Atopic Dermatitis Progression: Evaluating Intervention Strategies

Linda F. Stein Gold, MD,* and Lawrence F. Eichenfield, MD†

■ Abstract

Several risk factors have been identified that appear to be consistently and strongly associated with the development of atopic dermatitis (AD): a family history of atopy, an inherited genetic predisposition, and active and passive exposure to tobacco smoke. Recent studies also have demonstrated that a simple intervention from birth—the daily application of an emollient moisturizer—seems to protect susceptible infants from the development of AD.

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■ Keywords

Atopic dermatitis; eczema; emollients; filaggrin; food allergy; inflammatory cytokines; interleukin; T helper cells

A fundamental question concerning atopic dermatitis (AD) has been the topic of many recent studies: What are the relative contributions of genetics and environment in disease susceptibility and expression?

Genetic Predisposition and Family History

Evidence for a genetic predisposition in AD comes from a variety of studies. Most recently, a study comparing AD in identical and fraternal twins demonstrated concordance rates of up to 0.86 in monozygotic and 0.41 in dizygotic pairs, providing clear evidence for a genetic predisposition to AD.¹

In addition, Wen and colleagues² reported that about 70% of patients with AD have a positive family history for atopic diseases. Previous studies had demonstrated that the chances of a patient having AD are 2- to 3-fold if one parent has AD,

and 3- to 5-fold if both parents are atopic.^{3,4} Interestingly, Ruiz and colleagues⁵ demonstrated more than 2 decades ago that a maternal history of AD may be more predictive than a paternal history.

Exposure to Tobacco Smoke

A meta-analysis across 86 studies showed that both active and passive exposure to tobacco smoke increases AD risk, with an odds ratio of 1.87.⁶

Role of the Filaggrin Gene

The role of the filaggrin gene in the development of AD has become widely recognized within the past decade. In 2006, Irvine and McLean⁷ studied the histology of normal and atopic skin and demonstrated that the skin in AD has a defective barrier, with an absence of filaggrin-containing keratohyalin granules in the epidermal granular layer. These granules are known to be crucial to the formation of a tight, functional skin barrier.

Research regarding the nature and role of filaggrin has demonstrated that filaggrin is formed when profilaggrin—which is encoded by the filaggrin gene (*FLG*)—degrades. Later, as filaggrin itself breaks down, the resulting products contribute to the formation of natural moisturizing factor, which is important for epidermal hydration and barrier function. The absence of the filaggrin gene (ie, an *FLG* null mutation) is associated with a risk for the earlier onset of AD, as well as for more severe and persistent disease. Patients with an *FLG* null mutation have 1.2 to 13 times the risk for the development of AD.⁸

Although *FLG* mutations have been noted in patients with AD from various ethnic and geographic populations, demonstrating its importance in the pathogenesis of AD, some questions remain to be explored. For example, a substantial number of patients who have AD have no identifiable *FLG* mutations, whereas approximately 40% of individuals with *FLG* null alleles do not develop AD.⁸

Such questions raise the possibility that a filaggrin abnormality might develop, de novo, in patients who have no evidence of an inherited *FLG* mutation. Howell and colleagues⁹ explored this question in a study designed to determine whether *FLG* expression could be reduced in patients who had AD but were not carriers of any identified *FLG* mutations. These investigators enrolled 39 patients with no history of AD and 30 patients with moderate AD. Among their other findings, the researchers detected the presence of interleukin (IL)-4 and IL-13 in patients with AD; in these patients, keratinocytes showed significantly reduced filaggrin expression. They concluded that the patients with AD in this study had an acquired defect in filaggrin expression in the presence of an atopic inflammatory response.

*Director of Dermatology Research, Henry Ford Health System, Detroit, Michigan

† Chief, Pediatric and Adolescent Dermatology, Professor of Dermatology and Pediatrics, Rady Children's Hospital, University of California, San Diego School of Medicine, San Diego, California

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Lawrence F. Eichenfield, MD, *Advisory Board/Speaker*: Valeant Pharmaceuticals North America LLC. *Consultant*: Anacor/Pfizer Inc., Eli Lilly and Company, Genentech, Inc., Otsuka/Medimetriks Pharmaceuticals, Inc., Sanofi Genzyme/Regeneron Pharmaceuticals, TopMD, Valeant. *Investigator*: Sanofi Genzyme/Regeneron.

Address reprint requests to: Linda F. Stein Gold, MD, 2360 Heronwood Drive, Bloomfield Hills, MI 48302; lstein1@hfhs.org

AD Immunology

AD is an immunologic disorder characterized by T helper cell dysregulation, mast cell (basophil and eosinophil) hyperactivity, and immunoglobulin E (IgE) production; the latter may be a factor that occurs secondary to other events. In addition, AD is associated with an imbalance in T-cell subsets, with type 2 T helper (T_H2) cells predominating. The key T_H2 cytokines include IL-4, IL-5, and IL-13. In addition, a specific cytokine, IL-31, has been identified, informally referred to as the “pruritus-specific” cytokine.

Modulating Barrier Dysfunction in AD

Identification of the role of skin barrier dysfunction in patients with AD and extensive study of the underlying disease immunology has allowed investigators to explore the possibility of (1) identifying susceptible patients early in life and (2) preventing or minimizing the risk for the development of AD. Recent studies have demonstrated that both of these goals are achievable in many, if not all, patients with AD.

In a study of 1,903 newborns, Kelleher and colleagues¹⁰ evaluated skin barrier function at birth (on day 2) and at 2 and 6 months of age by assessing transepidermal water loss (TEWL) (so-called “leaky skin”). In addition, 1,300 infants were tested for the presence of *FLG* mutations. The investigators reported that 18.7% of the babies were diagnosed with AD at 6 months of age; at 12 months of age, 15.53% had AD. The upper quartile of TEWL measurement at day 2 was “significantly predictive” of an AD diagnosis at 12 months of age ($P<0.05$). Conversely, the lowest quartile of TEWL at day 2 was associated with protection against AD at 12 months of age. In addition, the upper quartile of TEWL measurement at 2 months of age also was significantly predictive of AD at 12 months ($P<0.05$). Parental AD history and infant *FLG* status were not factors in these results.

To explore the potential protective effects of minimizing TEWL, Simpson and colleagues¹¹ enrolled infants at increased risk for AD in a preliminary study of emollient use. The Barrier Enhancement for Eczema Prevention (BEEP) study was designed to determine whether parents would be willing to have their newborns randomized to receive either no emollients (the control group) or full-body applications of topical emollients at least once daily, beginning at 3 weeks of age (intervention group). The investigators reported that 42% of families agreed to the randomization. The primary endpoint was to establish whether emollient application was a feasible strategy. In addition, data were collected on the development of AD at 6 months of age in the intervention and control groups.

The authors reported that emollient use had a statistically significant protective effect, with a relative reduction in the risk of AD of 50% (relative risk, 0.50; 95% CI, 0.28-0.9; $P=0.017$). No emollient-related adverse effects were reported, and no differences in adverse effects were seen between the intervention and control groups. Although this study was small and was not designed to establish efficacy and safety, the results suggest that larger, randomized controlled trials are warranted.

Meanwhile, other small studies have yielded similar findings regarding the protective effects of emollient use in infants, including a study of 136 subjects from Great Britain¹² and a study from Japan involving 118 subjects.¹³

Predicting Long-Term AD Persistence

Clinicians know from experience that AD resolves over time in most children, with few having persistent AD into adulthood. However, predicting which individuals will have persistent disease has not been possible. In a recently published meta-analysis of 45 studies from 15 countries (involving 110,651 patients, for a total of 434,992 patient-years), Kim and colleagues¹⁴ found that three main factors were involved in the risk for persistence of AD into adulthood: (1) disease in childhood that persists for 10 years or more (compared to ≤ 5 years); (2) onset of AD later than 2 years of age; and (3) greater vs less severity of AD in childhood.

Role of Food Allergies in AD

Because some patients with mild to moderate AD also have food allergies, many parents (and some clinicians) assume that a causative relationship exists. Although older studies estimated an AD/food allergy comorbidity incidence for mild to moderate AD of 30% to 40%, more recent evidence shows that the incidence actually is about 15% in this subpopulation of patients¹⁵; the incidence of food allergy among patients with severe AD is approximately 35%.¹⁶ Interestingly, a review and meta-analysis of prospective studies shows that breastfeeding may decrease the incidence of AD.¹⁷

The strategy of blindly eliminating commonly allergenic foods—including cow’s milk, eggs, and peanuts—from the diets of all patients with AD is not effective in modifying the course of AD. Nevertheless, food and other allergies may contribute to AD in some patients. Consider referring patients to a pediatric allergist for evaluation when AD is moderate to severe, when skin disease is recalcitrant, and in the presence of a reliable history of exacerbation after exposure to certain foods. Teenagers or adults with severe AD also may benefit from an allergy evaluation.

Recent work by Du Toit and colleagues¹⁸ has demonstrated that exposure to foods actually may protect children from food allergies. This study, Learning Early About Peanut Allergy (LEAP), was a randomized controlled trial of early exposure to peanuts of children at high risk for developing a food allergy. The study population in LEAP consisted of 640 infants between 4 and 11 months of age with severe eczema, egg allergy, or both. All subjects received a skin-prick test to determine sensitivity to peanuts. All patients with a negative skin-prick test were randomized to either consume or avoid peanuts. Among children with positive skin-prick tests, children with wheals of 5 mm or larger were excluded from the study; children with wheals of 1 to 4 mm were randomly assigned to either consume or avoid peanuts.

At 60 months of age, the children were tested for peanut allergy by oral challenge. Among the children with initially negative skin-prick tests, the prevalence of peanut allergy was 13.7% in the avoidance group and 1.9% in the consumption group, a statistically significant difference ($P<0.001$). Among the enrolled patients with an initially positive skin-prick test, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group ($P=0.004$).

The results of this and other studies has led to a revision in guidelines for feeding and allergy testing in children with severe AD in the first year of life, calling for skin-prick testing or IgE screening to determine whether a child should have early peanut feeding. Dermatologists and pediatricians should collaborate with an allergist in managing the care of these patients.

Conclusion

Atopic dermatitis is a common relapsing inflammatory condition with genetic as well as environmental risk factors. New research has contributed to a better understanding of this disease and improved strategies for prevention and treatment.

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