dermatitis
Severe combined immunodeficiency (SCID)
<i>Staphylococcus aureus</i> infection
Wiskott-Aldrich syndrome (bleeding disorder, low platelet count)
Zinc deficiency

of age, the children were tested for food allergy by oral food challenge. The investigators found a significant reduction in food allergy in the early consumption group. As a result of the LEAP study findings, several groups of investigators are studying whether broad-scale population interventions may be appropriate to decrease the risk for peanut allergy.

For children at highest risk for developing food allergy, clinical guidance on intervention incorporating these new findings has led an interim guidance document on feeding of peanuts.³¹ Based on the findings in these studies, an expert panel convened by the National Institute of Allergy and Infectious Diseases (NIAID) is revising the previously published guidelines. The revised guidelines are expected to address whether children with severe AD and/or egg allergy should be considered for early peanut feeding. Because patients with very high skin prick reactivity were excluded from the LEAP study, data suggest that it may be appropriate to screen infants with severe AD for IgE reactivity using either serum IgE and/or skin prick testing. It is likely that the revised NIAID guidelines will provide detailed recommendations for regular peanut exposure to try to minimize the development of peanut allergy in these patients.

Additionally, it did not appear that AD was affected differentially in the two groups in the LEAP study patients—that is, the course of AD did not seem to be affected whether patients had been fed or avoided peanuts. This finding provides support for abandoning the traditional notion that avoidance of certain foods based on specific IgE or skin prick testing without clinical correlation improves AD, or that ingesting certain foods necessarily exacerbates the disease.

AD and Infectious Diseases

It is widely known that patients with AD have an increased risk for skin infections, primarily with *Staphylococcus* organisms.³² Microbiome studies have confirmed that AD flares are associated with *Staphylococcus aureus* colonization, and also have demonstrated that AD flares are associated with changes in microbiome diversity.^{33,34} Although patients with AD are not necessarily at high risk for infection, they may have a tendency to demonstrate more severe infections with herpesviruses, human papillomaviruses, molluscum contagiosum virus, and *Malassezia* species.³⁵ One avenue of insight into these more recent observations about herpetic infections, in particular, comes from Atopic Dermatitis Research Network (ADRN) investigators, who have published human clinical studies suggesting the possibility of a genetic predisposition for eczema herpeticum through variations in gene-regulating and interferon pathways.³⁶

Association Between AD and Obesity

The association between AD and obesity was suggested by observational studies of worldwide increases in both AD and obesity.^{37,38} In a retrospective, practice-based, case-controlled study, Silverberg and colleagues³⁹ reviewed the randomly selected records of 414 children and adolescents (age range, 0 to 21 years) with AD and 828 age-matched controls. They concluded that children were more predisposed to AD when obesity started before 2 years of age and when it was prolonged for more than 2.5 years. They also noted that obese children had more severe AD. Another retrospective, case-controlled study, in an adult population of 2,090 patients in an allergy clinic, showed that the prevalence of AD was higher in obese patients; it was not

increased in obese patients with asthma, allergic rhinoconjunctivitis, or food allergies without concomitant AD.⁴⁰

More robust evidence of the AD/obesity association came from cohort of Irish children in which the PEA POD whole-body plethysmography device⁴¹ was used to determine body composition in newborns.⁴² The babies with a higher percentage of body fat had a higher rate of AD, beginning early in life.

In addition, Zhang and Silverberg⁴³ published the results of a systematic review and meta-analysis of literature examining the AD/obesity relationship. They found that the association was significant in North American and Asian populations but not in Europeans.

Future large-cohort, prospective studies are required to confirm both the AD/obesity association and the possibility that weight control, beginning at an early age in patients with AD, may help to mitigate or reverse AD symptoms.

Other AD Comorbidities

Evidence is emerging on the role of AD in the development of psychosocial and mental health comorbidities in both children and adults. Some studies suggest that such AD comorbidities may include attention-deficit/hyperactivity disorder, autism, anxiety disorder, and depression.⁴⁴ Further studies using strict definitions are required to firmly establish the relationship between mental health diagnoses and AD. Itching and sleep loss may lead to a premature diagnosis of a mental disorder that is purely transient in nature and resolves with adequate control of the skin disease.

In addition, associations between AD and a number of other conditions have been reported in some databases; these include hypertension, cardiovascular disease, rheumatoid arthritis, osteoporosis, fractures, dental problems, alopecia areata, vitiligo, and a propensity for falling.^{44,45} However, replication of these findings is required in long-term, longitudinal studies before any of these associations can be further considered as true comorbidities of AD.

Conclusion

AD is a complex disorder involving skin barrier function abnormalities and skin inflammation. Given the urban rural gradient identified from epidemiologic studies, studies are under way on the role in AD development of environmental factors such as early microbial exposures and environmental pollutants. Interest in the prevalence, causes, and prevention of atopic and nonatopic comorbidities also is increasing.

Studies such as the LEAP study reveal that epidemiologic findings can provide the impetus for randomized controlled trials that help guide clinicians in patient care. For example, promoting early food antigen exposure rather than food avoidance may dramatically reduce the burden of food allergy in patients with severe AD. Future studies on the epidemiology of AD will focus on better defining the natural course of the disease, better understanding of the associated comorbidities, and testing novel approaches to disease prevention.

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